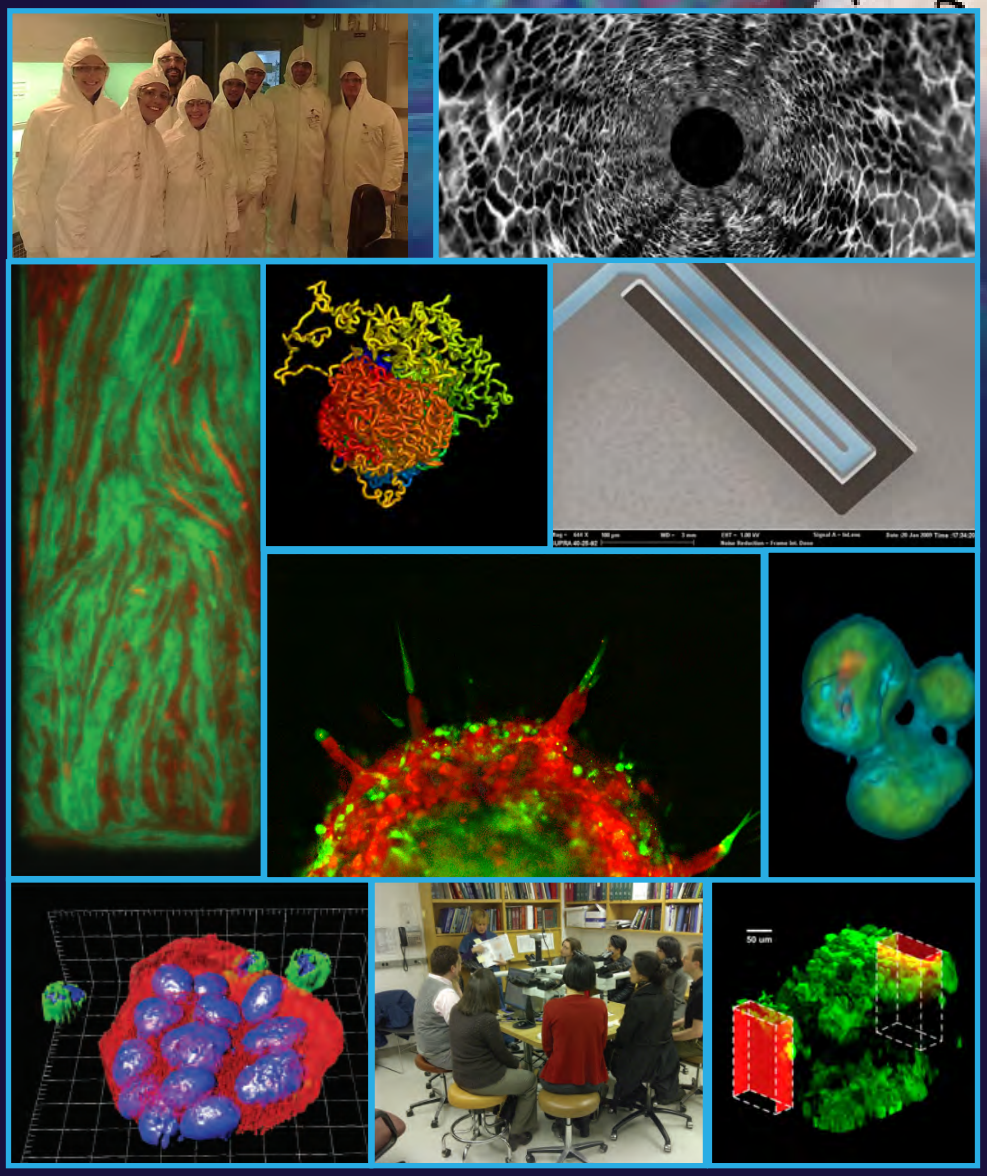
National Cancer Institute



PHYSICAL SCIENCES-ONCOLOGY CENTER PROGRAM

# Program Metrics: Year Three

Fall 2012

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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# 1. Executive Summary

## Rationale of Evaluation and Approach

In 2009, then President of the Massachusetts Institute of Technology (MIT), Susan Hockfield, emphasized the strategic importance of converging the physical sciences and life sciences fields, stating that:

> *"The United States can anticipate comparable world-changing innovations in the 21st century if we adapt our education and research funding strategies to capitalize on new opportunities emerging at the convergence of the life sciences with the physical sciences and engineering."*

At the time of this statement, the National Cancer Institute (NCI) had already begun exploring methods to more effectively engage the physical sciences in cancer research. During a series of strategic Think Tanks, convened during 2008, four scientific areas where physical sciences could impact cancer research were identified, and the formation of transdisciplinary centers comprising integrated physical sciences and oncology teams was recommended to overcome the traditional barriers and silos that have separated these two scientific communities. In the fall of 2009, the NCI Center for Strategic Scientific Initiatives (CSSI) launched the Physical Sciences-Oncology Centers (PS-OC) Program. The PS-OC Program consists of a virtual Network of 12 Centers that integrates physical scientists with oncologists and cancer biologists to develop the infrastructure, resources, and teams to study key questions in cancer research from a physical science perspective (PSP).

The PS-OC Program is dedicated to building transdisciplinary teams and infrastructure to better understand and control cancer through research at the intersection of the physical sciences and oncology. Several program elements separate it from other NCI programs, including the requirement for the Principle Investigator (PI) to be trained in the physical sciences, the availability of funds to support new collaborative projects, and a dedicated training budget. Because this is a new program structure, there is no established precedent for indicators and metrics to assess performance. Thus, the Office of Physical Sciences-Oncology (OPSO) built an infrastructure for a prospective program evaluation, in collaboration with the NCI Office of Scientific Planning and Assessment and evaluation offices from the National Institute of Allergy and Infectious Disease and the National Eye Institute and with scientific inputs from the NCI Division of Cancer Control and Population Sciences Transdisciplinary Research on Energetics and Cancer Centers Program and the Government Accountability Office (GAO). Such evaluation allows program officials to assess the PS-OC Program performance on an ongoing basis.

A combination process and outcome evaluation of the PS-OC Program was designed and conducted during the first three years of program operation to assess performance and adjust elements in the current program and in future phases. Based on an initial needs assessment conducted at the start of the PS-OC Program, the Science and Technology Policy Institute (STPI) determined appropriate study questions, performance measures, data collection methods, a logic model, and a process and outcome evaluation plan. This plan was implemented by the OPSO in collaboration with Discovery Logic, a Thomson Reuters company.

## Progress Toward Program Goals and Other Overarching Findings

The initial PS-OC Program RFA (CA09-009) concept outlined five specific programmatic goals that would be used to monitor progress of the PS-OC Program. Data from NIH semi-annual progress reports were used to generate program metrics. The metrics collected with respect to each goal are summarized below.

- Program Goal #1: Develop innovative (assumption-challenging) physical sciences-centered experimental approaches to gain new knowledge of cancer initiation and progression.

  In its first three years, the PS-OC Program has generated high-quality transdisciplinary publications (538 peer-reviewed publications, average impact factor 9.18, 40 percent transdisciplinary publications based on content), reported 23 patent

disclosures, and applied at least 14 advanced physical sciences-based technologies to cancer. While it is difficult to analyze the impact of PS-OC outcomes after a short period, a robust bibliometric analysis highlighted 18 potential breakthrough publications. Key scientific advancements by the Network include (1) relating the three-dimensional physical architecture of the genome to somatic copy number alterations; (2) defining optimal drug dosing schedules to delay the onset of drug resistance by using evolutionary models; and (3) identifying mechanisms of mechanical communication between cell populations during tumor progression.

- Program Goal #2: Develop and test new hypotheses/theories/models in cancer research.

  New and expanded theories of cancer have started to evolve from principles in polymer physics, control theory, and complex systems. Examples of these theories are outlined in Section 5. Publications that articulate these concepts are accumulating citations, suggesting that this work is starting to spread into the broader scientific community. The next years of the PS-OC Program will provide an opportunity to test and further refine many of these new theories and hypotheses.

- Program Goal #3: Establish an unprecedented network of Centers and transdisciplinary teams focused on solving cancer problems.

  Over the first three years of the PS-OC Program, individual Centers have become more integrated and have grown to include many new investigators from the scientific community. The broader PS-OC Network interactions have strengthened, resulting in at least a two-fold increase in the number of collaborations between key investigators from year one to year three. Additionally, there has been a three-fold increase in the number of transdisciplinary authorship collaborations by PS-OC investigators compared to the years preceding the PS-OC Program. Finally, the responses to survey questions indicate that PS-OC investigators are forming productive transdisciplinary collaborative teams, averaging four to seven investigators, that have allowed them to exchange knowledge and in some cases publish collaborative research results.

- Program Goal #4: Train a new generation of transdisciplinary scientists in the area of physical sciences in oncology.

  The PS-OC Program RFA emphasized the importance of training within the PS-OCs by specifying that $50,000 be set aside for student exchanges between Centers and that $50,000 be set aside for other education activities. The Program "tracks" trainees after leaving a Center to assess impact. While it is premature to measure the impact of the Program on graduating trainees, the trainees (students, post-doctoral fellows, and medical residents) have participated in a range of training activities offered by the PS-OC Network. Exchanges have been of particular value to the trainees, by helping to establish trans-Network collaborations and to stimulate the exchange of ideas. The PS-OCs have taught or developed 55 courses aimed either at trainees in the Network or more broadly to undergraduate and graduate students outside the Network. The survey results indicate that the majority of trainees plan on staying in this new field of research, and the progress reports show that a number have made successful career transitions that are consistent with the goal.

- Program Goal #5: Collaboratively disseminate information to the cancer research communities and the public.

  The PS-OC Program RFA emphasized disseminating research results and experiences to the broader scientific community to encourage continued support and enthusiasm for the convergence of physical sciences and oncology. The PS-OCs have disseminated research results through workshops, seminars, conferences, and publications. To date, PS-OC investigators have presented more than 3,000 times at conferences world wide. Additionally, the PS-OCs have

engaged seven patient advocates to participate in the PS-OC Program to assist in dissemination to the public and cancer patient communities. Section 10 highlights the emergence of physical sciences in oncology within new workshops, conferences, and initiatives outside of the PS-OC Program and in Europe.

In addition to the findings specific to individual Program goals, the evaluation results suggest a set of general findings that highlight the progress of the PS-OC Program:

- **Acceleration of the PS-OC Program to clinical research.** To date, there have been exploratory objectives integrated into five clinical trials that utilize theories, computational models, or technologies developed by the PS-OC Program. There has also been an increase in the number of investigators using clinical samples in their research. At the start of the Program, only six PS-OCs proposed experiments using clinical samples. After three years, all 12 of the PS-OCs have begun to incorporate clinical samples or retrospective clinical data into their research.

- **There is a need for more infrastructure support at research institutions to promote the convergence of physical sciences and oncology outside the PS-OC Program.** Establishing physical sciences in oncology as a sustainable new field requires continued support and infrastructure development. Early indicators of field convergence within the Network suggest that this nascent field has potential to be self-sustaining. Section 7 describes the impact of the PS-OC Program and the OPSO on the development of physical infrastructure, transdisciplinary courses, and program activities to support the convergence of physical sciences and oncology. Based on findings from the survey and NIH databases, continued investment in the PS-OC Program is needed to strengthen and sustain the necessary infrastructure.

- **The PS-OC Network has produced more publications per dollar during its first three years than other comparable U54 programs at the NCI.** Overall, the analysis indicates that when funding levels and timing are controlled for, the PS-OC Program was one of the most productive of the programs compared over several key metrics. The average PS-OC score for publications/$MM, weighted impact, high-impact publications/$MM, and number of patents was higher than comparable U54 programs and a control group of R01 grants. Continual monitoring of these statistics will be used to follow PS-OC Program progress in future years.

- **The prospective evaluation of the PS-OC Program has been instrumental in allowing OPSO program officials to monitor and provide constructive feedback to the PS-OC Program.** The side-by-side development of a data system with development and testing of collaboration metrics using extant and self-reported data has been an effective approach to the exploration of new metrics for team formation, collaboration, and knowledge generation, both within Centers and across the Network as a whole. There has been interest by other NIH, National Science Foundation (NSF), and GAO programs in the structure of this evaluation, including the logic model, the inter-Disciplinary Team Reporting and Query Resource (iTRAQR) system, and the extended scientific report (ESR) structure, in order to conduct similar prospective evaluations.

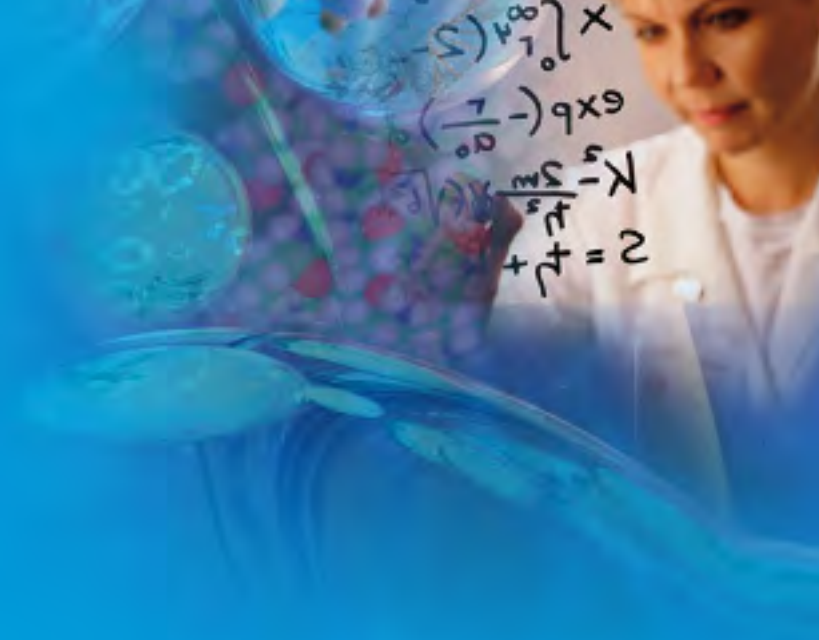
## Lessons Learned and Future Program Directions

As a whole, the PS-OC Program has demonstrated progress toward each of its goals. Overall, the "Center" concept, as recommended by expert participants in the Think Tanks, appears to be valuable for integrating physical scientists with oncologists and cancer biologists to develop the infrastructure, capabilities, and teams to study key questions in cancer research from a physical sciences perspective (PSP). Even with this progress, however, there are areas that OPSO program officials would like to improve and focus on in the future years of the PS-OC Program to ensure the successful continuation of the physical sciences in oncology field. Many of these lessons learned are direct results of the comprehensive prospective evaluation executed by the OPSO and Discovery Logic to date.

- Test and validate new theories of cancer experimentally and clinically. The PS-OC Program has published new and expanded theories of cancer that could potentially "shift" the way cancer researchers approach the prevention, diagnosis, and treatment of cancer. Hence, the PS-OC Program needs to focus more efforts on validating these theories experimentally and clinically in future years. Program staff and PS-OC investigators should facilitate more focused working groups, pilot projects, or teams within the PS-OC Network to test these theories.

- Continue to strengthen new transdisciplinary collaborations. The PS-OC Network provides an environment that appears to have promoted preliminary collaborations and interactions. The PS-OC Program investigators have reported more than 600 unique collaborations since the start of the PS-OC Program. As the Program matures, more focus should be placed on methods to increase the likelihood of successful outcomes from these collaborations. Many PS-OC investigators have stated that more team-building activities as part of PS-OC meetings might further enhance the effectiveness of transdisciplinary collaborations. Outreach pilot projects to bring in investigators outside of the PS-OC Network did not, on the whole, help form new collaborations and should be rethought or phased out in future years of the PS-OC Program.

- Continue to build infrastructure to support the convergence of physical sciences and oncology post-PS-OC Program. Currently, according to survey results, the PS-OC Program is the primary source of support for PS-OC investigator resources and infrastructure in the field of physical sciences in oncology. To sustain this field, a long-term infrastructure needs to be established. The PS-OC Program staff should focus more effort on disseminating the research outputs of the Program to other academic institutions and the cancer research community. The PS-OC Program should also support the formation of new study sections and the development of peer-reviewers specific to physical sciences in oncology. Currently, the success rate of physical scientists applying for R01 grants is below average, possibly because existing study sections lack the expertise to effectively review these applications.



# 2. Introduction

A combination process/outcome evaluation of the Physical Sciences-Oncology Centers (PS-OC) Program was initiated and performed in the first three years of program operation to assess program performance and to promote positive adjustments of the current Program and future phases. Based on an initial needs assessment at the kick-off of the PS-OC Program, the Science and Technology Policy Institute (STPI) determined appropriate study questions, performance measures, data collection methods, a logic model, and a Process/Outcome Evaluation plan. This plan was implemented by the Office of Physical Sciences-Oncology (OPSO) in collaboration with Discovery Logic, a Thomson Reuters company.

## 2.1 Program Overview

To explore how the National Cancer Institute (NCI) could more effectively engage the physical sciences in cancer research, three strategic Think Tanks were convened during 2008 uniting leaders from the fields of physical sciences and engineering with leaders in the fields of cancer biology and clinical oncology. There was a consensus among the participants on the need to establish transdisciplinary Centers comprising integrated physical sciences-oncology teams in order to overcome the traditional barriers (silos) that have existed between these two scientific communities. The Think Tank participants also agreed that if the NCI's goal was to bring the physical science perspective (PSP) to cancer research, the Centers should be led by a physical scientist with a senior co-investigator (SI) from the oncology or cancer biology field. Think Tank participants, in addition to establishing an integrated team of physical scientists/engineers with cancer biologists/oncologists within each Center, supported the idea that PS-OC investigators should also be closely integrated with investigators from different PS-OCs, forming a comprehensive and integrated PS-OC Network.

Four general themes emerged from these NCI-sponsored strategic Think Tanks as new areas of investigation at the intersection of physical sciences and oncology that are critical to understanding and ultimately controlling cancer.

- Physics (the Physical Laws and Principles) of Cancer: Defining the role(s) of thermodynamics and mechanics in metastasis and determining how this knowledge might be employed in new intervention strategies
- Evolution and the Evolutionary Theory of Cancer: Developing a comprehensive theoretical inclusive construct that would provide a foundation for understanding and predicting cancer heterogeneity
- Information Coding, Decoding, Transfer, and Translation in Cancer: Pursuing theoretical and supportive experimental approaches that define what information is and how it is decoded and managed in terms of cell signaling and contextual information translation in cancer
- De-convoluting Cancer's Complexity: Pursuing theoretical and experimental approaches from the physical sciences to cancer complexity that will inform a new fundamental level of understanding of cancer that may facilitate the prediction of viable pathways to develop novel interventions

As a first step of this initiative, the NCI Center for Strategic Scientific Initiatives (CSSI) launched the PS-OC Program in the fall of 2009. The Program consists of a virtual Network of 12 Centers that bring physical scientists together with oncologists and cancer biologists. Each Center has experts from the fields of physics, mathematics, chemistry, computer science, and engineering working with traditional cancer researchers to develop the infrastructure, capabilities, and programs to study key questions in cancer research from a PSP. The Centers receive approximately $30.1 million in funding per year through U54 cooperative agreements. Several aspects of the Program distinguish it from other NCI programs, including (1) the requirement of a Principal Investigator (PI) with a physical sciences degree who works closely with a Senior Scientific Investigator, who has formal training as a cancer biologist or as a clinician in oncology; (2) Pilot and Trans-Network set-aside funds to support high-risk innovative research ideas sprouting from collaborative discussions and results; and (3) a focus on training a transdisciplinary group of scientists at the intersection of physical sciences and oncology.

### 2.1.1 Overall Program Goals

The primary objective of the PS-OC Program is to unite the fields of physical sciences with cancer research to better understand the physical and chemical forces that shape and govern the emergence and behavior of cancer at all levels. Toward this objective, the PS-OC Program supports the formation of transdisciplinary teams and infrastructure to foster the development and testing of innovative approaches and generate new fields of study based on knowledge of physical sciences laws/principles that define normal and tumor systems at various length scales, from DNA to the patient. The long-term goal is to enhance the possibility for paradigm-shifting science with the potential to generate exponential progress in the fight against cancer. The Program has five main goals designed to meet these overarching objectives.

#### *PS-OC Program Goals*

- Establish an unprecedented Network of Centers[1] and transdisciplinary teams focused on solving cancer problems.
- Train a new generation of transdisciplinary scientists in the area of physical sciences in oncology.
- Develop innovative (assumption-challenging) physical sciences-centered experimental approaches to gain new knowledge of cancer initiation and progression.
- Develop and test new hypotheses/theories/models in cancer research.
- Collaboratively disseminate information to the cancer research communities and the public.

## 2.2 Evaluation Purpose and Objectives

The PS-OC Program builds transdisciplinary teams and infrastructure to better understand and control cancer through the convergence of the physical sciences and oncology fields. The program structure, including several unique elements, necessitated the development of indicators and metrics to assess program performance. Thus, the OPSO built an infrastructure for a prospective program evaluation that allows program officers to assess the Program on an ongoing basis relative to the start of the Program. Monitoring whether (and how) PS-OC funding builds infrastructure and sustains transdisciplinary team science at the awarded institutions over time helps program officers identify and maintain the most successful components of the Program going forward. This also allows program officers the ability to adjust or remove components that are ineffective during the program period.

### Evaluation of Team Science

The NIH has a relatively recent history of supporting and evaluating inter- and transdisciplinary teams, such as the PS-OC Program. Typically, the evaluation of these programs assesses collaborative processes and outcomes during the mid-term or later stages of an initiative. Recently, however, the Transdisciplinary Research on Energetics and Cancer (TREC) initiative developed metrics for assessing collaboration-enhancing or collaboration-impairing factors present during the first year of a large-scale, cross-disciplinary research and training initiative.[2] Many of the metrics put in place for the TREC program were integrated into the PS-OC evaluation plan to assess the impact of programmatic elements on enhancing or impairing collaborations.

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[1] *"The concept of an unprecedented Network of Centers refers to the inclusion of programatic elements that specifically promote the integration of physical sciences and oncology."*

[2] Hall, K.L., Sokols, D., Moser, R.P., et al. The collaboration readiness of transdisciplinary research teams and centers findings from the National Cancer Institute's TREC Year-One Evaluation Study. *American Journal of Preventive Medicine* (2008) **35**(2S):S161–S172.

The PS-OC Program evaluation has extended these efforts further by monitoring the formation and outputs of transdisciplinary collaborations over time and comparing pre- and post-award collaborations. Other efforts to analyze and catalog research output and collaborations have been previously limited to universities. The VIVO web application developed by Cornell University supports the discovery of cross-disciplinary research using data entered at the individual researcher level. Another system, Harvard Catalyst Profiles, allows researchers to use their own profiles to create "active" research networks with specific colleagues, while "passive" networks are automatically created using such information as co-authorship history and institutional affiliation.

### *Definitions*

The PS-OCs were constructed based on a transdisciplinary model with the objective of breaching disciplinary boundaries across fields as divergent as the physical sciences and oncology in order to allow a new understanding of cancer to emerge. Many authors discussing team science use terms such as "multidisciplinary," "interdisciplinary," "intradisciplinary," and "transdisciplinary." For our purposes, we use the following definitions for these terms as provided by Stokols, Hall, Taylor, and Moser (2008)[3] and Porter, Roessner, Cohen, and Perreault (2006)[4]:

> Multidisciplinary: Researchers in different disciplines work independently on the same problem, combining their work only periodically.
>
> Interdisciplinary: Researchers in different disciplines work together, using their specialized expertise to address the same problem.
>
> Intradisciplinary: Researchers in the same discipline work together, using their combined expertise to address the same problem.
>
> Transdisciplinary: Researchers from different disciplines work together to develop a framework or perspective that synthesizes their respective areas of expertise, and to create a new model (or models) and language to address the same problem. These researchers may have transdisciplinary backgrounds, themselves, in that they have educational and research backgrounds in more than one field of study that have combined to form a new scientific perspective.

## Program Evaluation Objectives

The PS-OC Program RFA concept states that, "Given the groundbreaking nature of PS-OCs, it is expected that ongoing evaluation of Centers, projects, Network maturation and synergy will be needed to assess progress…." As planned, the OPSO implemented a prospective evaluation at the onset of the Program. From the beginning, there were three primary objectives for this evaluation:

- Assess the extent to which the PS-OC Program is progressing toward meeting the goals or criteria provided out at the start of the Program. OPSO program officials will use novel metrics and indicators based on data collected from progress reports and surveys to monitor the progress of the PS-OC Network in reaching its goals.
- Determine whether the program is being conducted as planned. The PS-OC Program contains several elements to encourage innovative, high-risk, transdisciplinary team science. The prospective evaluation will monitor the program to ensure that these elements are being effectively implemented.

[3] The science of team science: Overview of the field and introduction to the supplement. *American Journal of Preventive Medicine* (2008) 35 (2S), 77-89.
[4] Porter, A.L., Roessner, J.D., Cohen, A.S., and Perreault, M. Interdisciplinary research: Meaning, metrics, and nurture. *Research Evaluation* (2006) 15, 187-195.

- Provide information on how the program can be improved. The PS-OC Program was built to be flexible so that it can make changes when needed to ensure high-quality science. Information from the prospective evaluation will be used to improve the Program's management and activities.

# 3. Evaluation Approach and Methodology

## 3.1 Evaluation Approach

In December of 2009 and January of 2010, STPI interviewed the PIs and SIs from eight of the newly awarded PS-OCs. Areas of discussion included the grant application process, areas of research for their Centers, infrastructure, communication between the OPSO and the Center, collaborations, and potential challenges. In March of 2010, STPI submitted an outcome evaluation plan based on interview findings.

The STPI evaluation plan was divided into three components: prospective evaluation, structured evaluation, and summative evaluation (Figure 3.1, for more information see Appendix). Currently, the program evaluation is in the "prospective data collection" stage (Component 1). This process involved an amalgamation of prospective data collection, interactive evaluation, and impact evaluation. The next phase of the evaluation is the structured evaluation via an expert panel (Component 2). The third and final part of the evaluation plan is to perform a summative (full outcome) evaluation at least 10 years after the start of the program (Component 3).

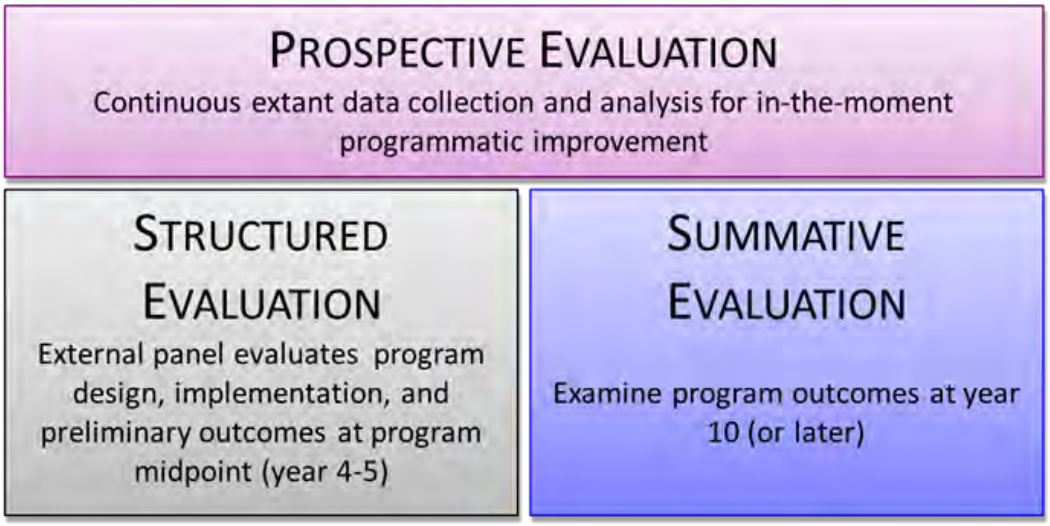


Figure 3.1. Graphic representation of STPI Evaluation Plan over time.

## 3.2 Logic Model

The intent of the PS-OC process/outcome evaluation was to assess the extent to which the PS-OC Program has been successful in reaching the goals stated in Section 2.1.1. To guide the evaluation process, STPI created a logic model (Figure 3.2) to help the OPSO identify the key inputs, activities, and outputs of the PS-OC Program. The outputs of this model include both long- and short-term outputs. Short-term outputs are labeled with an asterisk and have been the focus of the evaluation process to date. Long-term outputs will be the focus of evaluation in the next phase.

The following outputs from the logic model gave direction to the evaluative process:

"Normal" Research Disseminated*

- High-impact scientific publications/presentations are disseminated at cancer biology conferences.
- New approaches or techniques (including computational models) are developed.
- New approaches/techniques are disseminated outside of the PS-OCs.

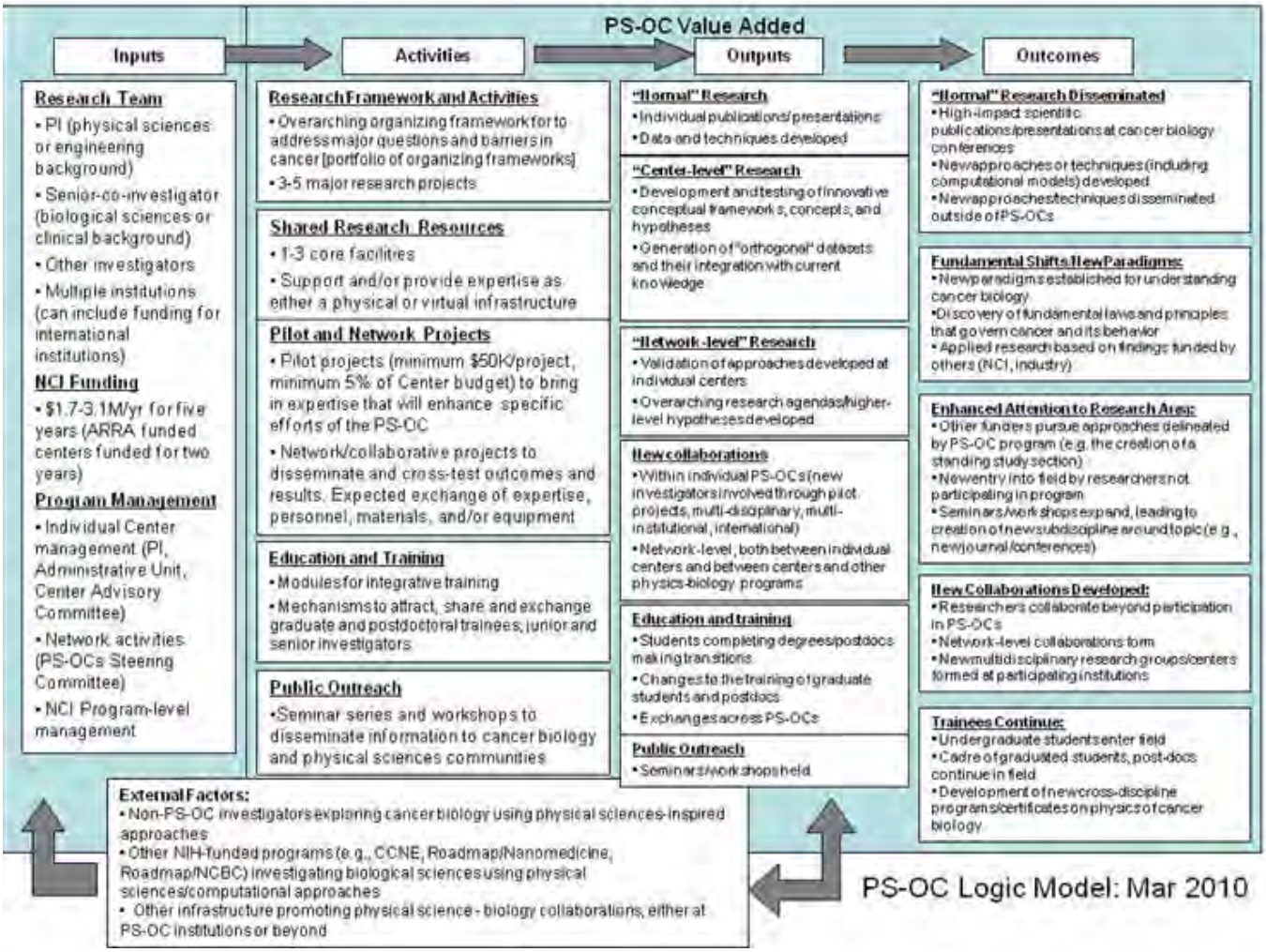


Figure 3.2. PS-OC Logic Model.

### New Collaborations Developed *

- Researchers collaborate beyond participation in PS-OCs.
- Network-level collaborations form.
- New multidisciplinary research groups/Centers formed at participating institutions.

### Trainees Continue*

- Undergraduate students enter the field.
- Cadre of graduated students, post-docs continue in the field.
- New cross-discipline programs/certificates in physics of cancer biology are developed.

### Fundamental Shifts/New Paradigms

- New paradigms are established for understanding cancer biology
- Fundamental laws and principles that govern cancer and its behavior are discovered.
- Applied research, based on PS-OC findings, is funded by others (e.g., the NCI, industry).

Enhanced Attention to Research Area

- Other funders pursue approaches delineated by the PS-OC Program (e.g., the creation of a standing study section).
- New researchers enter the field.
- Seminars/workshops expand, leading to the creation of new subdisciplines (e.g., new journals, conferences).

# 3.3 Data Collection and Analysis

## 3.3.1 Data Sources

Data were compiled from a variety of sources, including PS-OC semi-annual progress reports, scientific databases such as MEDLINE and Thomson Reuters Web of Science, PS-OC investigator publications, interviews with Center PIs/SIs, project lists, SPIRES, USTPO, survey results, web searches, and NIH administrative databases.

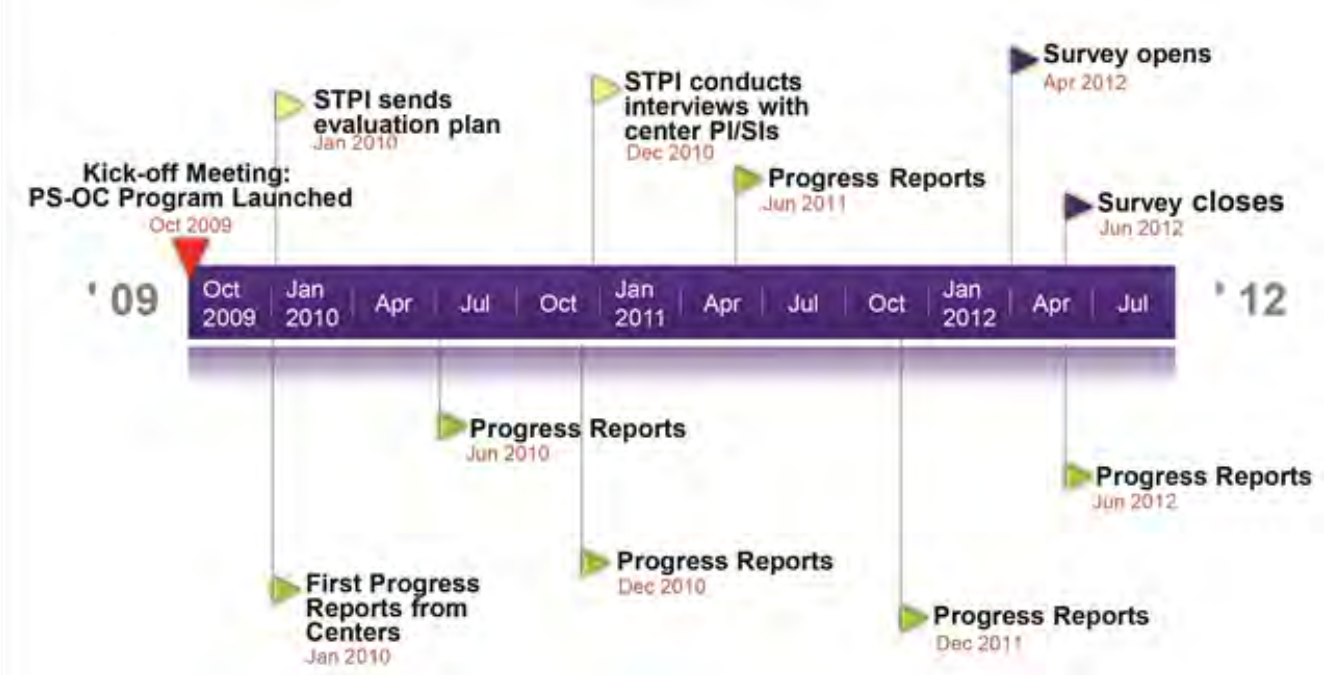


Figure 3.3. Evaluation Timeline. Includes types and occurrences of data collection.

### *Progress Reports*

The complex nature of the PS-OC Program requires a multilevel reporting structure that addresses the different Program components. The extended scientific report (ESR), designed by OPSO program officials and approved by the PS-OC Steering Committee, is submitted twice each year by each PS-OC to report outcomes during the six-month period and is required in addition to the annual PHS 2590 form. The ESRs are subdivided into five sections: overall Center progress, research projects, shared resource cores, Education and Training Unit, and Outreach and Dissemination Unit. Within each section, the investigators are required to fill out a series of subsections that are either free form or in table structure. Within the first two years of the program, the format of the ESR was altered to increase the clarity and quality of information collected. The ESR also requests information on collaborations, in-progress publications, leveraged funds, patents, trainees, courses, meetings, and outreach

activities. The information collected from these reports is critical to the prospective evaluation that was suggested as the best evaluation technique for the PS-OC Program. To date, six progress reports have been collected from each PS-OC.

### *Surveys*

A prospective customer satisfaction-type survey of the PS-OC Program was conducted as past of the program evaluation process. The survey targeted PIs, SIs, trainees, and experts in the fields of physical sciences and oncology (not directly associated with the PS-OC Program) to assess the state of the Program. Experts in the fields of physical sciences and oncology not currently involved in the PS-OC Program are defined as scientific researchers who are considered pioneers, leaders, or specialists in a field of study that is within the realms of physical sciences or cancer biology and oncology, including professors, medical doctors, and program directors. Table 3.1 shows the response rate of each group. The survey consisted of 8 to 25 questions per group related to the following topic areas (Appendix).

1. The four themes determined by the NCI-sponsored strategic Think Tanks
2. The overall goals of the PS-OC Program as described in Section 2.1.1
3. The quality, quantity, and types of collaborations occurring throughout the Network, including:
    a. The importance of said collaborations to the accomplishment of the overall goals. (i.e., could the project have been completed or undertaken without the cooperation of the collaborator[s]?)
    b. How often the respondent collaborates on projects versus works alone
    c. How the workload was divided? Is it a true collaborative effort or is someone included in name only?
    d. whether the respondent like to continue the current collaborations
    e. Whether there others with whom the respondent would like to try collaborating (in place of or in addition to the current collaborations)
4. "Lessons learned" in order to establish program strengths, weaknesses, and areas for improvement

Because of the prospective nature of the current evaluation and the young age of the Program, the "lessons learned" are intended to help develop the program as it matures. The survey, in conjunction with the sheer volume and diversity of data gathered for the evaluation, has enabled program staff to identify directions for the future of the Program and highlight the strengths of the program as it currently stands.

### PS-OC Kick-Off Interviews

At the request of OPSO program officials, STPI conducted interviews with Center PIs and SIs of eight of the newly awarded PS-OCs to discuss their experiences with the Program so far, expectations for the future, and other issues relevant to planning for future program evaluation. The final memo random from STPI, highlighting key findings, is provided in the Appendix.

Table 3.1. Number of Survey Respondents in Each Category.

| Survey Group | # Completed | Total Sent | % Completed |
|---|---|---|---|
| Trainees | 75 | 358 | 21% |
| Project Investigators | 47 | 164 | 29% |
| PI/SIs | 17 | 24 | 71% |
| External | 96 | 326 | 29% |
| Admins | 13 | 18 | 72% |
| Edu & Training | 4 | 10 | 40% |
| Outreach and Edu | 3 | 6 | 50% |
| Advocates | 7 | 9 | 78% |
| Total | 262 | 915 | 29% |

### 3.3.2 Data Collection and Processing

#### *iTRAQR*

The Interdisciplinary Team Reporting, Analysis, and Query Resource (iTRAQR) was created to help PS-OC Program staff analyze research outputs among the 12 PS-OCs. Research progress, outputs, and collaborative activities were monitored on an ongoing basis through comprehensive semi-annual progress reports. These reports were received in paper format, leaving few options to search and analyze data. The mission of iTRAQR is two-fold: first, to provide a way to enter and organize progress report data, and second, to facilitate convenient and flexible querying, exporting, and visualization of data. The results of such analyses were used to measure the extent to which the research output of the investigators and the Centers further the aims of the PS-OC Program.

#### Data Model

The iTRAQR system was built around a data model that conforms to the explicit and implicit structure of the ESRs submitted to PS-OC. The ESR template breaks down reported information by sections and projects, but implicit in the data are many more relationships than can be inferred from a report template. An entity-relationship diagram was created to express these relationships.

A key to this approach is taking categories of information that may be repeated and considering them entities in the data model. For example, a person reported in a progress report could exist in several different relationships. This person could serve in one or more roles, such as PI of a Center, co-investigator on one or more research projects, collaborator in a Trans-Network Project, or co-author on a publication, to name just a few. Similarly, a publication could be associated with both a pilot project and an explicitly reported collaboration.

Following this method, the complexity of such a model can grow quickly. Thus, the initial data model was created only to capture the relationships implicit in a single progress report. This is sufficient to individually analyze report contents, but the best and most comprehensive understanding of the progress of the PS-OC Program would come from cross-Center and time-series analyses that would be very difficult if progress reports were treated individually.

### Removal of Duplicate Data

The duplication of progress report data across Centers and over time presented one of the greatest challenges in the development of iTRAQR, but it was also one of the greatest opportunities to provide meaningful understanding of the data. Many categories of data required removing duplicate data, including those involving people, collaborations, publications, and meetings.

It was crucial in removing duplicate data from progress report data that the integrity of individually entered progress reports was maintained. That is, it was important that a record remained of the data as they were reported in a given progress report. For this reason, progress report entities were left unchanged and were instead linked to one another across Centers and time.

### Data Entry User Interface (UI)

With the data model established, the next challenge was to provide a comprehensive and efficient way to enter data into the database. A web application was ideally suited for this purpose. Leveraging Microsoft's Entity Framework object/relational mapping system, the data model was adapted to serve as the model in a Model-View-Controller (MVC) application. A Microsoft SQL Server database was created based on this model.

The UI made considerable use of Asynchronous JavaScript and XML (AJAX) to provide a responsive, interactive environment for data entry. AJAX modal dialog boxes served as a primary means for entering structured data.

Within a progress report, each element, such as a person, had to be entered only once and then could be linked in to other roles in the report as data entry proceeded. The UI was structured in a similar format to that of a paper ESR to streamline the data entry progress. Entities could be linked to either current data within an existing progress report or to previously reported data. The new data reported in the current progress report are entered in addition to these links, preserving the integrity of individual reports.

A quality assurance process was established through which individual report sections could be marked as completed, and then after careful checking, marked as verified. Only data marked as verified were made available to the analysis functions of iTRAQR.

## Analysis UI

The purpose of iTRAQR's analysis system is to leverage all previous data model and data entry UI work to support ongoing program evaluation. The analysis UI consists of two major parts. First, the "Report Cards" and export subsystem provides textual data about the progress reports. Second, the visualization subsystem allows data to be viewed in numerous ways, ranging from bar, pie, and line charts to network diagrams showing Center and investigator collaborations. Search functionality is also included to permit easy access to raw progress report data and to link to summary pages.

"Report Cards" are an element of the iTRAQR Analysis System providing summary data at a Network, Center, reporting period, project, or investigator level. This facilitates viewing, for example, how many unique publications an investigator has published, or how many unique trainees a Center has trained. It is then possible to export this data to a spreadsheet.

The visualization section allows the user to flexibly request many types of charts and graphs. It relies on queries similar to those used in the Report Cards and Export section. Filters can be applied by Center and reporting period. In particular, iTRAQR's network visualizations allow the user to see many types of collaborations at a glance (Figure 3.4).

To show investigator collaborations, iTRAQR generates a network graph. The nodes represent PS-OC investigators that have been involved in a reported collaboration, have co-authored a publication, or have been reported as a co-investigator on a project, and the edges represent the number of collaborations among investigators.

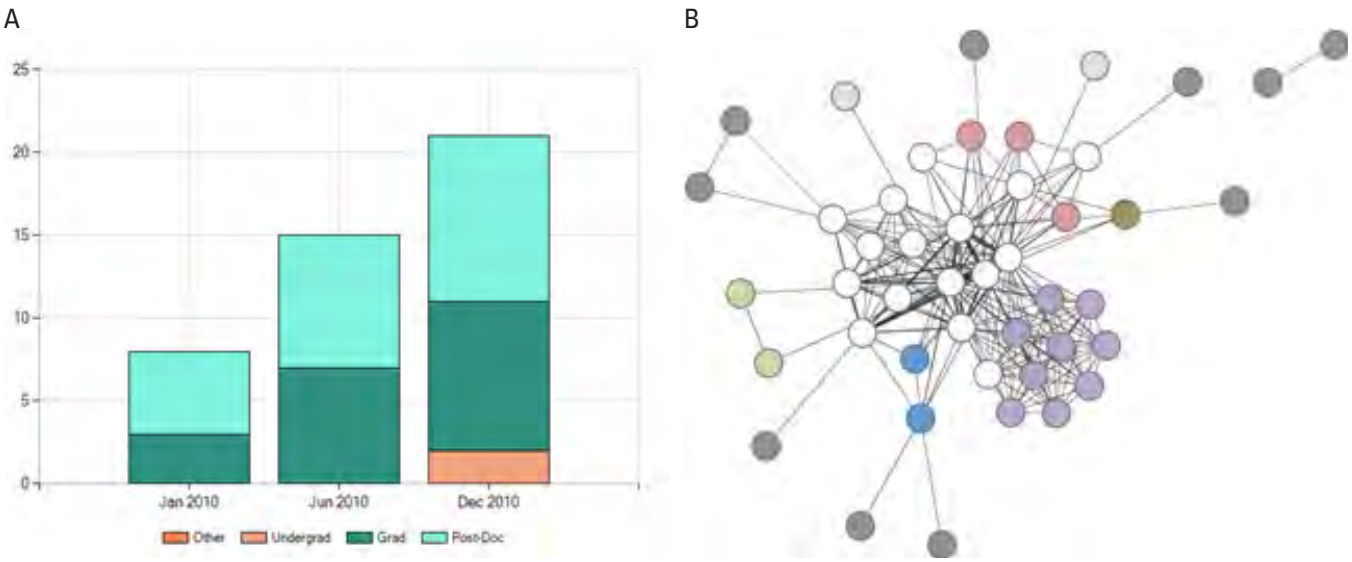


Figure 3.4. Visualizations created by iTRAQR. (A) A bar chart generated in iTRAQR showing students trained over several reporting periods (B) A network diagram generated in iTRAQR showing researcher collaborations over time within a Center (researcher names removed). Colors represent research projects.

To create these graphs, queries must be made to the database for unique investigators, collaborations, publications, and projects. The system aggregates this information into a custom data structure that is then used to generate a GraphML file consisting of nodes, edges, and associated colors to represent the investigators, the project(s) they belong to, and the number of collaborations between each pair of investigators.

Leveraging the Cytoscape Web visualization component, the generated GraphML file is graphically rendered on the page. This visualization is highly customizable, supporting user interaction with nodes and edges, image export, and other functions. From this page, the user can also export a spreadsheet containing network measures such as network density, node degree, closeness centrality, and betweenness centrality.

### 3.3.3 Independent Data Collection and Analysis

In addition to collecting and analyzing the data explicitly stated in the progress report, PS-OC Program staff were interested in collecting and analyzing outputs using other data sources and databases. The OPSO instructed Discovery Logic, a Thomson Reuters company, to conduct an independent collection and data analysis of the program metrics and indicators listed below. Using the MEDLINE and Web of Science databases, Discovery Logic was able to derive publication sets of key PS-OC investigators (PIs, SIs, and project leaders) from 2004 to June 2012, using name-matching algorithms augmented by author metadata, including e-mail address. These publication sets were used to analyze metrics before and after the PS-OC Program in order to compare the impact of the Program on investigator scientific output and collaborations. The results of these comparisons are described in Sections 4, 5, 6, and 9.

Bibliometric Analysis on PS-OC Network Publications – The following metrics were analyzed:

- Journal Impact Factor
- Citations
- Expected Citations: Compare the current performance of a publication with other similar publications using expected citations
- Bibliometric Percentiles: Rank publications from the same year and subject category by the number of citations recorded in the Web of Science database[5]
- Breakthrough Publications: Identify potential breakthroughs using a non-linear projection of a publication's citation velocity to predict the five-year citation level of a publication, and compare that directly with a citation threshold established based on known breakthrough publications in a given subject area

Analysis of Authorship Collaborations – Using self-identified disciplines provided by PS-OC investigators, Discovery Logic determined the number and types (transdisciplinary or intradisciplinary) of authorship collaborations among investigators in the PS-OC Network.

Field Convergence of Physical Sciences and Oncology – Discovery Logic established a list of terms to categorize PS-OC investigator publications into disciplines and identified transdisciplinary publications that have resulted from the collaborative knowledge and techniques of PS-OC Network physical scientists and oncologists.

Content Mapping of PS-OC Network Publications – Discovery Logic leveraged open source and propriety methods to derive terms, topics, and networks from PS-OC investigator publications and progress report text.

Analysis of "Burstiness " of Topics – Discovery Logic identified new terms and topics in PS-OC publications and PS-OC progress reports with a significant increase in activity using Kleinberg's "Bursty and Hierarchical Structures in Streams."

Impact of PS-OC Terms on Broader Scientific Research Community – Using "bursty" topics identified in the previous analysis, Discovery Logic provided the average citation number, expected citation number, and impact factor for publications outside the PS-OC Network that include these topics.

[5] Thomson Reuters, Scientific. Whitepaper using bibliometrics: A guide to evaluating research performance with citation data.

## 3.4 External Panel Review of Program

The assessment of the PS-OC Program was supported by a panel of five experts from a variety of backgrounds relevant to the evaluation:

- Dr. Michelle Bennett, Deputy Scientific Director, Division of Intramural Research, NHLBI
- Dr. Debbie Winn, Deputy Director, Division of Cancer Control and Population Sciences, NCI
- Dr. Ming Lei, Chief, Cancer Training Branch, NCI
- Dr. Tito Fojo, Head, Experimental Therapeutics Section, Medical Oncology Branch, Center for Cancer Research, NCI
- Dr. Dan Gallahan, Division Deputy Director, Division of Cancer Biology, NCI

The expert panel was asked to provide an assessment of the accomplishments of the Program and of the NCI program staff associated with the initiative. The assessment addresses the progress toward the criteria outlined in the original RFA (CA09-009) concept and panel comments, suggestions, and/or recommendations regarding the continued support of the various components supported by the initiative.

## 3.5 Independent Review of the Program

At the end of the third year of program operations, OSPA and the program asked STPI to review the draft of the evaluation's year three interim evaluation report. STPI was asked to comment on the following questions:

1. Whether the evaluation was done properly?
    - Assess to what extent the initial evaluation recommendation from STPI was implemented by OPSO.
    - Recommendations for continued and future evaluation. Point out and differences from initial needs assessment based on the evaluation to date.
2. Interpretation (to the extent of your ability) of whether the data indicate that the program is working well?
    - Summary of findings relative to specific program goals (include strengths and weaknesses of the program)
    - Any additional overarching findings drawn from the program metrics in addition to program goals.
    - Recommendations of changes to program structure or program staff participation to improve the program.

# 4. PS-OC Supported Research Early Outcomes

## 4.1 Publications

A list of PS-OC publications was compiled from semi-annual progress reports submitted by PS-OC investigators. A complete list of the peer-reviewed publications is located in the Appendix.

Based on this list, a total of 601 publications, including 538 peer-reviewed publications, were reported by PS-OC investigators, of which 10 are associated with more than 1 PS-OC (i.e., Trans-Network). Analysis of publication numbers and trends reveals several interesting observations. The number of publications per PS-OC varied substantially, with DFCI exceeding 100 publications, USC, Moffitt, JHU, and Northwestern publishing between 50 and 75 papers, and ASU, UCB, Cornell, TMHRI, MIT, Princeton, and Scripps between 18 and 47 (Table 4.1). The average number of publications per year also varied across PS-OCs. As expected, the number of publications has increased each year for most PS-OCs, with an average of more than 180 publications total per funding year. It took approximately 1.5 years for the PS-OC Program to reach its current level of publishing. Based on discussions with PS-OC investigators, PS-OC Program staff attribute a slower publication rate for the first 1.5 years to initial communication barriers among scientists and time required to form new collaborations.

Table 4.1. Breakdown of the number of PS-OC publications per year.

| Center | 2009 (Sept. - Dec.) | 2010 | 2011 | 2012 (Jan. - June) | Total Publications |
|---|---|---|---|---|---|
| ASU | 4 | 5 | 9 | 2 | 20 |
| UCB | 0 | 10 | 23 | 5 | 38 |
| Cornell | 0 | 16 | 20 | 11 | 47 |
| DFCI | 14 | 39 | 51 | 23 | 127 |
| JHU | 4 | 26 | 17 | 12 | 59 |
| TMHRI | 1 | 12 | 10 | 5 | 28 |
| MIT | 1 | 3 | 9 | 6 | 19 |
| Moffitt | 1 | 22 | 26 | 15 | 64 |
| Northwestern | 5 | 20 | 27 | 8 | 60 |
| Princeton | 1 | 5 | 8 | 1 | 15 |
| Scripps | 0 | 5 | 5 | 8 | 18 |
| USC | 6 | 22 | 29 | 13 | 70 |
| **Total** | **37** | **185** | **234** | **109** | |

Taken together, the total number of publications per year associated with the PS-OC Program has increased over time, while total programmatic funding has remained roughly constant since FY 2009 (Figure 4.1). The ratio of dollars per publication has decreased over the first three years of the program, with less than $150,000 per publication in FY 2011.

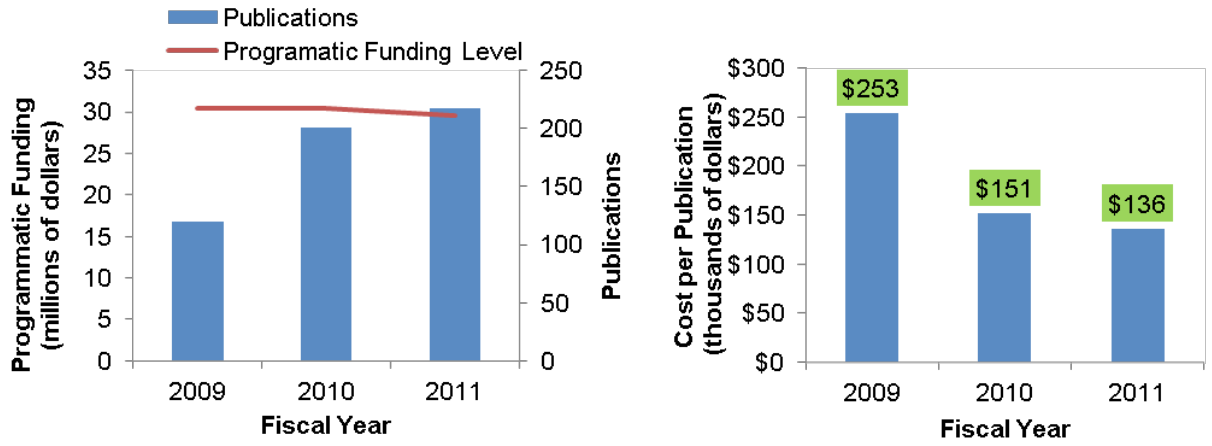


Figure 4.1. Ratio of PS-OC Programmatic Funding to Number of Publications. (Left) The total number of publications by PS-OC investigators per fiscal year (blue bars) has increased, while the funding levels have slightly declined (red line). (Right) The cost per publication has decreased to less than $150,000 in FY 2011.

## 4.2 Publication Quality

A list of PS-OC publications identified from the progress reports was submitted to Thomson Reuters(ISI) for bibliometric analysis, and data on 601 publications were matched to their databases. 538 of these publications were peer-reviewed articles. The following analyses are based on the bibliometric data acquired from these publications as of June 2012.

Table 4.2. Journals with Largest Number of Articles Thomson/ISI Indexed.

| Journal | Number of Publications | Journal Impact Factor (2009-2012) |
|---|---|---|
| PLoS One | 36 | 4.4 |
| Proceedings of the National Academy of Sciences of the United States of America | 28 | 9.8 |
| Physical Biology | 20 | 3.1 |
| Blood | 16 | 10.6 |
| Cancer Research | 14 | 8.2 |
| Nature | 11 | 36.1 |
| Nucleic Acids Research | 10 | 7.8 |
| Biophysical Journal | 8 | 4.2 |
| Clinical Cancer Research | 8 | 7.3 |
| Journal of Theoretical Biology | 8 | 2.4 |
| Plos Computational Biology | 8 | 5.8 |
| Biomaterials | 7 | 7.9 |

PS-OC research was published in 210 distinct journals spanning a range of fields, including cancer biology, computational biology, clinical oncology, and biophysics. Two journals, *PLoS ONE* and *Proceedings of the National Academy of Sciences (PNAS),* accounted for 11 percent of all PS-OC publications. These two journals are diverse in the type of science that they publish and appear to be fairly receptive to the transdisciplinary research from the PS-OC Network. Following these two journals, PS-OC research was published in a broad mix of journals. A list of the top 12 journals in which PS-OC research was published is provided in Table 4.2. These 12 journals (5 percent of the 210 total number of journals) accounted for 32 percent of the total

papers (174 of 538 peer-reviewed papers); impact factors of those journals ranged between 3 and 36 (Table 4.2). These include multidisciplinary journals (*PLoS ONE, PNAS, Nature, PLoS Computational Biology, Blood*), oncology journals (*Cancer Research, Clinical Cancer Research*), and physical science journals (*Biophysical Journal, Physical Biology, Biomaterials*).

Sixty-two PS-OC publications (11 percent) were in journals with impact factors of 20 or higher, including 11 in *Nature*, 5 in *Science*, 6 in *Cell*, and 1 in the *New England Journal of Medicine* (Table 4.3). Among all of the PS-OC publications, the average impact factor was 9.18, and the median was 8.97 per Center. The average impact factor was determined based on the average Web of Science journal impact factor determined for the year of each publication date.

**Table 4.3.** PS-OC Publications in Very High Impact Factor Journals.[6]

| Very High Impact Journals | Impact Factor (2009-2012) | Number of Publications |
|---|---|---|
| New England Journal of Medicine | 53.5 | 1 |
| Nature Reviews Cancer | 37.2 | 5 |
| Nature Genetics | 36.4 | 4 |
| Nature | 36.1 | 11 |
| Nature Reviews Genetics | 32.7 | 2 |
| Cell | 32.4 | 6 |
| Science | 31.4 | 5 |
| Nature Biotechnology | 31.1 | 6 |
| Nature Nanotechnology | 30.3 | 3 |
| Nature Medicine | 27.1 | 3 |
| Cancer Cell | 26.9 | 6 |
| Chemical Society Reviews | 26.6 | 1 |
| Cell Stem Cell | 25.9 | 4 |
| Accounts of Chemical Research | 21.8 | 1 |
| Nature Methods | 20.7 | 4 |

Another measure of the quality of PS-OC publications is the total number of times the publication has been cited by other researchers. The total number of citations per publication is dependent on the publication date. Older publications typically accumulate a higher total number of citations. Many of the PS-OC publications are less than two years old, so this value is not necessarily a good representation of the potential impact of the publication. Table 4.4 presents the number of times that the 538 peer-reviewed puplications reported by PS-OC investigators have been cited. There are 25 publications with no citation data available. Seven puplications (1.3 percent) have been cited more than 100 times in less than three years, and an additional 61 (11 percent) have been cited more than 20 times. These 12 percent of peer-reviewed publications represents two-thirds of the citations on publications in the PS-OC Network.

[6] Web of Science journal impact factor determined for the year of the publication date.

Table 4.4. Citations to PS-OC Publications.

| Citations Per Paper | Papers with # of Citations | Percentage of Papers |
|---|---|---|
| 101+ | 7 | 1.3% |
| 51 to 100 | 14 | 2.6% |
| 21 to 50 | 47 | 8.7% |
| 11 to 20 | 59 | 11.0% |
| 6 to 10 | 85 | 15.8% |
| 1 to 5 | 197 | 36.6% |
| 0 | 104 | 19.3% |
| No data available | 25 | 4.6% |

Journal impact factor is intended as a measure of the "quality" of the journals in which a paper is published, while the number of citations is normally interpreted as a measure of how useful the paper has been to the research community. The expected number of citations to a publication is a measure that aims to combine the two, normalizing the number of citations to an individual paper against others in the same journal and issue to determine whether the paper has been cited more often than expected. Actual citations were compared to expected citations for the papers published between October 2009 and July 2011 (328 publications) (Table 4.5); papers published after June 2011 were excluded because of limited availability of data on citations and reference publications. The mean actual-to-expected ratio (citation benchmark) was 2.08, suggesting that PS-OC-supported publications are on average cited more than two times more than their peer cohorts. The median citation value for all the Centers is 1.98. Over 4% of PS-OC publications had a citation rate five times higher than expected.

Table 4.5. Citation Benchmarks of PS-OC Publications (Ratio of Actual to Expected Citations).

| Ratio (Actual to Expected Citations) | Number of Papers with Ratio | Percentage of Papers |
|---|---|---|
| 5+ | 23 | 4.1% |
| 4.1 - 5.0 | 8 | 1.4% |
| 3.1 - 4.0 | 12 | 2.1% |
| 2.1 - 3.0 | 30 | 5.3% |
| 1.1- 2.0 | 58 | 10.3% |
| 0.1-1.0 | 86 | 15.2% |
| 0 | 111 | 19.6% |

Source: Publications published between October 2009 and July 2011 (328 publications).

To measure the impact of the PS-OC Program on the scientific performance of PS-OC investigators, an analysis was performed comparing the bibliometrics (average impact factor, first year citations, and citation benchmark) pre- and post-award of the PS-OC Program (awarded September 2009). The results indicate an slight increase in the quality of investigator output during the PS-OC Program. The average journal impact factor for PS-OC investigators increased from 7.3 to 9.18 (Figure 4.2). This is slightly higher than the average inflation rate of journal impact factor, 2.6% per year[7], indicating that PS-OC investigators are publishing in higher impact journals post-award. This increase is likley attributed to physical scientists publishing in more medically-affiliated journals that, on average, have a higher impact factor than physical science journals. Two other metrics

[7] Althouse, B.M., West, J.D., Bergstrom, T.C., and Bergstrom, C.T. Differences in Impact Factor Across Fields and Over Time. UC Santa Barbara: Department of Economics, UCSB. Retrieved from http://www.escholarship.org/uc/item/76h442pg (2008).

increased slightly: (1) the average first year citation rate of publications (5.8 to 6.54 citations in 1 year); and (2) the citation benchmark value (1.91 to 2.08).

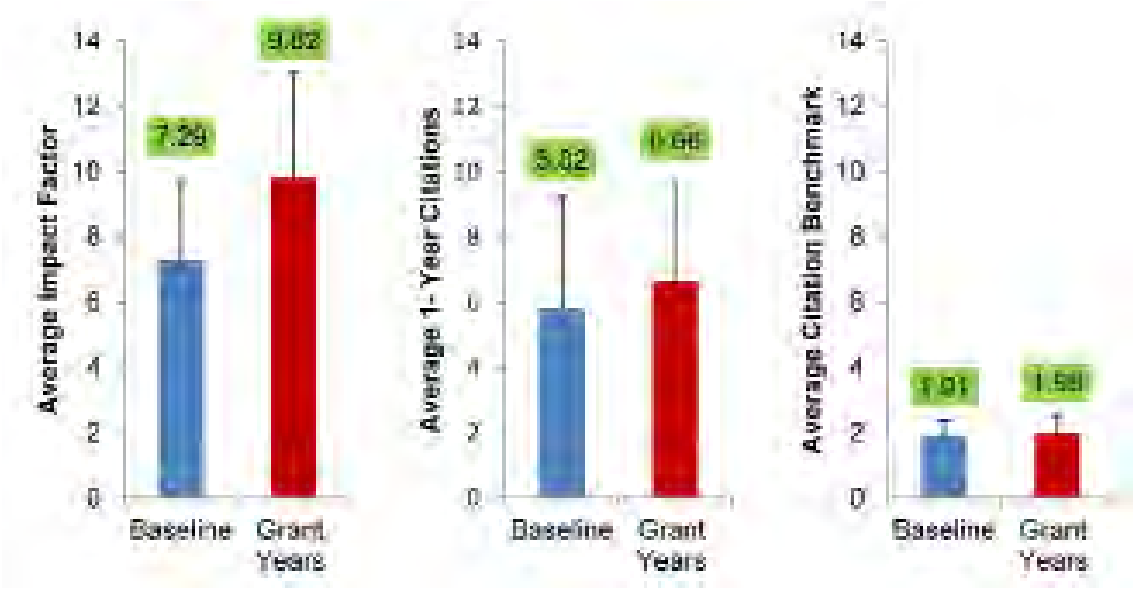


Figure 4.2. Comparison of PS-OC investigator publications before and after the start of the PS-OC Program. Average journal impact factor, one-year citations, and citation benchmark of investigator publications was calculated before (Baseline – 2004-2009, Blue) and after (Grant Years – October 2009 - June 2012, Red) the start of the PS-OC Program. Values for average one-year citations and citation benchmark during grant years only include publications through June 2011.

## 4.3 Potential Breakthrough Publications

The duration typically required to identify a breakthrough publication is roughly five years, which is how long it takes to accumulate a substantial number of citations relative to similar publications in that journal category. Because the PS-OC Program is only three years old, other methods were explored for identifying breakthrough science. Discovery Logic developed an algorithm to detect breakthrough publications earlier using citation velocity after 6, 12, or 24 months. This algorithm was applied to PS-OC papers published prior to July 2011 to identify potential breakthroughs. The algorithm uses a non-linear projection of the paper's citation velocity to predict the five-year citation level of a publication and compares that directly with a citation threshold of known breakthrough publications in a given subject area. If the level of citations is predicted to exceed the threshold, it is listed as a potential breakthrough publication.

Using this methodology, the PS-OC Program has reported 18 potential breakthrough publications identified from the progress reports, January 2010 through July 2011. Nine out of 12 PS-OCs have reported a potential breakthrough publication. The DFCI and JHU PS-OCs, with four, have the highest number of potential breakthrough publications, followed by the following PS-OCs with two potential breakthrough publications each: ASU, Moffitt, USC, and Cornell (Table 4.6). Due to the limitations in the methodology, the potential breakthrough publications are mostly from the first year of the Program and may contain information collected prior to Program initiation.

Table 4.6. Breakthrough Publications in the PS-OC Network.

| | Number of Papers (Year Published) | |
|---|---|---|
| PS-OC Name | 2010 | 2011 |
| ASU | 2 | 0 |
| Berkeley | 0 | 0 |
| Cornell | 2 | 0 |
| DFCI | 3 | 1 |
| JHU | 3 | 1 |
| TMHRI | 1 | 0 |
| MIT | 1 | 1 |
| Moffitt | 1 | 1 |
| Northwestern | 1 | 0 |
| Princeton | 0 | 0 |
| Scripps | 0 | 0 |
| USC | 1 | 1 |

A selected numer of potential breakthrough publications are highlighted below. These publications represent projects outlined in more detail in the Program Update volume. All potential breakthrough publications reported in the progress reports are listed in the Appendix.

## List of Selected Breakthrough Publications

1. Fraley, S.I., *et al.* A distinctive role for focal adhesion proteins in three-dimensional cell motility. *Nat Cell Biol* **12**, 598-U169 (2010).

2. Huang, S., *et al.* Identifying single bases in a DNA oligomer with electron tunnelling. *Nat Nanotechnol* **5**, 868-873 (2010).

3. Mukherji, S., *et al.* Micrornas can generate thresholds in target gene expression. *Nat Genet* **43**, 854-859 (2011).

Several PS-OC papers have been published over the last year that have impressive citation rates—greater than 10 for the first year (or more than 5 in 6 months)—but due to their nascent status they do not meet the criteria required to identify a potential breakthrough publication. These include the following publications.

## New Publications with High Citation Rates

1. Chmielecki, J., *et al.* Optimization of dosing for egfr-mutant non-small cell lung cancer with evolutionary cancer modeling. *Sci Transl Med* **3**, 90ra59 (2011).

2. De, S. & Michor, F. DNA secondary structures and epigenetic determinants of cancer genome evolution. *Nat Struct Mol Biol* **18**, 950-955 (2011).

3. Zhang, Q., *et al.* Acceleration of emergence of bacterial antibiotic resistance in connected microenvironments. *Science* **333**, 1764-1767 (2011).

4. Lu, C., *et al.* Idh mutation impairs histone demethylation and results in a block to cell differentiation. *Nature* **483**, 474-478 (2012).

5. Turcan, S., *et al*. Idh1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature* **483**, 479-U137 (2012).

6. Marks, D.S., *et al*. Protein 3d structure computed from evolutionary sequence variation. *PLoS One* **6** (2011).

7. Wong, C.C.L., *et al*. Hypoxia-inducible factor 1 is a master regulator of breast cancer metastatic niche formation. *Proc Natl Acad Sci U S A* **108**, 16369-16374 (2011).

8. Haeno, H., *et al*. Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies. *Cell* **148**, 362-375 (2012).

9. De, S. & Michor, F. DNA replication timing and long-range DNA interactions predict mutational landscapes of cancer genomes. *Nat Biotechnol* **29**, 1103-1108 (2011).

10. Patel, J.P., *et al*. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med* **366**, 1079-1089 (2012).

11. Fudenberg, G., Getz, G., Meyerson, M. & Mirny, L.A. High order chromatin architecture shapes the landscape of chromosomal alterations in cancer. *Nat Biotechnol* **29**, 1109-1113 (2011).

12. Itzkovitz, S., *et al.* Single-molecule transcript counting of stem-cell markers in the mouse intestine. *Nat Cell Biol* **14**, 106-114 (2011).

13. Darshan, M.S., *et al.* Taxane-induced blockade to nuclear accumulation of the androgen receptor predicts clinical responses in metastatic prostate cancer. *Cancer Res* **71**, 6019-6029 (2011).

14. Marrinucci, D., *et al.* Fluid biopsy in patients with metastatic prostate, pancreatic and breast cancers. *Phys Biol* **9**, 3 (2012).

## 4.4 Key Scientific Advances as Described by PS-OC Investigators

In the PS-OC survey, investigators were asked to self-identify a "key" scientific advancement of their Center. More than 60 PS-OC investigators responded to this survey question. Researchers either selectively highlighted specific aspects of their work or the work of their Center as a whole. The key advancements that were identified represent the four themes of the PS-OC Program as described in the PS-OC Program Update–Year Three, Section 3. A subset of the responses are listed below. Many are similar to the publications identified above or identified by the PS-OC Program staff in the PS-OC Program Update–Year Three. The names and PS-OCs of the survey respondents are unknown.

- "Understanding mechanisms generating mutations in cancer genomes" (PS-OC Program Update, Section 3.2.3)
- "Optimized dosing strategies for lung and brain cancers" (PS-OC Program Update, Section 3.2.1)
- "Critical role of extracellular matrix stiffening by collagen fiber formation/crosslinking in breast cancer metastasis" (PS-OC Program Update, Section 3.2.2)
- "Integrate a multitude of apparently disparate results from various fields, all relating to the role of mechanics in tumor progression and metastasis. This integrated view of tumor mechanics is now allowing us to: (1) calculate how cells and tumors respond to altered tissue mechanics; (2) develop new ways of detecting and quantifying altered tissue mechanics in human tissue; and (3) identify fundamentally new extracellular targets for clinical intervention."
- "Build a computational methodology for coupling fluid, elastic, mechanical, and geometric solvers to model cell growth, division, and interactions, analyzing structural and mechanics forces and stabilities. Our solvers rely on first principles and include second-order projection methods for incompressible fluid flow, non-linear Eulerian reference map elasticity solvers, and multiphase multi-interfaces coupled dynamics solvers" (PS-OC Program Update, Section 3.2.4)
- "Finding of tumor cell clusters" [in the circulation]
- "Develop strategies to dissect tensional homeostasis between tumor cells and the ECM using biophotonics approaches. We have developed strategies to measure the mechanical properties of contractile structures in different portions of living cells, relate these properties to specific myosin activation pathways, and combine them with FRET probes to connect cytoskeletal exertion of tensile forces to tension experienced at the cell-matrix interface"
- "We found that simple changes to cell morphology by changing the physical environment can induce over-expression of an important cytokine involved in cancer"

## 4.5 Patents and New Technologies

### 4.5.1 Patents

Searches of the U.S Patent and Trademark Office (USPTO) database were performed to identify whether the PS-OC Program was acknowledged as providing support to U.S. patents awarded to PS-OC-affiliated investigators. However, given the long lead times associated with patent filings, there were no granted patents attributable to PS-OC activities found in the database. A search of the NIH iEdison database and the PS-OC progress reports was also performed to identify whether any invention disclosures have been filed or patent applications submitted. As of June 2012, 23 patent applications from 8 PS-OCs were reported in the PS-OC progress reports. Applications include novel imaging technologies, contrast and therapeutic agents, devices for capturing circulating tumor cells, image analysis and processing algorithms, and techniques for modulating the tumor microenvironment. A complete list of these patent disclosures can be found in the Appendix.

Examples of Patents from the PS-OC Network Include:

Gillies, R. and Morse, D. Method for Reducing Intratumoral pHe and Acid-Mediated Invasion. *Moffitt PS-OC.*

Dravid V., Sharma S., Tomita T., Viola K., and Klein W. Magnetic Nanostructures as Theranostic Agents. *Northwestern PS-OC.*

Decuzzi, P.. MRI Contrast Agents in Nanoporous Particles. *TMHRI PS-OC.*

### 4.5.2 New Technology

In addition to patents, there have been several publications highlighting new technologies in the PS-OC Program and their application to cancer research. Novel technologies adopted from other fields are able to provide unique datasets that may lead to innovation in the field when combined with existing more traditional data. All 12 Centers have developed new technology or applied existing technology from the physical sciences to cancer. Publications related to technology development by PS-OC investigators are listed below in alphabetical order by PS-OC.

#### ASU PS-OC

1. Nandakumar, V., *et al.* Isotropic 3d nuclear morphometry of normal, fibrocystic and malignant breast epithelial cells reveals new structural alterations. *PLoS One* **7**, 5 (2012).

2. Nandakumar, V., Kelbauskas, L., Johnson, R. & Meldrum, D. Quantitative characterization of preneoplastic progression using single-cell computed tomography and three-dimensional karyometry. *Cytometry A* **79**, 25-34 (2011).

#### Cornell PS-OC

3. Cerf, A., Tian, H.C. & Craighead, H.G. Ordered arrays of native chromatin molecules for high-resolution imaging and analysis. *ACS Nano* **6**, 7928-7934 (2012).

4. Cipriany, B.R., *et al.* Real-time analysis and selection of methylated DNA by fluorescence-activated single molecule sorting in a nanofluidic channel. *Proc Natl Acad Sci U S A* **109**, 8477-8482 (2012).

5. Kirby, B.J., *et al.* Functional characterization of circulating tumor cells with a prostate-cancer-specific microfluidic device. *PLoS One* **7** (2012).

6. Santana, S.M., Liu, H., Bander, N.H., Gleghorn, J.P. & Kirby, B.J. Immunocapture of prostate cancer cells by use of anti-psma antibodies in microdevices. *Biomed Microdevices* **14**, 401-407 (2012).

#### DFCI PS-OC

7. Cheng, Y.K., *et al.* A mathematical methodology for determining the temporal order of pathway alterations arising during gliomagenesis. *PLoS Comput Biol* **8**, 5 (2012).

8. Mumenthaler, S.M., *et al.* Evolutionary modeling of combination treatment strategies to overcome resistance to tyrosine kinase inhibitors in non-small cell lung cancer. *Mol Pharm* **8**, 2069-2079 (2011).

### JHU PS-OC

9. Wu, P.H., *et al.* High-throughput ballistic injection nanorheology to measure cell mechanics. *Nat Protoc* **7**, 155-170 (2012).

10. Celedon, A., Hale, C.M. & Wirtz, D. Magnetic manipulation of nanorods in the nucleus of living cells. *Biophysical Journal* **101**, 1880-1886 (2011).

### MIT PS-OC

11. Shaw, J., Payer, K., Son, S., Grover, W.H. & Manalis, S.R. A microfluidic "baby machine" for cell synchronization. *Lab Chip* **12**, 2656-2663 (2012).

12. Itzkovitz, S., Blat, I.C., Jacks, T., Clevers, H. & van Oudenaarden, A. Optimality in the development of intestinal crypts. *Cell* **148**, 608-619 (2012).

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## 4.6 Clinical Trials

PS-OC research in the first three years unexpectedly informed the development of exploratory objectives for clinical trials and transitioned into using clinical samples faster than anticipated. To date, there have been five clinical trials that have incorporated theories, computational models, or technologies developed by the PS-OC investigators into the trial objectives. There has also been an increase in the number of investigators using clinical samples in their research. At the program launch, only six PS-OCs proposed experiments using clinical samples. After three years, all 12 of the PS-OCs are incorporating clinical samples or retrospective clinical data into their research. All of these clinical trials are supported by funds external to the PS-OC Program.

### Ongoing Clinical Trials with Exploratory Objectives Informed by PS-OC Research

1. **Cornell PS-OC (Project 3):** Identify drug crossover points for castrate resistant prostate cancer (CRPC) patients using prostate specific antigen measurements and analysis of circulating tumor cells (CTC) captured on GEDI microchips.

2. **DFCI PS-OC (Project 3):** Evaluate high-dose weekly erlotinib (type I EGFR kinase inhibitor) treatment schedule for EGFR mutant glioblastoma.

3. **Moffitt PS-OC (Project 2):** Determine if oral bicarbonate improves overall survival or progression free-survival in patients with unresectable pancreatic cancer.

4. **Moffitt PS-OC (Project 2):** Evaluate the efficacy of oral sodium bicarbonate as an adjuvant pain reliever in patients with tumor related moderate to severe pain.

5. **Scripps PS-OC (Core 1):** A phase I study to evaluate the safety and efficacy of Temsirolimus and Sorafenib in subjects with Hepatocellular Carcinoma. The collection of HD-CTCs will provide information in understanding potential impacts of the therapeutics on HD-CTCs.

## Planned Clinical Trials with Exploratory Objectives Informed by PS-OC Research

1. DFCI PS-OC (Project 1): Planning clinical trial with intermittent lapatinib dosing for EGFR mutant glioblastoma and using mathematical modeling to provide guidance regarding the dose and dosing-schedule for lapatinib.
2. TMHRI PS-OC (Core 2): Initiating a pilot clinical trial in collaboration with the University of Botswana for early detection of cervical precancer. Accrued 14 patients to the study.
3. TMHRI PS-OC (Core 2): Initiating a clinical trial in collaboration with two sites in China, for screening of cervical precancer and esophageal precancer.

## PS-OC Research in Conjunction with Ongoing Clinical Trials

1. Cornell, Moffitt, Scripps, & USC PS-OCs (PS-OC Trans-Network Project): The main clinical material for this project will come from 40 patients with metastatic CRPC about to received docetaxel based chemotherapy who consent to an optional prospective correlative study for blood and data acquisition.

## PS-OC Research Using Clinical Samples

1. ASU PS-OC (Project 2): Perform cell computed tomographic (CT) imaging on human esophageal biopsy samples.
2. DFCI PS-OC (Pilot Project): Performed mutational analysis of 18 genes in 398 patients with AML younger than 60 years of age randomized to receive induction therapy including high-dose or standard dose daunorubicin and validated our prognostic findings in an independent set of 104 patients. Genetic predictors of outcome were identified that improved risk stratification in AML independent of age, WBC count, induction dose, and post-remission therapy.
3. JHU PS-OC (Pilot Project): High-throughput physical phenotyping of colorectal and breast cancer cells.
4. MIT PS-OC (Project 3): Weighed glioblastoma multiform tumor cells from patient sample within 2 hours following resection in the OR (in collaboration with Keith Ligon, DFCI). The Ligon lab has immediate access to patient samples through collaboration with the DFCI/BWH Neurooncology Program.
5. MIT & Princeton PS-OCs (Trans-Network Project): Mapping the landscape of tumor heterogeneity of breast cancer tissue by quantitative single-cell assays.
6. Northwestern PS-OC (Project 3): Studies using partial wave spectroscopy (PWS) have demonstrated that chromatin compaction (quantified by a parameter referred to as the disorder strength, Ld, which is proportional to the amplitude and the spatial correlation length of local macromolecular density variations) is a universal early event in carcinogenesis, as confirmed by our data in the colon, pancreatic, lung, esophageal, and ovarian carcinogenesis.
7. Scripps PS-OC (Project 1): Initiated a HD-CTC processing campaign of previously collected non-small cell lung cancer samples representing all stages of the disease. The complete data set encompasses now 88 patients across all stages.
8. Scripps PS-OC (Pilot Project): Determining whether the HD-CTC Fluid Biopsy can be used to detect tumor cells in patients with liver cancer and, eventually, be used to augment the current tumor-staging modalities that are available for hepatocellular carcinoma.

9. Scripps PS-OC (Pilot Project): Analyze the correlation of HD-CTCs in patients with resectable breast cancer and recurrence rates. Human blood and tissue samples will be taken from the participants at time of resection, prior to breast cancer diagnosis. HD-CTC images will be analyzed and then cross referenced with clinical data regarding positive or negative diagnoses and rates of recurrence.

10. Scripps PS-OC (Pilot Project): Evaluation of RAD001 with Docetaxel and Bevacizumab in patients with Metastatic androgen independent prostate cancer.

11. Scripps (Core 1): Exploring tumor cell heterogeneity across geography, by multiple geographically designed samplings of a primary tumor, its locoregional metastases, and CTCs from various blood vessel locations, all simultaneously.

12. UCB PS-OC (Pilot Project): Profiling tissue mechanics in premenopausal AA women (1) during breast cancer initiation and (2) in breast biopsy tissue from pre-menopausal AA women with palpable versus non-palpable breast cancer.

13. UCB PS-OC (Project 2): Fresh breast tumor specimens that can be used for nano AFM analysis. By way of progress on this work the Weaver laboratory has developed a novel in situ force mapping protocol that will permit the spatial mapping of the materials properties of human breast specimens as a function of tumor progression.

14. USC PS-OC (Pilot Project): Simultaneous mappings of multiple mutations in colorectal cancer tissue slices by microfluidic PCR matrix.

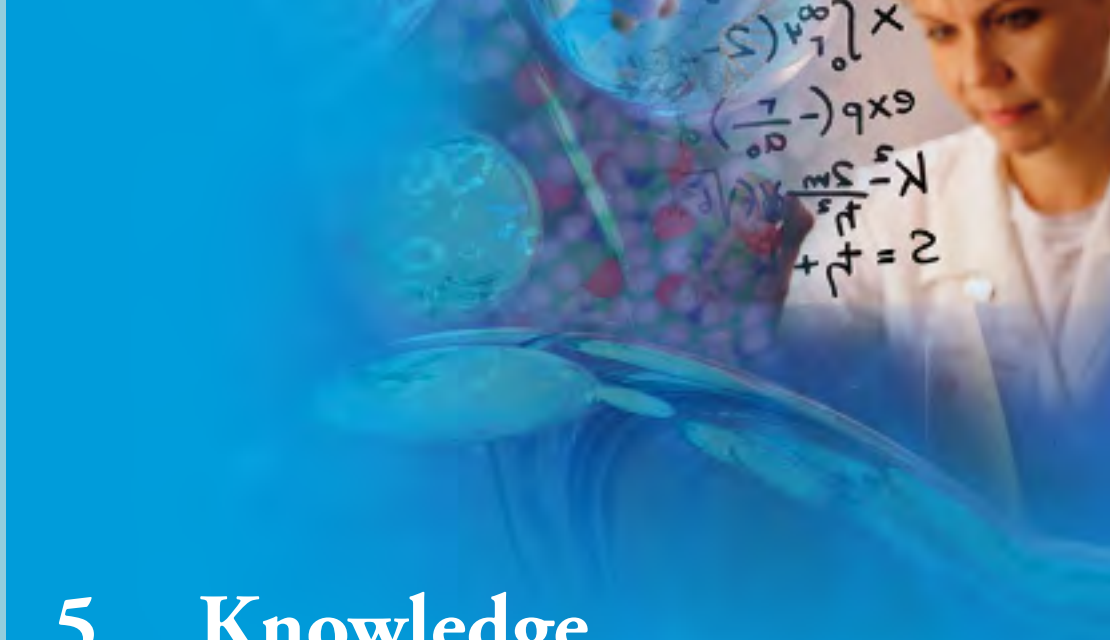
### PS-OC Retrospective Clinical Trials

1. USC PS-OC (Project 3): Performing a retrospective clinical trial in which they are mining patient data for 360 patients with CLL (chronic lymphocytic leukemia), SLL (small lymphocytic lymphoma), or SMZL (splenic marginal zone lymphoma) to search for correlations between blood pressure (which was found to spike upon cell burst) and white blood cell/ lymphocyte counts. We are also stratifying according to patients on ACE inhibitors and statins.

2. Moffitt PS-OC (Core 1): Twenty-five retrospective cases of invasive breast cancer with Nottingham Grade scores of I, II, and III were selected and indentifying information was blinded. Three H&E sections and 30 unstained 4µm histology sections were collected. The H&E slides were reviewed by a pathologist to confirm diagnosis and grade stage. Unstained slides were immunohistochemically stained in triplicate against optimized HIF1$\alpha$ , GLUT1, MMP7, MMP9 biomarkers and are being stained against KI67, CD31 and hypoxyprobe. Furthermore, multiplex test samples are being stained for multiple biomarker combinations including HIF1$\alpha$/GLUT1 and MMP7/MMP9. Triplicate stains are cross references for internal validation of scoring algorithms and staining consistency.

## 4.7 Summary

In its first three years, the PS-OC Program has generated high-quality publications, patent disclosures, and new advanced technologies. The PS-OC Network is transitioning faster than expected to using more clinical samples; five clinical trials incorporate exploratory objectives based on PS-OC research. While it is difficult to analyze the impact of PS-OC publications after just three years, a robust bibliometric analysis highlighted 18 potential breakthrough publications from 2010-2011, and several more recent publications have high citation velocities, greater than 10 citations per year. There have been key scientific advancements by the Network, such as relating three-dimensional (3D) architecture of the genome to single copy number alterations and identification of the emergent mechanical communication between glandular acini during tumor progression. A complete overview of these research highlights can be found in the PS-OC Program Update for year three.



# 5. Knowledge Generation and Broader Impacts in Cancer Research

The PS-OC Program aims to bring scientists from the physical sciences to cancer research to gain "new knowledge" in the understanding of controlling, preventing, and treating this disease. New knowledge is expected as an outcome of the generation of new orthogonal datasets to complement existing genomics and proteomics datasets and the development and testing of new theories and hypotheses in cancer research. The PS-OC Program is uniquely positioned to encourage the new and innovative theories and datasets by enabling a collaborative transdisciplinary environment along with support for new pilot projects. After three years of operation, the PS-OC Program has made progress toward generating new knowledge. This section describes the new knowledge identified by PS-OC investigators, as well as new datasets and new or expanded theories generated using PSPs. A more detailed assessment of the impact of this new knowledge will be performed as part of the summarative evaluation.

## 5.1 New Knowledge Defined by PS-OC Investigators

One way the generation of new knowledge stimulated by the PS-OC Program was measured was by directly querying investigators through the PS-OC Program survey. PS-OC investigators were asked, "What do you know now that you didn't know before the PS-OC Program?" The OPSO received responses from more than 60 investigators. Several researchers described the knowledge transferred between scientists in the physical sciences and oncology fields and others chose to selectively highlight specific findings from their own research. Selected responses are listed below. Many of these are aligned with the breakthrough publications identified earlier or identified as research highlights in the PS-OC Program Update.

The responses were broken into two groups. The first group focused on what PS-OC investigators have learned from collaborating and interacting with scientists in separate fields. The responses suggest that the cancer biologists and oncologists and the physical scientists have learned broad concepts from each other.

- "Role of physics in understanding biologic systems"
- "—in many cases it's possible to obtain cancer stem cells from individual patients, fully sequence these cells, "bank" them in culture, and recapitulate the tumor by implanting them into mice, such that one has full access to genotype, phenotype, and clinical history. The potential to relate in vitro cell biophysics to cell biology to clinical course has never been greater"
- "The relative value of CTC in diagnosis/treatment of certain cancers"

The second group of responses identified knowledge that was gained from specific research within the PS-OC Program. These relate to the key advancements highlighted in the previous section and in some cases have fostered new trans-Network project proposals.

- "Chromatin organization/structure/function and mechanical force.....interplay between microenvironment and gene expression/networks as well as epigenetics" (see Research Highlights from Mirny and Michor in PS-OC Program Update Section 3.2.3)
- "How gradients of stress drive evolution" (see Research Highlights from Austin and Gatenby in the Program PS-OC Program Update Section 3.2.1)
- "(1) Cells are in contact with the ECM, which provides mechanical integrity to tissues and also chemical and mechanical signals to cells, influencing differentiation, development, and pathogenesis. (2) Tissue hardening due to changes in collagen crosslinking status and composition has been causally implicated in tumor progression in mice. (3) Normalizing tissue mechanics reduces the rate with which tumors grow and significantly reduces the probability of metastasis" (see Research Highlight from Liphardt in the PS-OC Program Update Section 3.2.2)

- "…the interplay between fluid, mechanical, elastic, and geometric forces in cell cluster stability, interactions with basement membranes, and the role that these forces play in creating and maintaining organized structures" (see Research Highlights from Bissell and Sethian in the PS-OC Program Update Section 3.2.2)

Together, these survey responses highlight both general and specific examples of new knowledge and knowledge transfer that were facilitated within the PS-OC Program and that improved our understanding of the emergence and behavior of cancer on all scales.

## 5.2 New Cancer Datasets

New knowledge in cancer research is expected to correlate with the generation of orthogonal datasets to complement or expand existing approaches, data, and understanding of cancer. This includes new advanced technologies enabling more spatial and temporal information, high-content single-cell data, and data on the physical parameters of cancer cells and tumors (e.g., modulus, pressure, stiffness, pH, migration patterns). Several types of datasets acquired by the PS-OC Network are highlighted below, including data from the Cell Line Pilot Study (see the PS-OC Program Update Section 5.2 for more details). Data generated by the PS-OC Network will be deposited into the PS-OC Data Coordinating Center (DCC) where PS-OC investigators will be able to probe and analyze the data from the PS-OC Network to inform experimental and modeling approaches and to gain new knowledge in their specific areas of cancer research.

### 5.2.1 High-Content Single-Cell Analysis Datasets

High-content analysis techniques are unique in that they bridge the gap between depth and throughput of biological experiments, allowing scientists to not only capture large quantities of data but also multiple types of data in one assay. Several laboratories within the PS-OC Network have used a combination of high-content techniques, measuring multiple parameters per sample with high-throughput single-cell analysis. The combined information provides a more detailed understanding of cell heterogeneity, and of physical parameters of cancer cells, as well as the subsequent ability to relate these to the biological heterogeneities. Highlighted below are two examples of high-content single-cell datasets generated by PS-OC investigators and their potential impact on the cancer research field.

#### *High-Content Cell Phenotyping*

*Denis Wirtz, JHU PS-OC*

Denis Wirtz and colleagues have developed a high-throughput scanning microscope that can be used to generate an extremely robust, multiparameter phenotypic signature of single cells. This approach was used to generate a phenotypic signature of cancer metastasis for pancreatic cancer patients. Analyzing this new dataset illustrated that the degree of phenotypic heterogeneity is decreased in cells that have metastasized to the liver compared to cells from primary tumors (Figure 5.1). Through collaborations with a range of investigators from the PS-OC Network, this approach is being extended to determine single-cell phenotypic signatures predictive of drug responsiveness and time of survival in a wide range of cancers, including prostate cancer, ovarian cancer, and leukemia.

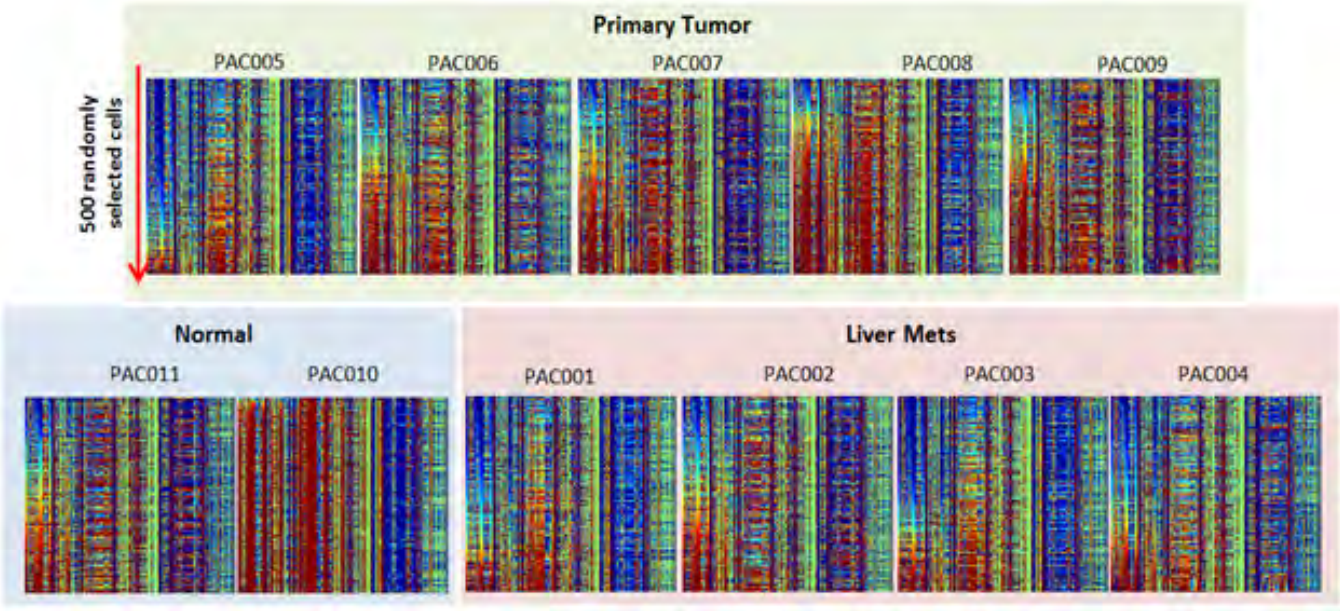



Figure 5.1. A dataset of morphological and behavior parameters of 500 single cells collected from patient samples.

## *Correlation of Single-Cell Migration Distance and Secretomic Signature*

*Rong Fan, Yale University, DFCI PS-OC; Denis Wirtz (JHU PS-OC)*

Rong Fan and colleagues have developed a single-cell barcode chip that combines microfluidics and proteomics approaches to measure the profile of secreted proteins from individual cells. This device was used to perform simultaneous measurement of secretomic and migratory signatures in single cells. Human lung cancer cells were loaded into microchambers containing an antibody barcode array patterned to detect 13 secreted proteins. Then the microchip loaded with cancer cells was incubated for 12 to 24 hours to allow proteins to be secreted from the cells and captured by the antibody microarray. The device was simultaneously imaged using an automated imaging cytometry approach (Wirtz lab) before and after the secretion assay to quantify the number of cells in each microchamber and measure the migration distance of each single cell. A live cell imaging approach (Wirtz lab) was also employed to measure the migration trajectory. In the end, the migratory proprieties were correlated to the corresponding protein secretion signature for each single cell. Figure 5.2a shows the migration of three representative single cells. Figure 5.2b is a heatmap representing the combined migration and secretome data for 442 single cells; cells are sorted by increasing migration distance. For each cell the migration distance along with the abundance of the 13 secreted proteins is shown. Figures 5.2c-e are the scatter plots depicting the levels of three representative proteins versus the migration distance. Each dot represents a single cell, and each plot indicates the correlation between a selected cytokine and cell migration distance. The results explicitly show distinct correlation behavior among different cytokines. MCP-1 and IL-8, which coincidently are both chemoattractant proteins, exhibit strong positive correlation with migration distance, while IL-6, a proinflammatory cytokine, shows negative correlation with migration distance. This is a new discovery that has implications in the identification of invasive tumor cell phenotypes.

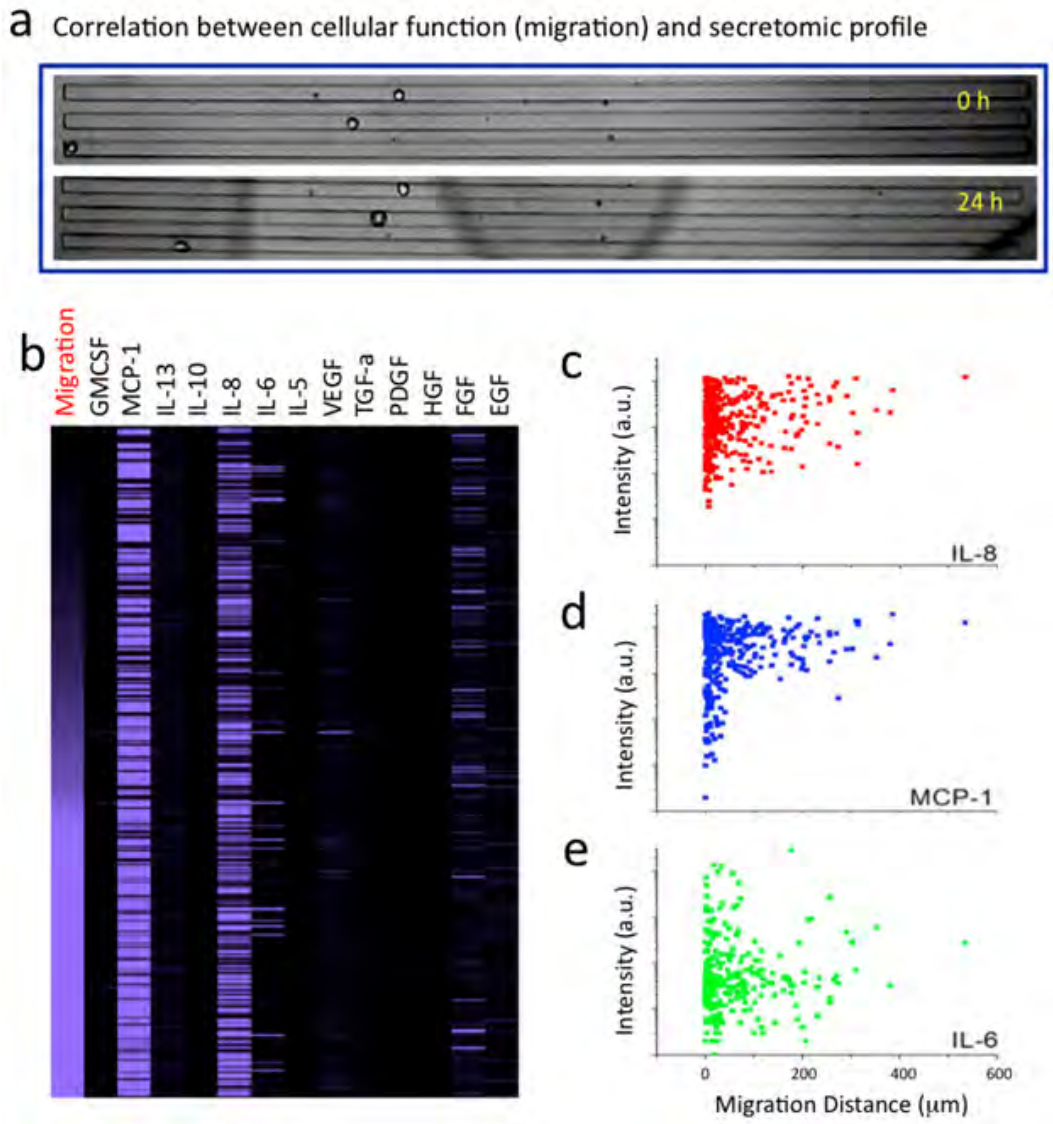



Figure 5.2A-E. Correlation of cell migration and protein secretion profile at the single-cell level. a. Light field micrograph showing three cells that migrate within their own microchannels over the period of incubation, during which a panel of proteins was allowed to be secreted from captured single cells and measured by the antibody barcode array. b. Heatmap showing the measurement of 13 secreted proteins from 442 single cells sorted by the migration distance. c, d, and e. Scatter plots showing the level of three proteins (MCP-1, IL-8, and IL-6) versus migration distance. Each dot represents a single cell.

### 5.2.2 Measuring Physical Properties of Cancer Cells In Vivo

Prior to the PS-OC Program, technological hurdles limited the ability of researchers to examine the physical properties of cancer cells in vivo, such as cell stiffness and external pH. While significant work had been done exploring in vitro differences in physical properties during cancer progression, translation of these finding to the clinic is limited by lack of in vivo validation. Advances in measuring these physical properties in vivo could potentially help validate these observations and support a more comprehensive picture of cancer. To date, there have been two examples of PS-OC investigators overcoming technical hurdles to integrate technologies facilitating the in vivo measurement of physical properties. Each of these approaches combines existing physical sciences technologies and intravital microscopy to generate new in vivo physical parameter datasets. These are described in more detail below.

### *In Vivo Cell Stiffness*

*Sanjiv Sam Gambhir (USC PS-OC); Denis Wirtz (JHU PS-OC)*

Collaborative research among trainees from the Wirtz and Gambhir labs, funded through a PS-OC Young Investigator Trans-Network Award, employed their combined expertise to measure the mechanical properties of MDA-MB-231 breast cancer cells during tumor development in living mice. By combining the particle-tracking microrheology expertise of the Wirtz lab with the intravital microscopy techniques of the Gambhir lab, the group was able to perform microrheology measurements in live mice to assess the role and dynamic nature of cell mechanics in tumor formation (Figure 5.3). This is the first dataset measuring the mechanics of tumor cells in vivo, and it provides temporal information about how the mechanics change during tumor development. Together, this dynamic in vivo data are expected to contribute to our understanding of the role of mechanical stiffness of cells throughout cancer progression.

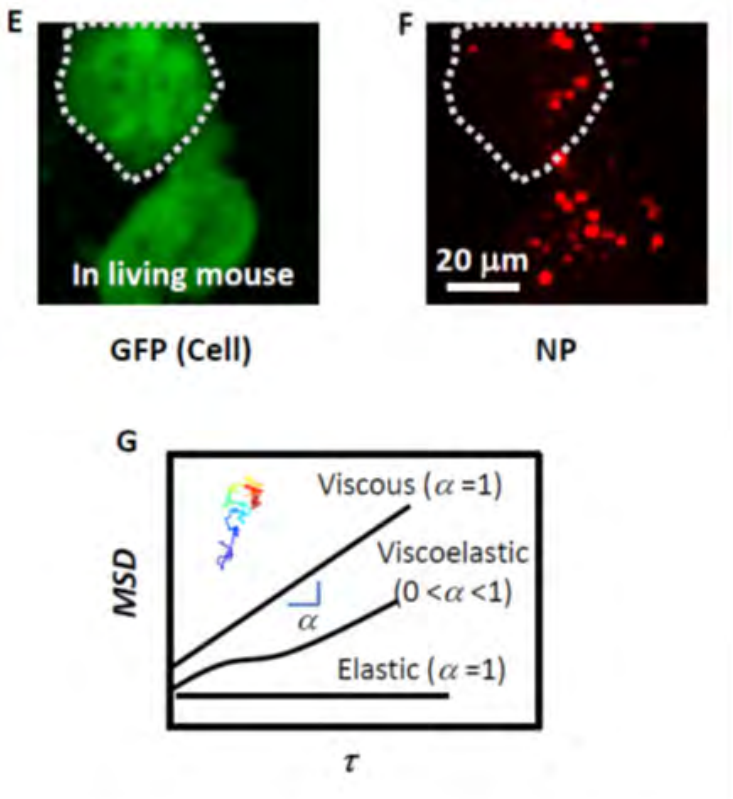



Figure 5.3. Real-time tracking of cellular mechanics in developing tumors. (E) Intravital microscopy was used to observe the formation of tumors in mice by MBA-MD-231 cells. (F) Balistically injected nanoparticles were evident in MDA-MB-231 cells during tumor formation. (G) Analysis of the nanoparticle movement was used to calculate cellular mechanical properties.

### *Extracellular pH In Vivo*

*Robert Gatenby and Robert Gillies (Moffitt PS-OC)*

Combining intravital microscopy with the use of the pH-sensitive fluorescent label SNARF (carboxyseminaphthorhodafluor-1), a team led by Robert Gatenby and Robert Gillies has generated datasets mapping the in vivo extracellular pH of a breast tumor during cancer progression (Figure 5.4). Strikingly, the group has found that the invasive cells grow toward the more acidic regions of the tumor. This finding has led to the hypothesis that invasive cancers speciate as they develop in response to the heterogeneity of the tumor microenvironment (see Section 5.3 below). In other words, tumors are made up of multiple habitats and multiple species of malignant cells. In fact, an examination of various molecular markers within tumors showed that the cells at the edge of a tumor were different than those in the core. This may indicate that cells in the interior of a tumor invest in niche development, while those at the edge of a tumor invest in developing invasiveness. Analysis of invasive cancers must be undertaken with caution and should at least consider this heterogeneity.

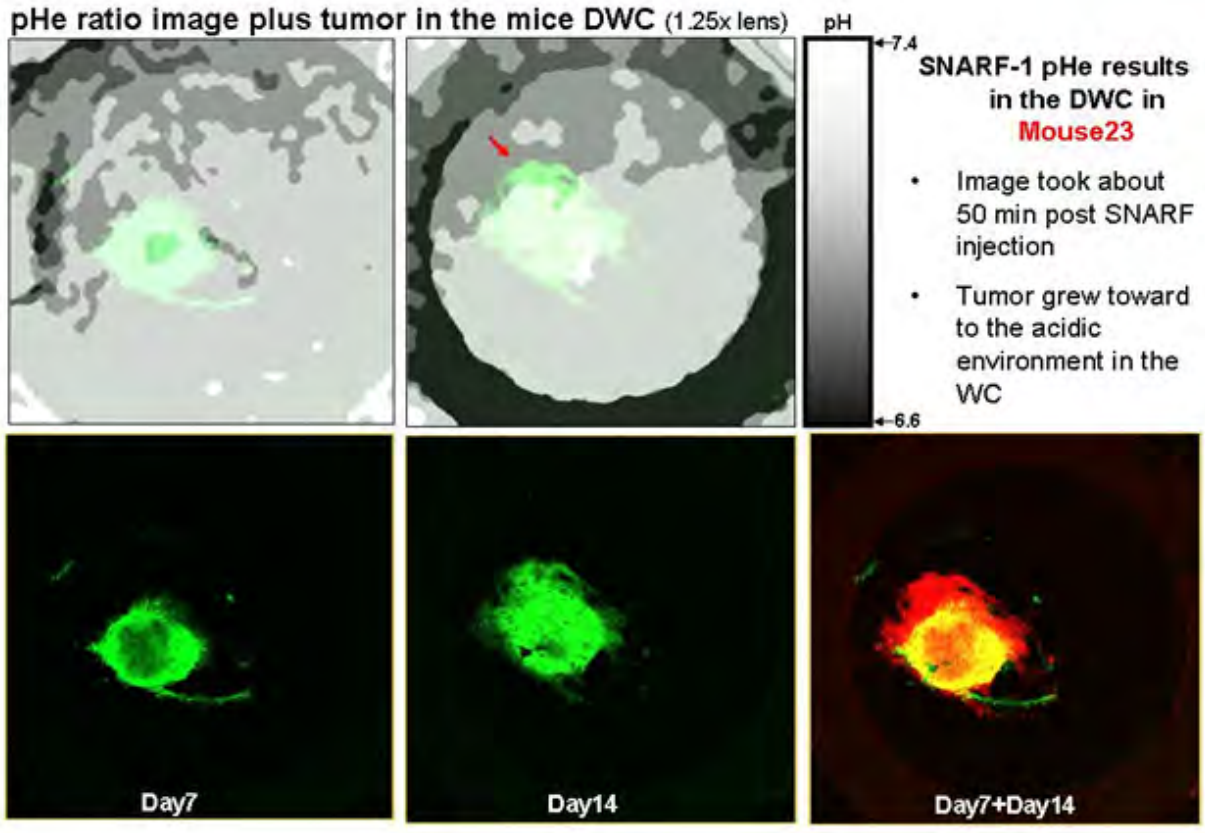



Figure 5.4. Intravital microscopy imaging of extracellular pH dynamics in a growing tumor.

### 5.2.3 PS-OC Cell Line Pilot Study Datasets

The Cell Line Pilot Study was initiated in November 2009 by the PS-OC Steering Committee to test the feasibility of providing a standardized "benchmark" protocol for showcasing the diverse physical science technologies across the PS-OC Network. All 12 PS-OCs participated in the Cell Line Pilot Study, generating datasets from an array of technologies across a range of length scales on the same lots of metastatic MBA-MD-231 and non-malignant MCF-10A mammary epithelial cell lines. As expected, the exercise resulted in a wealth of data generated by different technologies across the PS-OC Network. Collectively, the Centers decided to cluster these datasets into four categories: (1) morphology; (2) cell behavior; (3) survival and stress response; and (4) an overarching network model. The cell behavior and stress response datasets are highlighted below.

#### *Cell Behavior Data Sets — Migration Patterns, Elasticity, Traction Force, Rolling Adhesion*

*Robert Ross (ASU PS-OC); Cynthia Reinhart-King (Cornell PS-OC); Michael King (Cornell PS-OC); Denis Wirtz (JHU PS-OC); Sharon Gerecht (JHU PS-OC); Konstantinos Konstantopoulos (JHU PS-OC); Robert Austin (Princeton PS-OC)*

Datasets describing the comparative cell behaviors of two different cell lines, metastatic MDA-MB-231 and non-malignant MCF-10A, were collected by seven laboratories across the PS-OC Network. The laboratories then integrated the datasets to generate and support a more comprehensive understanding of changes in cell behavior during cancer progression, such as cell migration and mechanics.

One of the distinguishing hallmarks of metastatic cells is their capacity to transit through multiple physical microenvironments such as the ECM of the stromal space and, following intravasation, along vasculature walls. Traditionally, cell motility studies have been performed in two-dimensional (2D) environments (i.e., flat substrates). For the Cell Line Pilot Study, cell motility was evaluated in one-dimensional (1D), 2D, and 3D environments (Figure 5.5a). These multidimensional experiments revealed that regulation of cell speed and maximum displacement were dependent on the dimensionality of the environment. Given the dimensional constraints of the cellular environment, the non-malignant cells tended to move faster than the metastatic cells, but remained within a limited circular area, while metastatic cell motility was linear and did not exhibit the same distance limitations.

Consistent with observations of amoeboid movement of invasive cancer cells, the ability of a cell to move through multiple tissue compartments, often via small portals, relies on amoeba-like deformability. The mechanical deformability and cytoplasmic viscosity of MCF-10A and MDA-MB-231 cells were measured by atomic force microscopy (AFM) and ballistic injection nanorheology (BIN; movement of nanoparticles in a viscoelastic material), respectively. AFM identified that mechanical loads are transduced through the cytoskeleton differently in the two cell lines. The metastatic MDA-MB-231 cells showed increased elasticity with increasing indentation depth (Figure 5.5f). Consistent with the AFM results, the movement of particles in the cytoplasm measured by BIN suggested that the MDA-MB-231 cytoskeleton was significantly softer than that of MCF-10A cells (Figure 5.5g). Both of these results were consistent with the ability of the metastatic MDA-MB-231 cells to traverse narrow matrices.

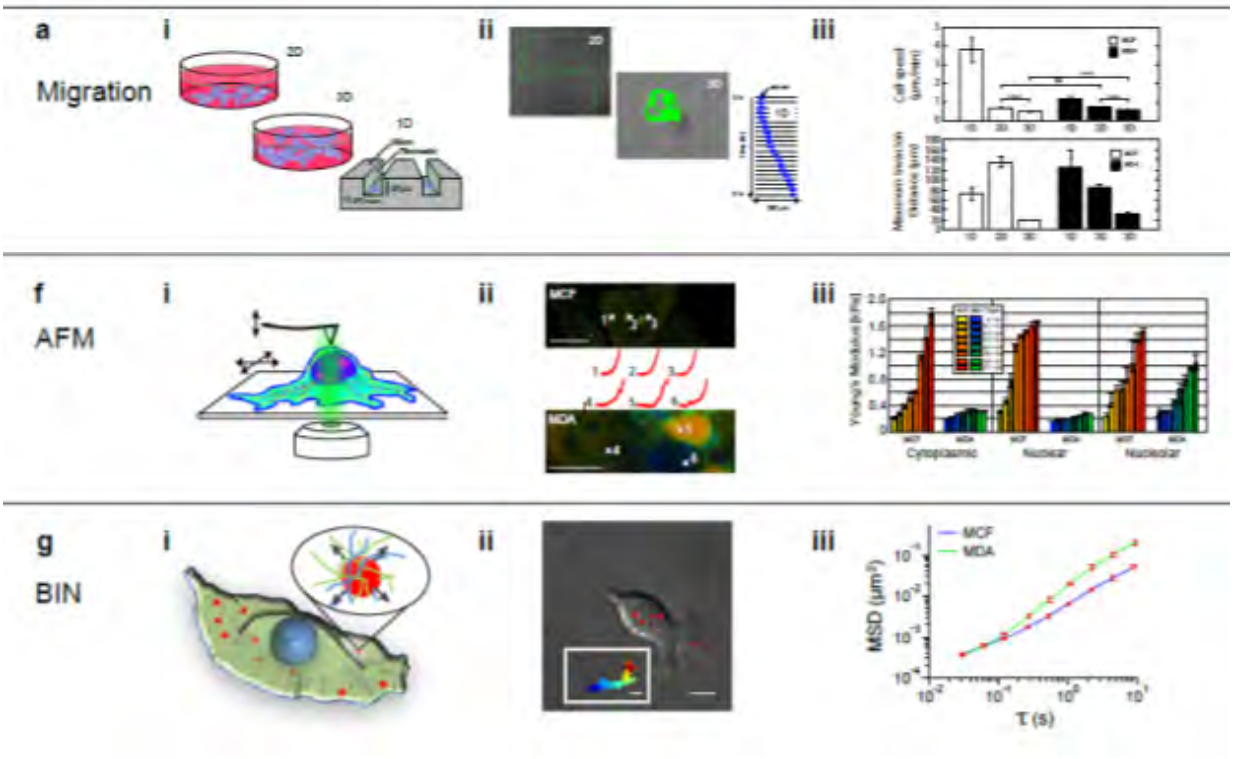



Figure 5.5. Comparative cell motility and mechanics. (a) Cell Migration: Three different substrates were used to monitor cell motility: 2D collagen-coated glass substrate, 3D collagen matrix, and 1D fibronectin-coated microchannels etched in silicon. (f) Atomic Force Microscopy (AFM): AFM probe was aligned with confocal fluorescence microscope lens to allow indentation of specific subcellular regions (cytoplasm, nucleolus, and nucleus). Corresponding force-indentation curves used to calculate Young's elastic moduli and bar graphs representing elastic moduli of MCF 10A and MDA MB 231 cells. (g) Ballistic injection nanorheology (BIN): Fluorescent nanoparticles injected into the cells and trajectory monitored over time. Representative live cell image monitored in real time and graph of mean square displacement (MSD) values over cumulative time.

## *Cell Response to Stress — Evolutionary Dynamics Datasets*

*Robert A. Gatenby (Moffitt PS-OC); Robert J. Gillies (Moffitt PS-OC); Parag Mallick (USC PS-OC)*

Preferential survival under stressful conditions is a characteristic of metastatic cancer cells. To examine this phenomenon from a PSP, measurements of cell response (viability and oxygen consumption) following exposure to external stresses characteristic of the tumor physical microenvironment (hypoxia and low pH) were collected as part of the Cell Line Pilot Study. The effects of hypoxia on cell viability, growth and recovery, and oxygen consumption were tested in a 2D environment as well as in a pathologically relevant 3D culture environment. In both environments, under ambient conditions, MCF-10A and MDA-MB-231 cells exhibited similar oxygen consumption rates. However, their response to hypoxic (1 percent oxygen) pretreatment differed, with no changes observed in MCF-10A oxygen consumption, while MDA-MB-231 cells reduced oxygen consumption four-fold when precultured in hypoxia (Figure 5.6b). When cells were grown under acidic conditions, pH 6.8 versus neutral pH 7.4, and cell proliferation was monitored at fixed time points, non-malignant MCF-10A cells exhibited a decrease in viability to 70 percent of the control by 24 hours (Figure 5.6a), while the viability of malignant MDA-MB-231 cells was not significantly affected. The observed changes were hypothesized to be due to an increased adaptation potential of the MDA-MB-231 consistent with the increased tumorigenic potential of this cell line.

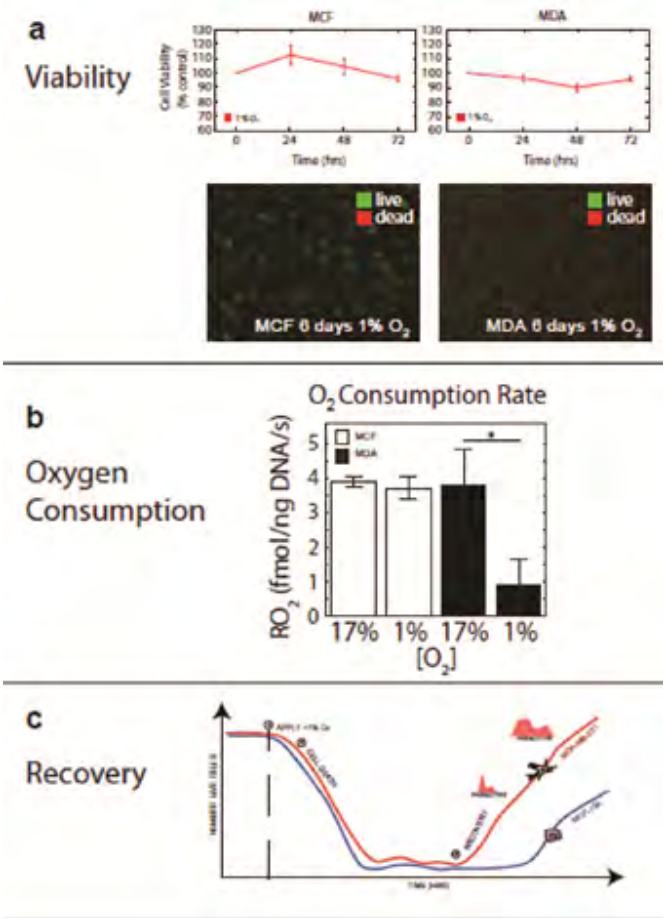



Figure 5.6. Comparative Stress Repsonses (a) Using a 3D culture environment, cell viability was monitored for the two cell lines. Cell viability was monitored by DNA content per scaffold and normalized to day-1 levels (b) O2 consumption rates determined for cells seeded in alginate discs at day 6 of 1 percent or 17 percent O2 3D culture. Cells were cultured in neutral pH (pH 7.4) growth medium at 17 percent or 1 percent oxygen for 72 hours after first being seeded in medium with 17 percent oxygen for 24 hours. Viability was determined every 24 hrs and imaged with an inverted microscope. Data displayed are averages of three wells per sample and normalized to the untreated samples. (c) Schematic of hypoxia stress (from 17 percent to 1 percent O2) and cell viability over time for MCF 10A and MDA MB 231 cells.

### 5.2.4 Data Coordinating Center

The datasets collected by PS-OC investigators will be deposited into the DCC, currently under construction. The DCC will be a unique database that combines datasets from physical scientists and cancer researchers and from length scales ranging from subcellular to host level. The diversity of data collected in the PS-OC Network will be available at the DCC for all PS-OC investigators to integrate and collectively use to address challenges in cancer; additionally, as data are published they will become available to the broader scientific community. Combining datasets is expected to generate new information and knowledge and enable the PS-OC investigators to challenge current assumptions in cancer research (Figure 5.7).

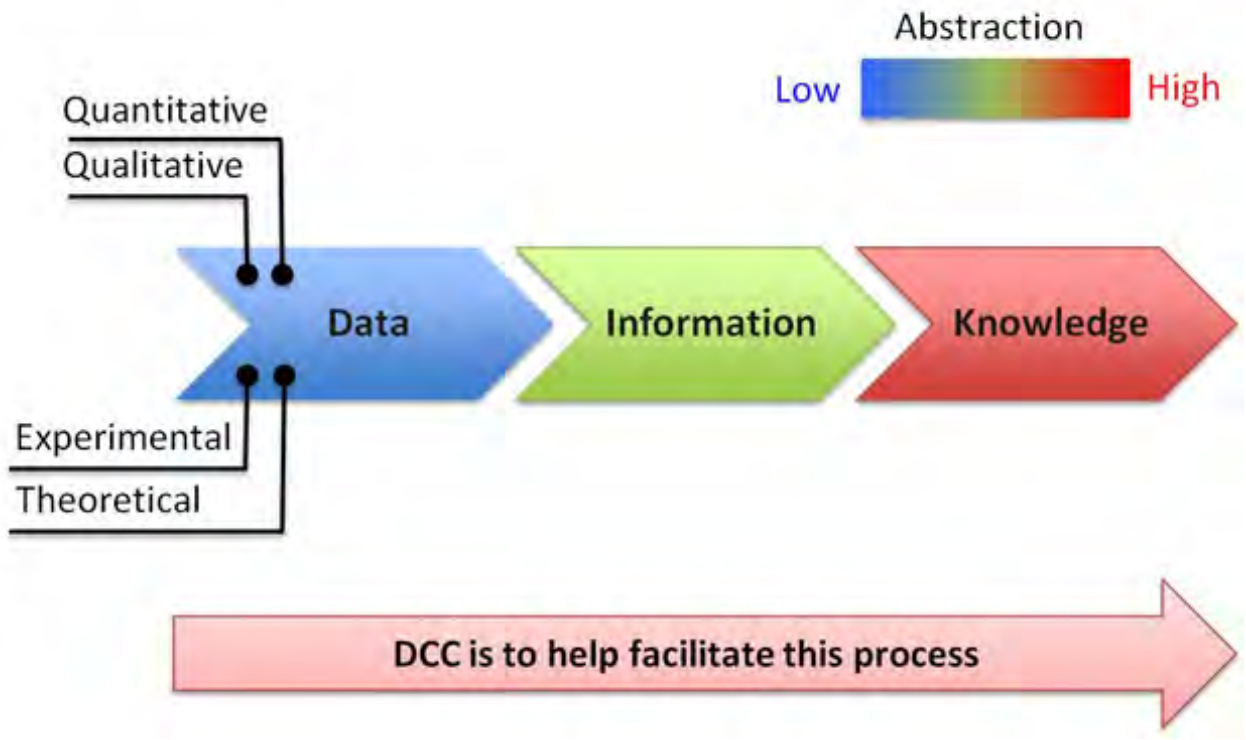



Figure 5.7. The DCC will help extract knowledge from the integration of diverse datasets across the PS-OC Network.

## 5.3 New Theories and Hypotheses

A major goal of the PS-OC Network is to develop new hypotheses/theories/models in cancer research using PSPs and approaches. To date, the PS-OC Network has generated several theories based on physical sciences experimental approaches, computational physics models, and comparable biological systems that display phenomena similar to cancer. Some of these theories are new. Others expand on or broaden existing theories of cancer using a novel PSP. This includes new takes on current theories, such as the role of chromatin architecture on biological processes and the evolution of cancer. Many of these theories were not predicted as part of the original applications but have blossomed from collaborations initiated between physical scientist and cancer biologists. In the future, the PS-OC Network plans to explore many of these theories and hypotheses potentially challenging current dogma in cancer research. Key examples of these new and expanded theories are highlighted below.

### *Chromatin Architecture Shapes the Landscape of Chromosomal Alterations in Cancer*

*Franziska Michor (DFCI PS-OC); Leonid Mirny (MIT PS-OC)*
Projects in Progress: Trans-Network Project

Using computational physics, Franziska Michor and Leonid Mirny set out to identify the mechanisms underlying the location and length distribution of genomic alterations that occur during the development of cancer and to determine if the mutagenic potential of various regions of the human genome are encoded in the genomic sequence, in the epigenome, or in the three-dimensional structure of the chromosome in the nucleus. Using HiC chromatin conformation capture datasets, they identified a number of genomic factors that influence the genome-wide distribution of genomic alterations and used the distribution of alterations to predict a novel, fractal globular organization of the genome. While previous research has identified the significance

of chromatin architecture in genomic stability, Drs. Michor and Mirny were able to propose the following expanded theories about the role of the 3D architecture of the genome in cancer using novel physical sciences approaches. This includes the following:

- The distribution of chromosomal alterations in cancer is dependent on the 3D genomic architecture.
- Spatial proximity of the genome in normal cells influences the location of genomic alterations in cancer.
- Temporal proximity of genome replication timing influences the location of genomic alterations in cancer.
- Both epigenetic modifications and the formation of higher order structures such as G4 heteroduplexes influence the location of genomic alterations in cancer. Since epigenetic patterning is tissue specific, this model has the potential to explain tissue specificity of mutational landscapes.

### References


De, S., & Michor, F.. DNA replication timing and long-range DNA interactions predict mutational landscapes of cancer genomes. *Nat Biotechnol* **29**(12): 1103-1108 (Citations: 8) (2011).

Fudenberg, G., Getz, G., Meyerson, M., & Mirny, L.A. High order chromatin architecture shapes the landscape of chromosomal alterations in cancer. *Nat Biotechnol* **29**(12): 1109-1113 (Citations: 6) (2011).


## *Cancer Heterogeneity Is a Result of Speciation of Cells Within the Tumor Microenvironment*

*Robert Gatenby and Joel Brown (Moffitt PS-OC)*
Projects in Progress: Pilot Project at Moffitt PS-OC

Robert Gatenby, PI, of the Moffitt PS-OC, and Joel Brown, an ecologist, have started a new collaboration to understand evolution within a progressing tumor. Typically, evolution of cancer is depicted as a sequence of mutations or genomic alterations resulting in a cancerous genotype. However, Gatenby and Brown claim that this ignores two fundamental questions necessary to answer for understanding carcinogenesis: (1) How exactly does a mutation confer a proliferative growth advantage? and (2) What are the environmental selection forces that control phenotypic evolution? According to the two investigators, evolution selects phenotypes not genotype. Fitter phenotypes proliferate at the expense of those less fit, but the fitness of any phenotype is contextual and depends on environmental selection forces that are dynamic and that change in space and time. It is well established that tumors are heterogeneous on a cellular level, but little is known about the heterogeneity of the physical microenvironment of the tumor that may induce stress on cells, such as hypoxia and pH. To date, Gatenby and his team have developed experimental protocols to measure the heterogeneity of the physical microenvironment and have started to identify "species" of cancer cells that "dominate" specific regions. Further development of this theory may have an impact on our understanding of the role and implications of tumor heterogeneity.

## *Self-Seeders, Spreaders, and Sponges*

*Paul Newton (USC, Scripps PS-OC); Peter Kuhn (Scripps PS-OC); Larry Norton (MSKCC, DFCI PS-OC)*

In 2006, Larry Norton, Memorial-Sloan Kettering Cancer Center (MSKCC), first asked the question "Is cancer a disease of self-seeding?" Since then, several experiments have reported the phenomena of self-seeding tumors in breast cancer. In collaboration with Dr. Norton, researchers at the Scripps PS-OC expanded this theory to include new descriptions of tumors as "spreaders" and "sponges." Using an autopsy dataset, Paul Newton, a Scripps PS-OC investigator, developed a Markov chain

model to map the connections between a primary lung tumor and the probability of dissemination to specific secondary sites. This diagram revealed a few surprises, including the fact that the adrenal glands have a high probably of becoming the first metastatic site, and that re-seeding of metastases back into lungs, both from the primary tumor itself and from metastatic sites, has a high probability of occurring (Figure 5.8). This type of analysis also identified secondary sites of metastasis that are seeded from other metastases.

Further analysis of this metastatic pathway diagram suggested that there are two types of metastatic sites: "spreaders" and "sponges." Spreaders are defined as those sites that have high probabilities of transitions in and out of the organ, while sponges are defined as those sites that have more and higher-probability paths into the organ. Spreaders, which would include lymph nodes, the liver, and adrenal glands, have many incoming and outgoing pathways. Sponges, such as the kidney, have more paths into the organ than out. Experiments are now under way to test whether the predictions made from this diagrammatic representation of metastases holds true in patients. Additionally, the analysis is being expanded into other cancer types.

### *Bang-Bang Theory*

*Dr. Alexander van Oudenaarden (MIT PS-OC)*

Alexander van Oudenaarden and colleagues developed a new theory of how biology optimizes stem cell fate to grow organs. For the mouse intestine the optimization goal in organ development is to rapidly generate intestinal crypts in neonatal

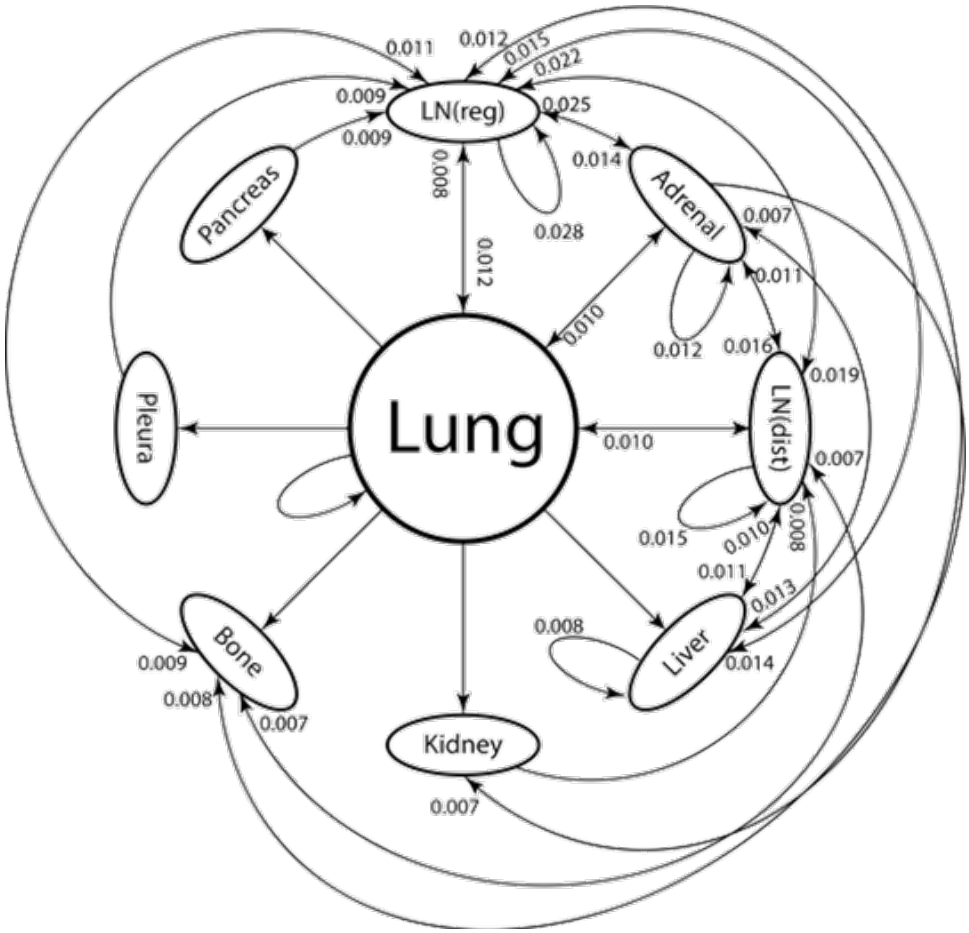



Figure 5.8. Visual representation of dissemination probabilities.

mice to allow absorption of nutrients through the gut rather than through the placenta. There are a large number of possible solutions mice could use to solve this developmental problem. Taking a physics approach to solving the problem of how a single stem cell will divide to minimize the time required to develop a crypt composing a fixed proportion of stem and differentiated cells, the MIT group turned to computational modeling. They created a model that solved the almost infinite number of possible pathways to go from a budding crypt to a fully mature crypt and determined the two optimal solutions: (1) stem cells undergo only symmetric divisions to produce more stem cells followed by a sudden switch to asymmetric cell division and (2) stem cells undergo only asymmetric divisions followed by a sudden switch to purely symmetric divisions.

These two scenarios, called "bang-bang" control, were proven mathematically to be the fastest routes to a mature crypt, but the question remained regarding whether this type of control occurred in the mouse intestine (Figure 5.9). In a laborious set of experiments that counted the number of stem and non-stem cells in developing crypts, the MIT group showed that, indeed, bang-bang control was operating in the mouse intestine—at time zero, the number of stem cells increased linearly and then suddenly leveled off to a constant number. At that very same time, the number of non-stem cells began increasing linearly. Dr. van Oudenaarden's group confirmed this finding using short-term lineage tracing, which showed clearly that in small crypts, all the stem cell divisions are symmetric, while in larger crypts they are asymmetric. Hence, the development of intestinal crypts exhibits a temporal order in which stem cells first establish their adult census and then switch to produce non-stem cells. This temporal order is optimal for minimizing the time to achieve a mature crypt.

A remaining question is whether the "bang-bang" control theory applies to cell fate determination during cancer progression. Do cancer cells optimize the number and type of cell divisions to achieve a malignant tumor?

Itzkovitz, S., Blat, I.C., Jacks, T., Clevers, H., & van Oudenaarden, A. Optimality in the development of intestinal crypts. *Cell* **148**(3): 608-619 (2012).

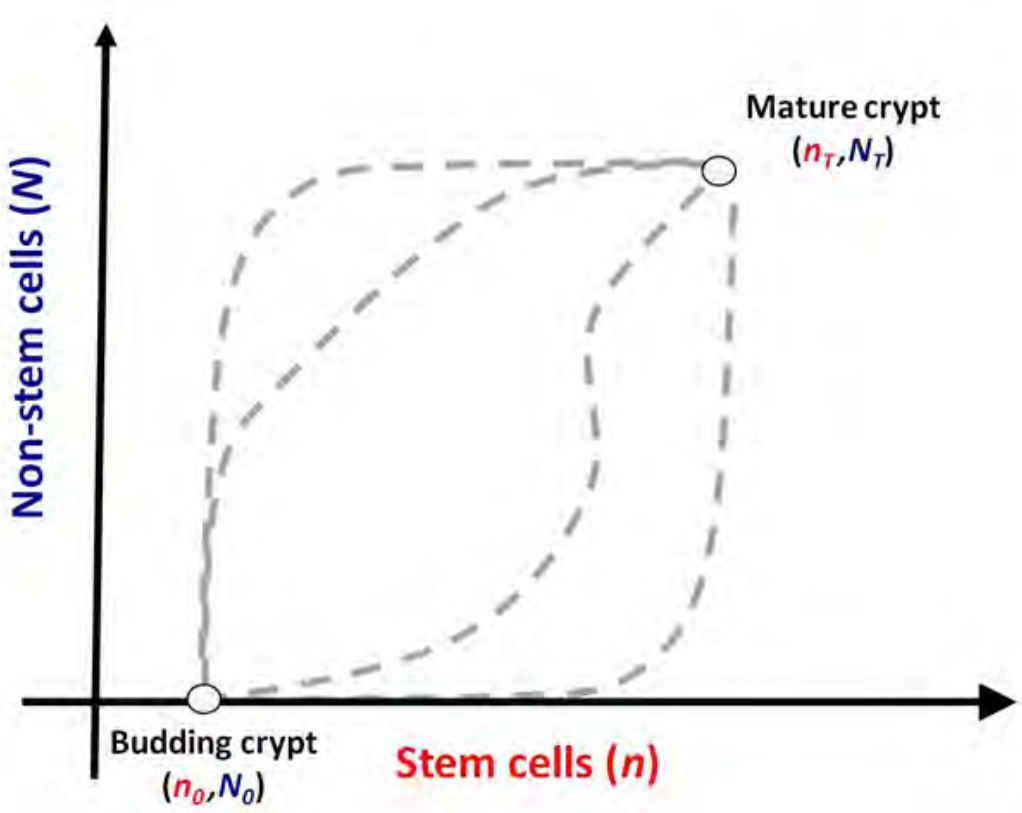



Figure 5.9. Bang-Bang theory.

## 5.4 "Bursty" Topics in PS-OC Research

Comprehensively measuring the progress toward the PS-OC goal of "generating of new knowledge in cancer research" is a challenge after only three years of operation. Typically, it takes 10 years or more to assess the impact of the scientific breakthroughs on the cancer research community. To facilitate the prospective evaluation of the PS-OC Program, a metric was developed to track scientific topics emerging from the PS-OC Program as the Program matures that could be used to guide program elements as needed. In collaboration with Discovery Logic, OPSO program officials developed an indicator of new scientific topics emerging from the PS-OC Network using content mapping techniques and burst detection algorithms. This analysis generated 68 topic clusters of 5 or more terms that are derived from their frequency and co-occurrence in PS-OC publications and progress reports and color-coded based on their increased frequency or "burstiness" during the PS-OC grant years. The results of the analysis correspond with several potential breakthrough publications and new knowledge identified by the PS-OC investigators.

### 5.4.1 Content Mapping and Burst Detection

A novel content network analysis, based on the co-occurrence of double-word terms in the titles and abstracts of publications and in the PS-OC progress reports, was generated to evaluate and visualize emerging topics in PS-OC research. The abstracts and titles of 601 PS-OC publications and the text from 84 progress reports were used to define PS-OC topic clusters. Discovery Logic identified two consecutive words of the original text to qualify as a term to simplify the system. All terms were filtered to remove non-specific terms. Using an affinity propagation clustering algorithm,[8] terms were clustered based on their co-occurrence in text. Terms with greater than 100 degrees (i.e., connections with other terms) were eliminated to remove common scientific words that distort the topic clusters. These include terms such as cancer cell (410), tumor cell (334), mathematical model (230), and breast cancer (129). Double-word co-occurrences that did not occur in more than 3 documents were also removed, leaving 1,186 double-word terms and 5,246 co-occurrences. A complete map of all these terms, color-coded by topic clusters, is shown in Figure 5.10. Overall there were 68 topic clusters with greater than five terms.

To measure the emergence of the topics, Discovery logic analyzed the frequencies of double-word terms and, more importantly, the co-occurrence of double-word terms in publications from PS-OC investigators. The term and co-occurrence frequencies were compared for publications from PS-OC Program years and publications from the five years prior to the start of the Program using a burst detection algorithm.[9] Edges, or term co-occurrences, in the topic clusters were color-coded based on their burst weight. A burst weight greater than zero indicates that the co-occurrence was bursty during the PS-OC grant years (2010-2012). A higher burst weight indicates a more strongly emerging topic.

[8] Bodenhofer, U., Kothmeier, A., and Hochreiter, S. *APCluster: An R package for affinity propagation clustering.* Bioinformatics, 2011. **27**:2463-2464.

[9] Kleinberg, J.. *Bursty and Hierarchical Structure in Streams.* Proc. 8th ACM SIGKDD Intl. Conf. on Knowledge Discovery and Data Mining, 2002.

### 5.4.2 Potential Emerging Topics in Cancer Research

The 68 topic clusters identified with content mapping cover a diversity of topics. Within these clusters, three broad thematic areas with burst co-occurrence during the PS-OC Program years were identified across several topic clusters: cell forces (e.g., mechanics, migration, and adhesion), evolutionary dynamics, and stochastic single-cell dynamics.

For Figures 5.11, 5.12, and 5.13, edges and double-word terms were binned for visualization purposes to illustrate topics that have emerged during the PS-OC Program years. Note that it is possible for a term to appear with a lower frequency during the PS-OC Program years (green nodes) but still be connected to another term more frequently during the Program years (red edge), indicating an emerging topic area. Edges represent the co-occurrence of double-word terms.

- An edge with burst weight < 0.54 is green (below median)
- An edge with burst weight >= 0.54 or <=0.74 is colored blue (around median)
- An edge with burst weight > 0.74 is red (greater than median)

Nodes represent double-word terms and were color-coded based on a sum of their co-occurrence burst weights with connecting terms. A higher value, greater than 2.64, indicates that the term is involved in bursty co-occurences.

- A node with summed burst weight < 2.44 is green (below median)
- A node with summed burst weight >=2.44 and <=2.64 is colored blue (around median)
- A node with summed burst weight > 2.64 is red (above median)

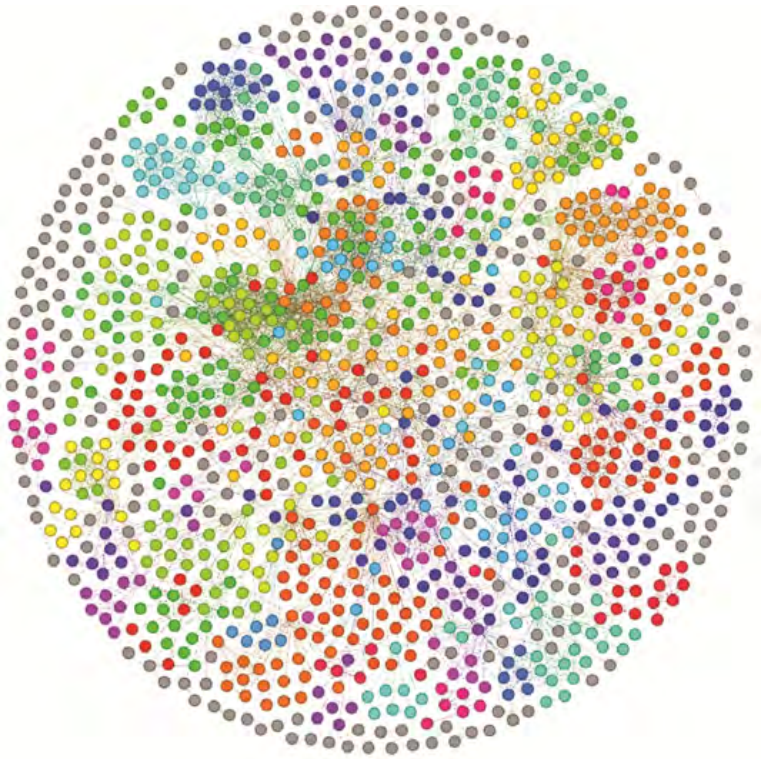


Figure 5.10. Content map of PS-OC double-word terms (node) and their co-occurrences (edges) in PS-OC publications and progress reports. The terms were clustered with an affinity propagation clustering algorithm to segment the terms into 68 clusters. The nodes are color-coded by cluster.

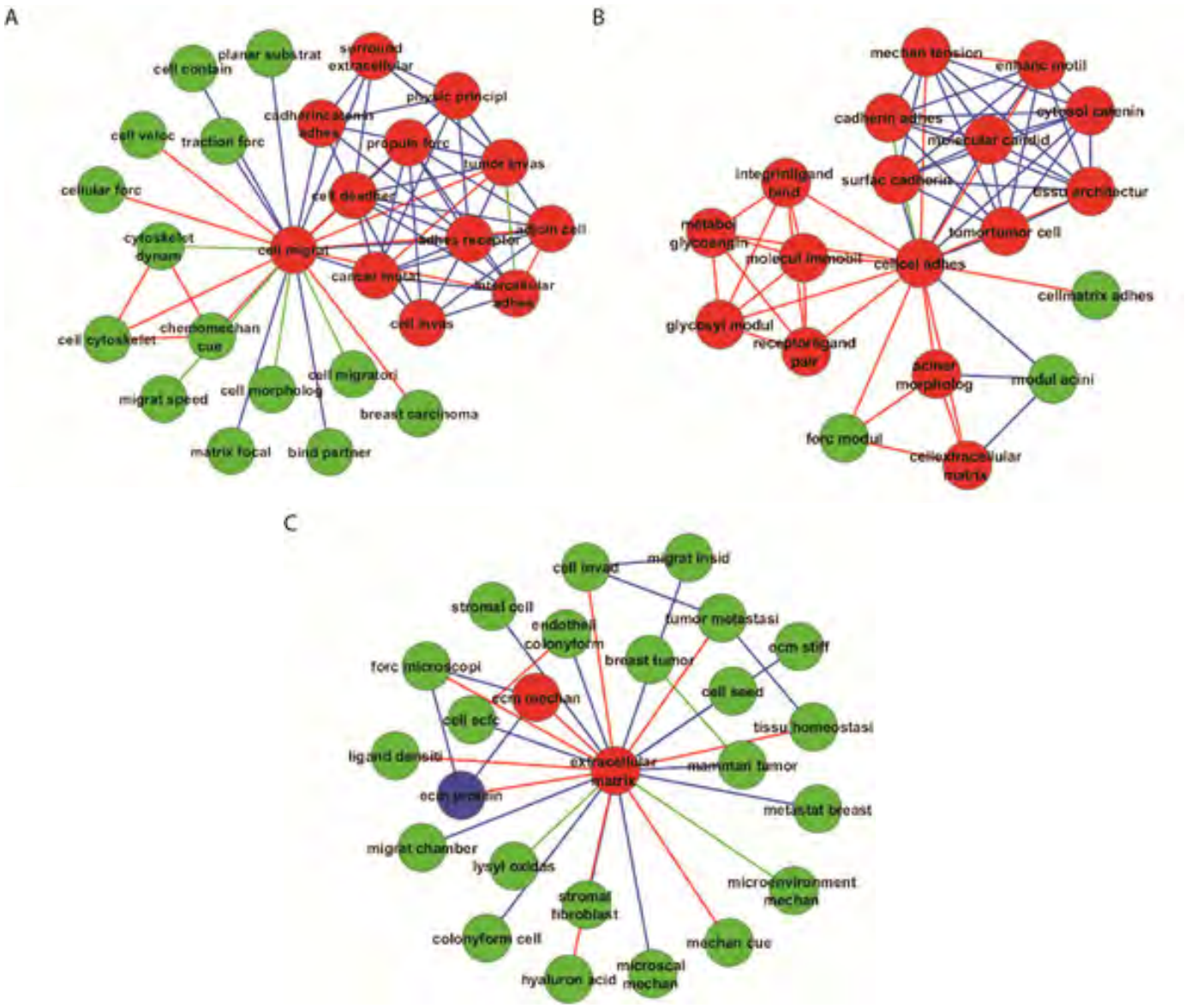



Figure 5.11. Several topic clusters pertaining to cell forces were identified as emerging during the PS-OC Program. Topics centered on (A) cell migration, (B) cell-cell adhesion, and (C) extracellular matrix are shown in detail. Red node and edges indicate the specific terms and co-occurrences in the clusters that were found to have high burst weights and indicate emergence of the topic in the PS-OC Program. Blue nodes and edges represent mean burst weights, and the green nodes and edges had low burst weights.

### *Cell Forces*

The physics of cancer is an overarching theme explored by four Centers and therefore it was unsurprising that related topic clusters were identified by the emerging term analysis. Three of these topic clusters are displayed in Figure 5.11. The first topic is clustered around "cell migration." From "cell migration" there are a number of red edges branching out to other terms, including "cellular force," a subcluster related to "cytoskeleton dynamics" and "chemomechanical cues," "cell velocity," and "extracellular adhesion." This cluster appears to highlight new findings focused on the role of mechanical cues from the extracellular matrix and the cytoskeleton on cell migration published by the UCB, Cornell, and JHU PS-OCs.

Khatau, S.B., *et al.* The distinct roles of the nucleus and nucleus-cytoskeleton connections in three-dimensional cell migration. *Sci Rep* **2**, 488 (2012).

Kraning-Rush, C.M., Califano, J.P. & Reinhart-King, C.A. Cellular traction stresses increase with increasing metastatic potential. *PLoS One* **7**, 28 (2012).

A second cluster centered around "cell-cell adhesion" (Figure 5.11B) highlights interesting emerging connections between "cell-cell adhesion" and "tissue architecture," "enhanced mobility," "mechanical tension," "acinar morphology," and "metabolic glycoengineering." The PS-OCs have recently published a few key publications that emphasize the role of cell-cell adhesion forces on architecture of tissues and mobility of cancer cells in a normal epithelium. This analysis further demonstrates that these are potential new emerging topics in the cancer field.

Lee, M.H., *et al.* Mismatch in mechanical and adhesive properties induces pulsating cancer cell migration in epithelial monolayer. *Biophys J* **102**, 2731-2741 (2012).

Tanner, K., Mori, H., Mroue, R., Bruni-Cardoso, A. & Bissell, M.J. Coherent angular motion in the establishment of multicellular architecture of glandular tissues. *Proc Natl Acad Sci U S A* **109**, 1973-1978 (2012).

Extracellular matrix (ECM) is a term that appears in multiple bursty co-occurrences. One cluster of co-occurrences is shown in Figure 5.11C. While many scientists are investigating the role of ECM on cancer progression and metastasis, the measurement of the mechanical properties of the ECM during cancer progression is potentially a new topic emerging within the PS-OC Network. Groups at the UCB and JHU PS-OCs have published evidence that the mechanical properties of the tumor ECM change with increase progression using atomic force microscopy measurements.

Lopez, J.I., Kang, I., You, W.K., McDonald, D.M. & Weaver, V.M. In situ force mapping of mammary gland transformation. *Integr Biol* **3**, 910-921 (2011).

### *Evolutionary Dynamics*

During the development of the PS-OC Program, there was a large emphasis placed on looking at cancer through an evolutionary lens. Common principles used in evolutionary sciences such as population dynamics are being applied to cancer within the PS-OC Network. "Evolutionary dynamics," "evolutionary force," and "evolutionary mathematics" were double-word terms extracted with the text mining that relate to this theme. One topic cluster was focused around "evolutionary dynamics" (Figure 5.12A). While many of the terms in this cluster are not new terms in cancer research, the co-occurrence of these terms is unique. The application of evolutionary dynamics to investigate intratumor heterogeneity, cancer prevention, and acquired resistance is potentially an emerging area of research using physical science concepts.

Basanta, D., Gatenby, R.A. & Anderson, A.R.A. Exploiting evolution to treat drug resistance: Combination therapy and the double bind. *Molecular Pharmaceutics* **9**, 914-921 (2012).

Iwasa, Y. & Michor, F. Evolutionary dynamics of intratumor heterogeneity. *PLoS One* **6** (2011).

### *Stochastic Dynamics*

The third theme identified by emerging topic analysis is the stochastic dynamics of single cells. A major theme in the PS-OCs is de-convoluting the complexity of cancer using physical sciences approaches. Stochastic dynamics and models have been widely used in physical sciences to explain complex mechanisms. Interestingly, "stochastic models," "stochastic dynamics," and "stochastic mathematics" were double-word terms emphasized in three different topic clusters. One of these topic clusters displayed in Figure 5.12B indicates that the co-occurrence of stochastic dynamics and single-cell transcription is a "bursty" topic. Researchers at the MIT and DFCI PS-OCs have both published stochastic dynamics and mathematical models to explain single-cell heterogeneity in processes such as stem cell division and hematopoietic cancers. The convergence of stochastic dynamics with these cancer-related single-cell processes potentially reflect a new emerging area in cancer research utlizing a PSP.

Hanna, J., *et al.* Direct cell reprogramming is a stochastic process amenable to acceleration. *Nature* **462**, 595-601 (2009).

## 5.5 Broader Impacts of PS-OC Research

The goal of this section is to answer the question, "Have approaches and topics from the PS-OC Program been disseminated outside of the PS-OC Network?" While it is premature to assess the broad impacts of the PS-OC Program on cancer research, it is feasible to begin monitoring the dissemination of research topics in publications and grants using publication search tools and NIH grant databases. Discovery Logic identified several "bursty" topics in PS-OC publications and progress reports based on the double-word co-occurrences discussed in Section 5.4 above. Using these topics, advanced searches were completed using Web of Science to query the impact of PS-OC publications on all publications in these topical areas. The results highlight two broad topics where the PS-OC Program has already begun making contributions to the field: evolutionary dynamics and the role of mechanics in cancer. Not surprisingly, both of these topic areas were identified by PS-OC investigators or bibliometric analysis as being key advancements by the PS-OC Network.

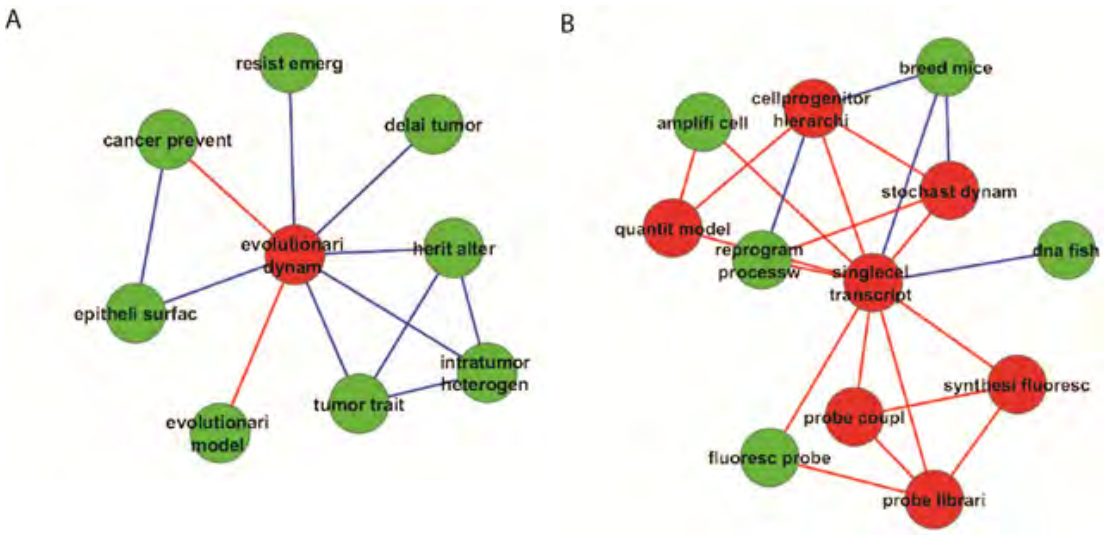



Figure 5.12. Topic clusters pertaining to (A) evolutionary dynamics and (B) stochastic dynamics that were identified as emerging concepts in the PS-OC Program. Red node and edges indicate the specific terms and co-occurrences in the clusters that were found to have high burst weights and indicate emergence of the topic in the PS-OC Program, blue nodes and edges represent mean burst weights, and green nodes and edges indicate low burst weights.

### 5.5.1 Broader Impact Metrics

Using Web of Science, Discovery Logic identified publications covering PS-OC topic areas identified in section 5.4. A query was set up to identify publications where both terms (A and B) appeared in an abstract and/or title. Synonyms and stemmed terms were considered in the search. To increase the number of publications, single-term synonyms were considered, and double-word terms were not placed in quotations. In total, more than 33 term-term occurrences and their variants were queried in a total of 669 individual queries. Two of these queries are highlighted in Table 5.1.

To determine the impact of PS-OC publications on specific topic areas three metrics were calculated for each of the publication searches. (1) The number of PS-OC publications per search. (2) The number of primary citations (i.e., non-PS-OC publications directly citing PS-OC publications). (3) The number of secondary citations (i.e., non-PS-OC publications citing primary citations).

Table 5.1. Examples of Two Queries Performed in Web of Science to Quantify the Impact of PS-OC Research in Topical Areas.

| Topic | Term 1 | Term 2 |
|---|---|---|
| A | Cell Invasion | ECM Stiffness |
| | Cell Morphology | Ligand Density |
| | Metastasis or Morphogenesis | Mechanotransduction |
| B | Evolutionary Dynamics | Epigenetic Alterations |
| | | Intratumor Heterogeneity |

### 5.5.2 Results

As identified in Section 5.4, there were three broad topic areas where the PS-OC Network appears to be publishing more frequently. This includes stochastic dynamics, evolutionary dynamics, and cell forces. This section examines the dissemination of these topic areas into the broader scientific community. A large number of searches were performed to query the number of publications in each topic area. In some cases, topic clusters were combined to increase the number of publications per topic to generate a more robust analysis. After complete analysis of multiple topics, two topic areas were chosen to examine in more depth for this study. Examples of the terms used in these two topic searches are listed in Table 5.1. The first topic is centered on cell forces co-occurence clusters (Figure 5.11). Specifically, these searches focused on the role of ECM stiffness, ligand density, and mechano-transduction on cell behaviors (invasion, morphology, metastasis, and morphogenesis). The second topic examined centers around employing evolutionary dynamics to understand epigenetic alterations or intratumor heterogeneity.

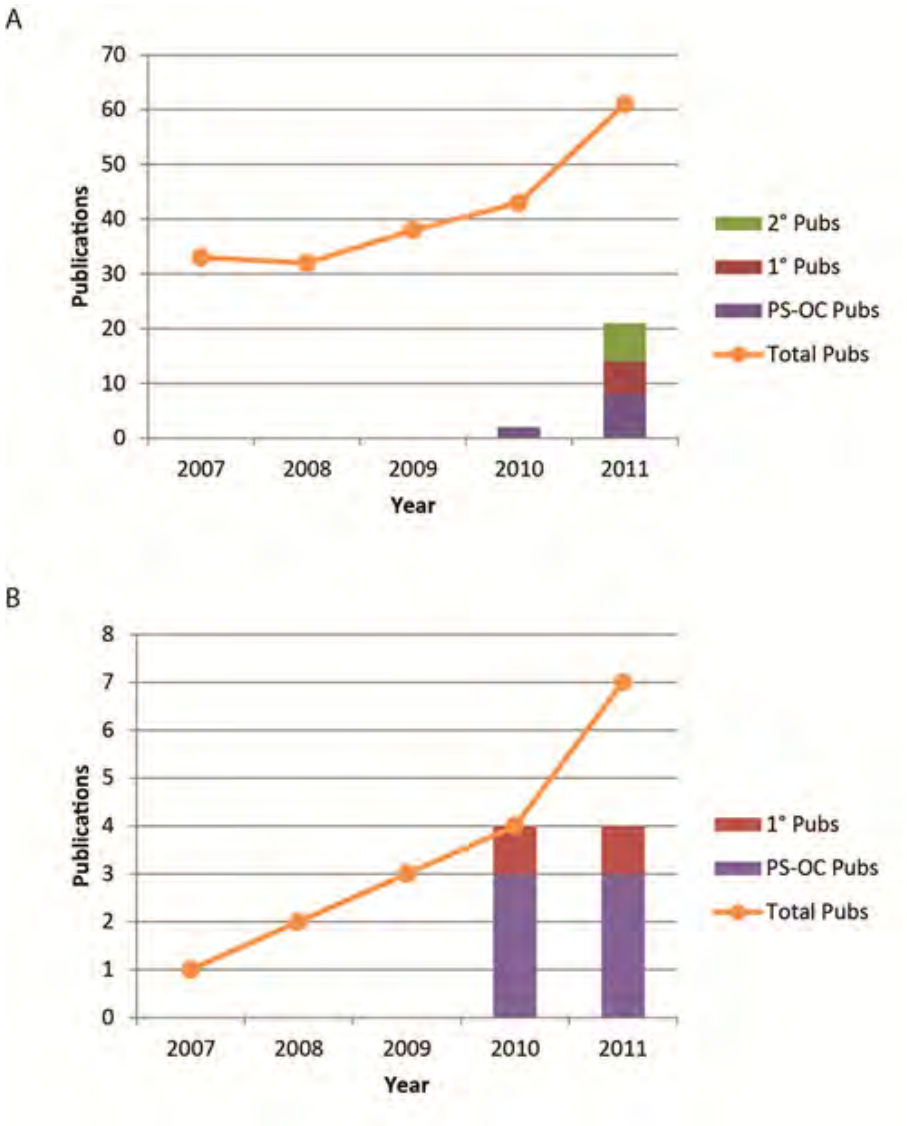



Figure 5.13. Impact analysis of PS-OC topic clusters based on publication data from Web of Science.

For the cell forces topic, a total of 352 publications covering the topic area were identified from 2000 to 2012 (Figure 5.13A). Prior to the PS-OC Program, the number of publications in this area was increasing slowly. While there was interest in the topic, there was never a large increase in publications. Starting in 2010, the PS-OC Network appears to alter the publication dynamics of this area. In 2011, the number of publications jumped 1.5-fold from 40 publications per year to 60 publications per year, representing the largest yearly increase in publications in this topic area. Of the 60 publications in 2011, 20 of them were PS-OC publications or publications citing PS-OC publications (Figure 5.13A).

There were a smaller number of publications documenting the use of evolutionary dynamics in cancer research. Since 2000, only 20 publications were identified through Web of Science queries and half of these publications have occurred in 2010 and 2011. The PS-OC Network contributed to all of these publications in 2010 (PS-OC publication or primary citation) and half of the publications in 2011. The PS-OC Network research and publications appear to be driving publications with terms in this topic area.

## 5.6 Summary

The PS-OC Program's primary objective is to bring new scientists and perspectives to cancer research. With new perspectives and technology from physical sciences, the Program aims to generate new datasets, theories, and knowledge in the cancer field. OPSO program officials have partnered with Discovery Logic and other collaborators to complete a thorough assessment of new knowledge, theories, and topics produced by the PS-OC Program after just three years of operation. While many indicators of new knowledge and potential impact on the field are preliminary, there is already some early evidence of new topic areas emerging in the PS-OC Program and disseminating into the broader cancer research field. Potential new topic areas converge physical sciences terms, such as "cellular forces" or "stochastic dynamics," with oncology specific terms. PS-OC Program funding and unique Network activities (e.g., the Cell Line Pilot Study and Trans-Network Projects) have already contributed to the formation of new collaborations and teams that combined resources and technology to produce novel datasets, such as the ability to dynamically measure the elasticity of cells within a tumor in vivo. New and expanded theories of cancer have started to evolve from principles in polymer physics, control theory, and ecology. The full impact of these theories and datasets will be observed over time. Publications summarizing these concepts are already accumulating citations. The next years of the PS-OC Program will largely focus on testing and evolving many of these theories and hypotheses experimentally.

# 6. Collaborations and Team Science

Along with providing input on scientific focus, the series of Think Tank workshops that stimulated the development of the PS-OC Program helped shape the overarching goals of the Program. Based on input from Think Tank participants and NCI program staff, one of the milestones established for the PS-OC Program is to establish an unprecedented Network of Centers and transdisciplinary teams focused on solving cancer problems. The concept of an unprecedented Network of Centers refers to the inclusion of programatic elements that specifically promote the integration of physical sciences and oncology. A number of components were incorporated into the PS-OC Program to facilitate meeting this milestone. First, the program was organized as a series of Centers, each encompassing transdisciplinary teams working on integrated projects that together formed a broader Network focused on addressing problems in cancer with a PSP. Second, program components were included to facilitate interaction within Centers, including the combined leadership of a physical scientist and cancer biologist, meetings of Center Advisory Committees, and the availability of Center and Outreach Pilot Project funds to allow the Centers to continue to evolve. Third, a series of components were included to facilitate interaction within the Network, including twice monthly meetings of the PS-OC Steering Committee, an Annual PS-OC Network Investigators' Meeting, and the availability of Trans-Network funds to support collaborative projects within the Network. To comprehensively and prospectively measure the progress toward this milestone, PS-OC investigators were asked to report twice a year on the state of their PS-OC-relevant collaborations. Additionally, during the third year of the program, PS-OC investigators were surveyed to evaluate how the PS-OC Program and its various components helped facilitate these collaborations. The data provided by these reports and surveys include information on the numbers of collaborations being established, collaboration outcomes, transdisciplinary publications emerging from the collaborations, the role of the PS-OC Program in facilitating collaborations, and challenges and lessons learned.

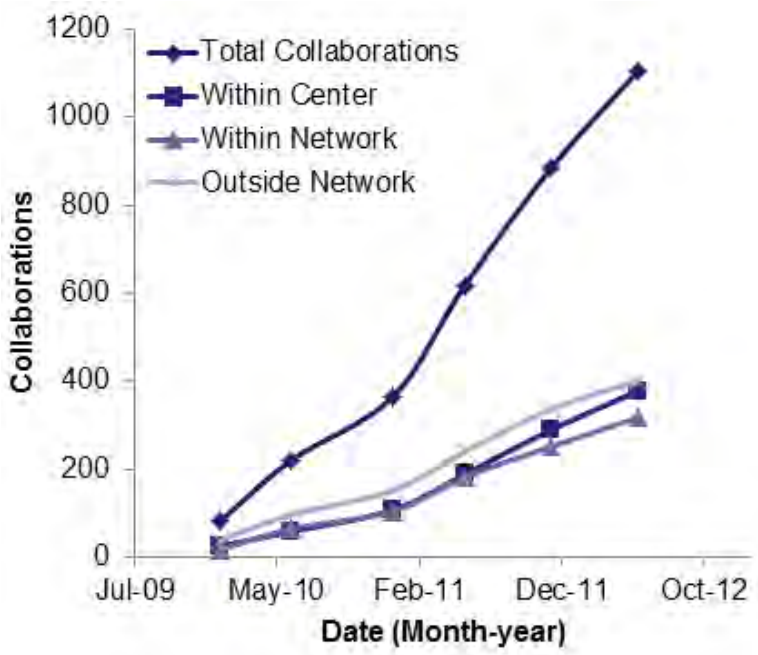



Figure 6.1. The rate of PS-OC collaboration formation increased in the second year of the program. The cumulative number of PS-OC collaborations reported in each progress report is plotted. Diamonds represent total collaborations, squares represent within Center collaborations, triangles represent within Network collaborations, and Xs represent outside of Network collaborations.

## 6.1 PS-OC Network Collaborations

In each progress report, PS-OC investigators are asked to report on all PS-OC-related collaborations in which they are involved. Investigators are asked to provide information about the state of the collaboration, whether the collaboration is within the Center, within the PS-OC Network, or outside of the PS-OC Network, and a brief description of the collaboration. This information has been used to enumerate the total number of collaborations that have developed from the PS-OC Program. Figure 6.1 shows the cumulative number of collaborations over each reporting period. These data have been hand-annotated to remove duplicate information so that a collaboration appears in the graph only the first time it appears in a progress report. The graph illustrates an increased rate of collaboration formation starting with the fourth progress report, indicating that the PS-OC Network took about 1 to 1.5 years to mature to the state that collaborations could more effectively form.

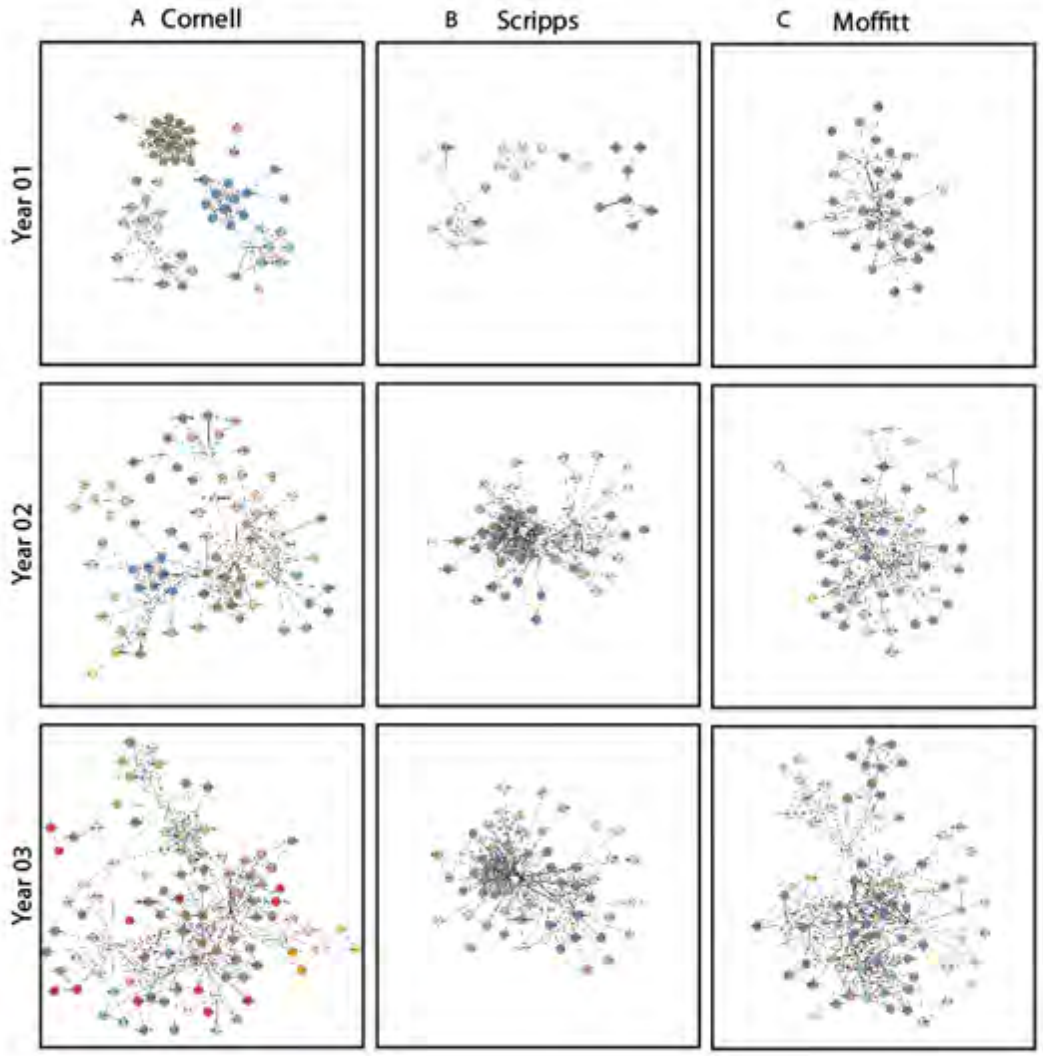



Figure 6.2. Centers expand and larger and more connected over the course of the PS-OC Program. iTRAQR was used to plot the network interaction maps of the (A) Cornell, (B) Scripps, and (C) Moffitt PS-OCs over time. Network interaction maps represent all within-Center and within-Network collaborations. Year 01 represents January and June 2010 progress reports, Year 02 represents December 2010 and June 2011 progress reports, and Year 03 represents December 2011 and June 2012 progress reports. The color of the nodes represents the project an investigator is involved in within the Center. Investigators involved in more than one project are denoted with a white node.

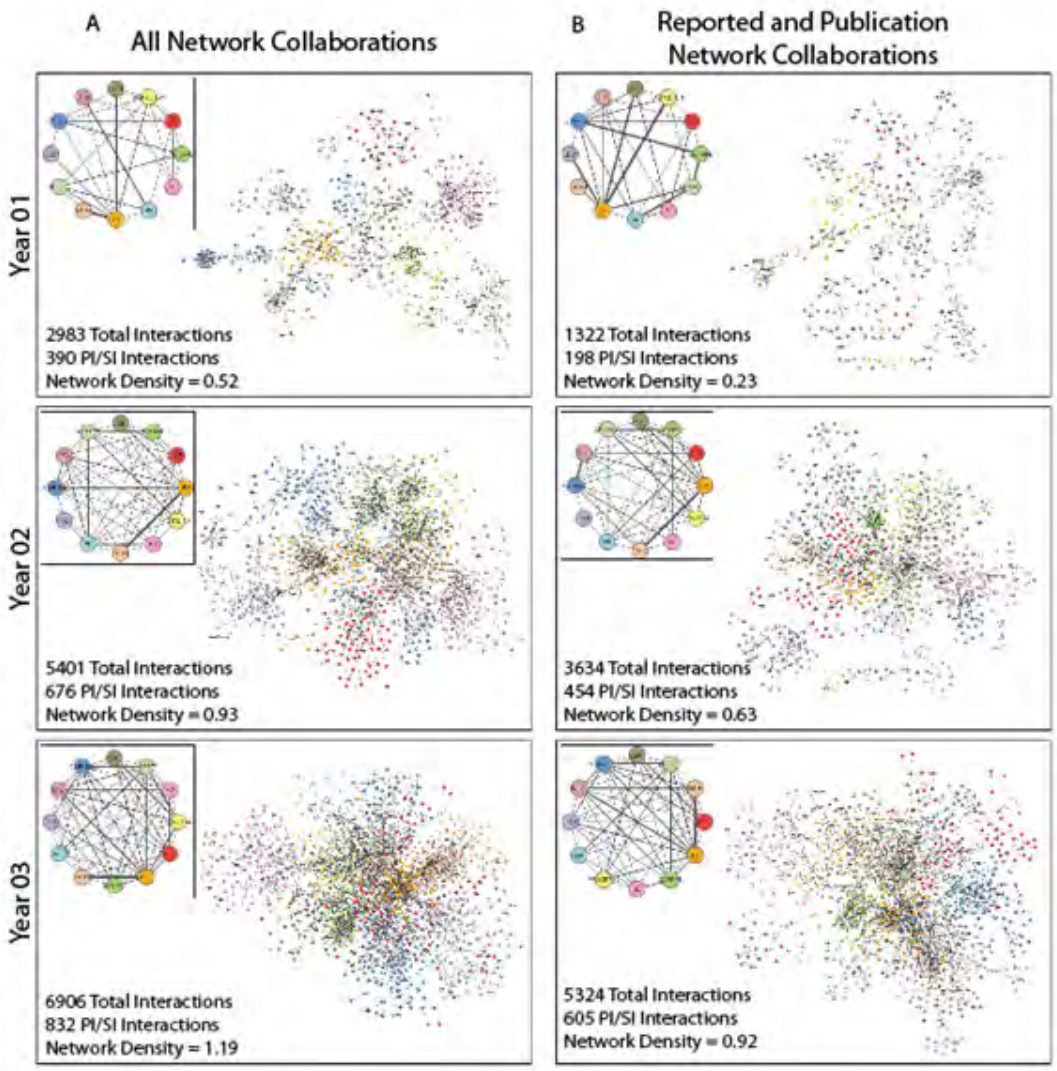



Figure 6.3. The landscape of the PS-OC Network becomes more integrated over the course of the PS-OC Program. iTRAQR was used to plot the network interaction maps based on (A) all collaboration types and (B) reported and authorship collaborations over time. Insets represent a summary of all of the interactions on a Center level. Year 01 represents January and June 2010 progress reports, Year 02 represents December 2010 and June 2011 progress reports, and Year 03 represents December 2011 and June 2012 progress reports. Node color represents the PS-OC with which an investigator is associated.

The data from the PS-OC progress reports has been uploaded to the iTRAQR to be used for more sophisticated analysis. iTRAQR can track three types of collaborations: (1) collaborations between investigators that contribute to the same PS-OC project; (2) collaborations reported by investigators; and (3) collaborations inferred from co-authorship. The iTRAQR network analysis tool was used to investigate the collaboration and integration within individual Centers. Plotting the network interaction maps for each PS-OC reveals that the Centers are both expanding and becoming more connected over time (Figure 6.2). Evaluation of the Center collaborations over time revealed two types of dynamics. Some Centers, including Cornell and Scripps, were initially only loosely integrated, and through the first three years of the PS-OC Program these Centers have both connected and expanded (Figure 6.2A-B). Other Centers, including Moffitt, initially reported a core set of integrated investigators that has expanded overtime through initiating Center Pilot Projects, Outreach Pilot Projects, Trans-Network Projects, and other collaborations (Figure 6.2C).

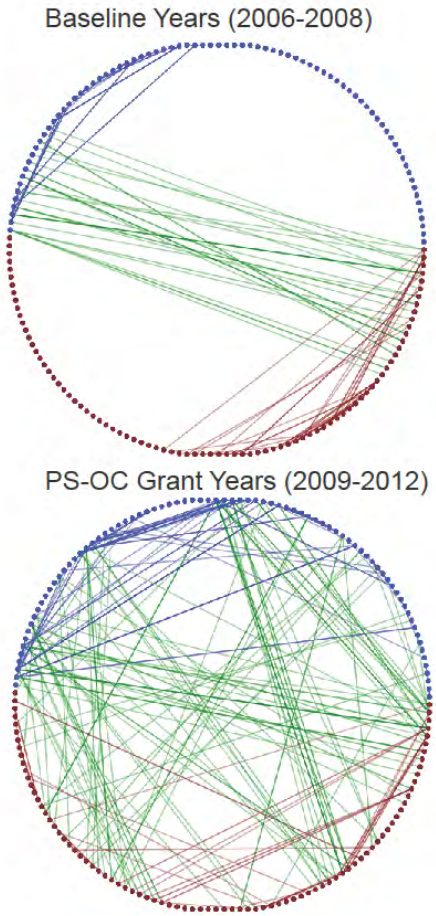



**Figure 6.4.** PS-OC investigators authored more cross-disciplinary publications during the PS-OC grant years than the years preceding the program. Co-authorship information was used to plot interaction between 262 key PS-OC investigators in (A) the three years preceding the PS-OC Program and (B) the first three years of the PS-OC Program. Blue dots represent physical scientists (134), and red dots represent cancer biologists/oncologists (128). Blue lines represent co-authorship collaborations between two physical scientists, red lines represent co-authorship collaborations between cancer biologists, and green lines represent cross-disciplinary co-authorship collaborations.

The iTRAQR network analysis tool was also used to examine the evolution of the PS-OC Network-wide collaboration landscape. Collaborations and integration of the Network were investigated using all collaboration types or only reported and authorship collaborations (Figure 6.3). Qualitatively, it is clear that over the first three years of the PS-OC Program the accumulation of collaborations illustrated in Figure 6.1 has resulted in a more integrated Network of investigators (Figure 6.3). When considering all PS-OC collaboration types, the Network density, a measure of the total interactions versus all possible interactions, has more than doubled from year 1 to year 3. When only reported and authorship collaborations are measured, the Network density has increased more than four-fold over the first three years of the program. Similar trends are seen when only looking at the collaborations reported for the Center PIs and SIs. Taken together, the collaboration data illustrate that collaborative teams have become more connected at both the Center and Network levels. The goal will be to see if this level of collaboration can increase or at least be sustained over time.

## 6.2 PS-OC Transdisciplinary Collaborations

To evaluate the impact of the PS-OC Program on transdisciplinary collaborations, the collaboration history of a set of 262 key PS-OC investigators was examined for the PS-OC grant years and the three years preceding the program. The 262 investigators were self-identified as either physical scientists (134) or cancer biologists/oncologists (128), and their publication histories were used to represent collaborations. Each publication was annotated to be (1) single author, with a single physical scientist or cancer biologist author; (2) intradisciplinary, with multiple physical scientist or cancer biologist authors; or (3) transdisciplinary, with at least one physical scientist and one cancer biologist author. A plot depicting each of the 262 investigators and his or her co-authorship collaborations illustrates an increase in both overall collaborations and transdisciplinary collaborations (green lines) during the PS-OC grant years (Figure 6.4). The statistics for the change in the collaboration landscape can be examined on either a type of collaboration level or on an investigator level. On a collaboration level, there was at least a two-fold increase (from 76 to 185) in the number of authorships (Table 6.1). Additionally, there was a 17 percent increase in the percentage of transdisciplinary publications, from 29 percent of baseline year collaborations to 46 percent of PS-OC grant year collaborations. At the investigator level, intradisciplinary collaborations remained relatively flat, with approximately 25 percent of investigators participating in intradisciplinary collaborations during baseline and grant years (Table 6.2). However, there was an approximately three-fold increase (from 12.6 percent to 34.0 percent; p-value < $1x10^{-8}$) in the percentage of investigators involved in transdisciplinary collaborations during the PS-OC grant years. Overall, the data show that the PS-OC Program has had a positive impact in promoting transdisciplinary collaborations. Additionally, the fact that the data are based on co-authored publications provides evidence that many of the collaborations fostered by the PS-OC Program are productive ones that lead to scientific advances.

**Table 6.1.** Collaboration-Level Statistics for Baseline and PS-OC Grant Years.

| | Baseline Years (2006-2008) | | Grant Years (2009-2012) | |
|---|---|---|---|---|
| | N | % | N | % |
| **Collaborations** | **76** | -- | **185** | -- |
| **Intradisciplinary Collaborations*** | 54 | 71.1% | 100 | 54.1% |
| PS authors only | 18 | 33.3% | 60 | 60.0% |
| OC authors only | 36 | 66.7% | 40 | 40.0% |
| **Transdisciplinary Collaborations*** | **22** | **28.9%** | **85** | **45.9%** |

* Intradisciplinary collaborations include two or more in-Network investigators from the same discipline.

*Transdisciplinary collaborations include at least 1 in-Network investigator from both the physical sciences and cancer biology.

**Table 6.2.** Investigator-Level Collaboration Statistics for Baseline and PS-OC Grant Years.

| | Baseline Years (2006-2008) | | Grant Years (2009-2012) | |
|---|---|---|---|---|
| | N | % | N | % |
| **Investigators** | 262 | – | 262 | – |
| **Intradisciplinary Co-Authors*** | 67 | 25.6% | 73 | 27.9% |
| **Transdisciplinary Co-Authors*** | 33 | 12.6% | 89 | 34.0% |

* Intradisciplinary co-authors are those who authored at least one publication with another in-Network investigator of the same discipline.

*Transdisciplinary co-authors are those who have authored at least one publication with another in-Network investigator of a different discipline than him/herself.

## 6.3 Collaboration Productivity

To get a more in-depth understanding of PS-OC collaborations, Center PI and SIs, investigators, and trainees were asked to respond to a series of survey questions focused on the nature of the transdisciplinary collaborations, the outcome of these collaborations, and how these collaborations were shaped by the PS-OC Program. The first aim of this survey was to determine the composition of PS-OC collaborations in terms of who participated in the collaborations, what their roles were, and the effectiveness of the collaborations. PS-OC participants were asked to identify "a successful transdisciplinary collaboration" that they were involved in as part of the PS-OC Program and to indicate how many participants were involved in the collaboration (Figure 6.5A). The data illustrated a bimodal distribution with a small peak of two-person collaborations and a larger peak of collaborations involving four to seven collaborators. The bimodal distribution suggests that effective physical sciences-oncology collaboration occur at both small and large scales. The survey also indicated a shift to larger collaborative teams during the PS-OC Program compared to the teams they previously worked with (Figure 6.5B). It is possible that the increase in team size reflects the diverse expertise required in a transdisciplinary collaboration.

PIs and SIs, project investigators, and trainees were then asked to indicate the different roles that they played within a transdisciplinary collaboration (Table 6.3). Three distinct clusters of roles were identified. The first cluster of roles involved leadership and project direction and were mainly taken on by Center PIs and SIs and to a lesser extent by project investigators. The second cluster of roles involved providing critical technologies and reagents for a collaboration, and these roles were shared more or less equally among all three groups. The third cluster involved data analysis and project participation, and these roles were handled mainly by trainees and to a lesser extent by project investigators.

Next, participants were asked to rate a variety of aspects of the collaboration (Figure 6.5C). All aspects of the transdisciplinary collaborations from scientific impact and productivity to a number of metrics of team science were rated excellent by 75 percent to 85 percent of respondents. Overall, the responses to this set of survey questions illustrate that PS-OC participants are forming transdisciplinary collaborative teams of a range of sizes in which individuals have relatively well-defined roles and teams are productive and working well together.

The second aim of conducting these surveys was to define the outcomes of the PS-OC transdisciplinary collaborations and to identify the components of the collaborations that were essential for success. Participants were asked to identify all outcomes from the transdisciplinary collaboration identified above (Figure 6.6A). Nearly 80 percent of respondents indicated that the collaboration was ongoing and had generated new knowledge, suggesting that the majority of the collaborations have been productive. Additionally, 40 percent to 50 percent of respondents indicated that collaborations have led to publications, presentations, and new projects or directions, providing some concrete measures of success. Participants were then asked to identify critical aspects of the collaboration required to facilitate the outcomes described above (Figure 6.6B). More than 70 percent of respondents indicated that a transdisciplinary collaboration and support from the PS-OC Program were essential to achieving the outcomes, and nearly 60 percent of respondents indicated that all team members played an essential role. Only 10% or fewer of the respondents indicated that each of these collaboration attributes was not essential for success. Overall, these results show that these are effective collaborations that produce outcomes that would not be possible in the absence of the transdisciplinary nature of the collaboration.

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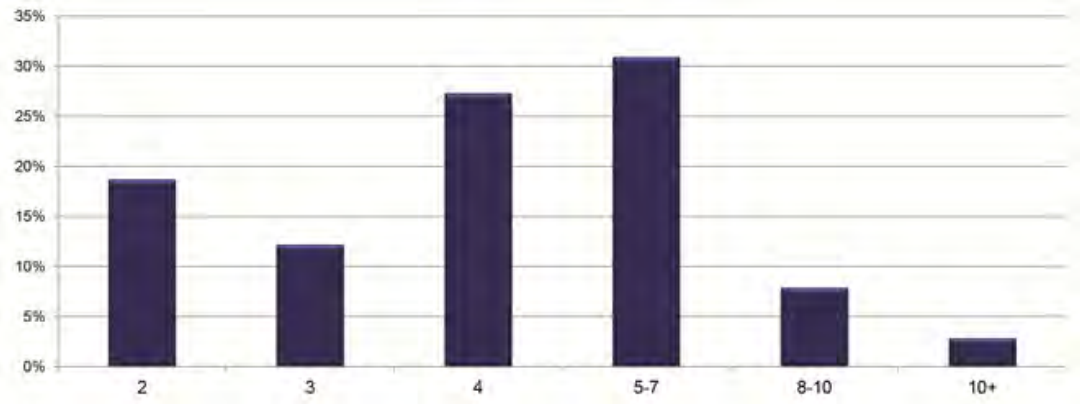


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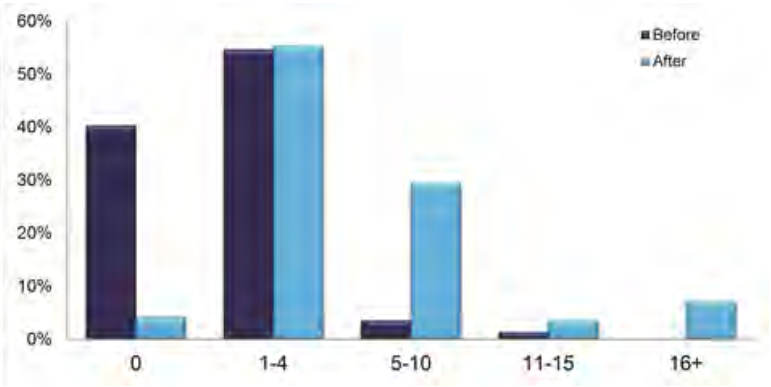


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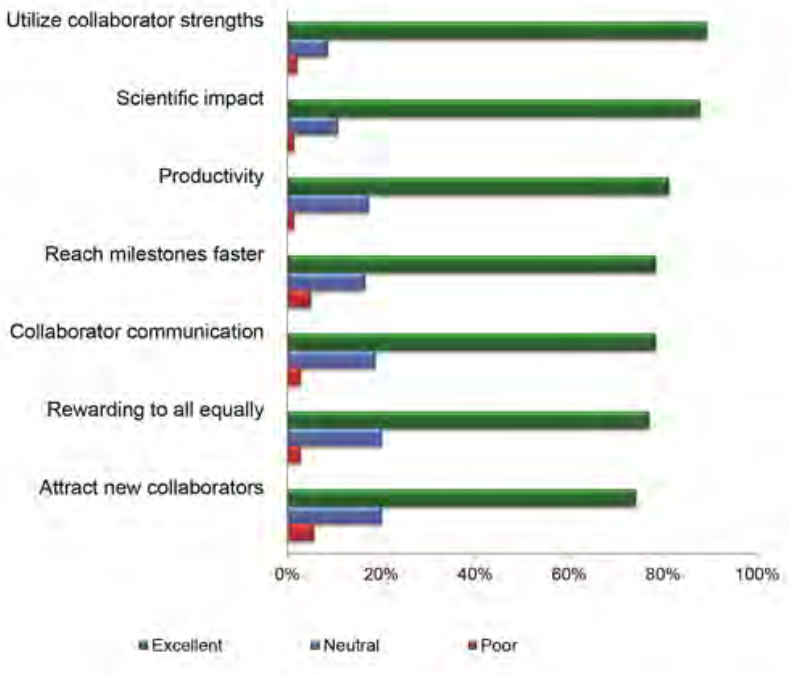


**Figure 6.5.** PS-OC investigators form effective transdisciplinary teams of a range of sizes. Participants responded to survey questions assessing (A) the size of PS-OC transdisciplinary collaborative teams, (B) the size of teams before and during the PS-OC Program, and (C) the effectiveness of these collaborations. In B, dark blue bars represent collaborations prior to the PS-OC Program, and light blue bars represent collaborations during the PS-OC Program. In C, green bars represent excellent, blue bars represent neutral, and red bars represent poor.

Table 6.3. Roles Played by Different Groups of PS-OC Investigators in Transdisciplinary Collaborations.

| | PI/SI | Project Investigator | Trainee |
|---|---|---|---|
| Provide Strategic Direction | 82% | 68% | 32% |
| Organize Team Communication | 71% | 36% | 15% |
| Leader | 71% | 36% | 8% |
| Advisor | 53% | 38% | 0% |
| Create Reports | 53% | 28% | 27% |
| Communicate to Stakeholders (i.e., NCI) | 53% | 17% | 5% |
| Interface with Institutional Leadership | 47% | 17% | 4% |
| Provide Training | 35% | 34% | 12% |
| Provide Technology or Skill | 65% | 72% | 64% |
| Provide Cells or Reagents | 29% | 43% | 29% |
| Participant | 18% | 51% | 63% |
| Data Analysis | 35% | 38% | 60% |
| Combine Data | 24% | 23% | 31% |

The final aim of the survey process was to understand how the PS-OC Program best facilitates the formation of these effective transdisciplinary collaborations and to identify key challenges to forming such collaborations. Participants were asked to rate the effectiveness of a variety of PS-OC events and infrastructure in facilitating the development of transdisciplinary collaborations (Figure 6.7A). Respondents indicated that the most effective PS-OC activities for facilitating the formation of collaborations were the Annual PS-OC Network Investigators' Meeting and other PS-OC workshops and symposia. Two other mechanisms that the majority of respondents considered very effective in facilitating collaborations were the PS-OC Pilot and Trans-Network Project programs. The PS-OC Outreach Pilot Projects and Data Jamboree were considered less effective than the other programs.

PS-OC participants were also asked to describe the most significant challenges in establishing effective transdisciplinary collaborations and to assign a severity score for each challenge (Figure 6.7B). The most commonly identified and highest severity concern was a lack of funds to support the collaboration. The other common challenges identified related to team interaction and function, including differences in goals, lack of defined roles, and difficulty communicating across disciplines. It is clear that having PS-OC investigators meet face to face at meetings is essential to developing a strong Network. Additionally, the responses indicating the importance of the PS-OC Pilot and Trans-Network Projects and the challenge of needing additional funds suggest that these innovative program components are also critical for integrating and growing the PS-OC Network.

Finally, the team-based challenges identified by the survey suggest that more team-building activities as part of PS-OC meetings might further enhance the network of transdisciplinary collaborations.

## 6.4 Summary

Overall, analysis of the collaboration data from progress reports and responses to survey questions focusing on the effectiveness of PS-OC transdisciplinary collaborations demonstrate progress toward the milestone of establishing an unprecedented Network of Centers and transdisciplinary teams focused on solving cancer problems. Over the first three years of the PS-OC Program, individual Centers have become more integrated and have grown to include new disciplines and collaborators, and the broader PS-OC Network has become more connected. Additionally, there has been an increase in transdisciplinary publications by PS-OC investigators compared to the years preceding the PS-OC Program. Finally, the responses to survey questions indicate that PS-OC investigators are forming strong transdisciplinary collaborative teams that have allowed them to make progress addressing important scientific questions that would not otherwise have been possible.

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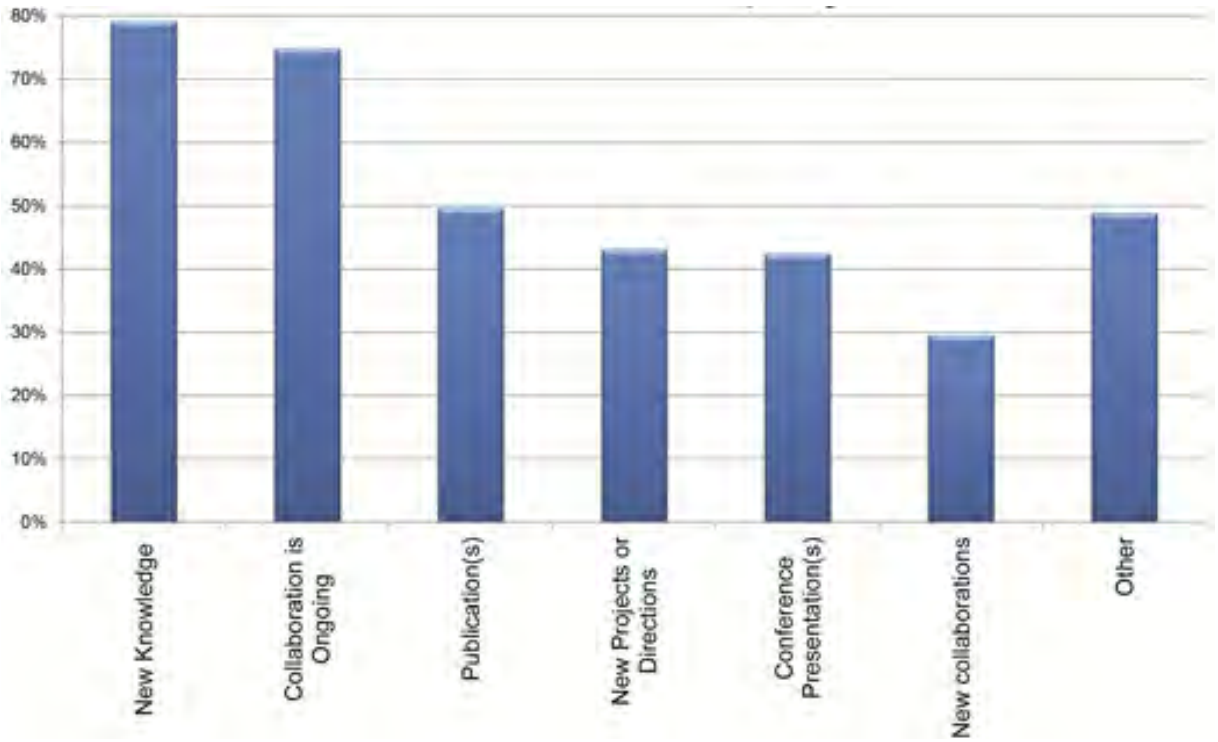


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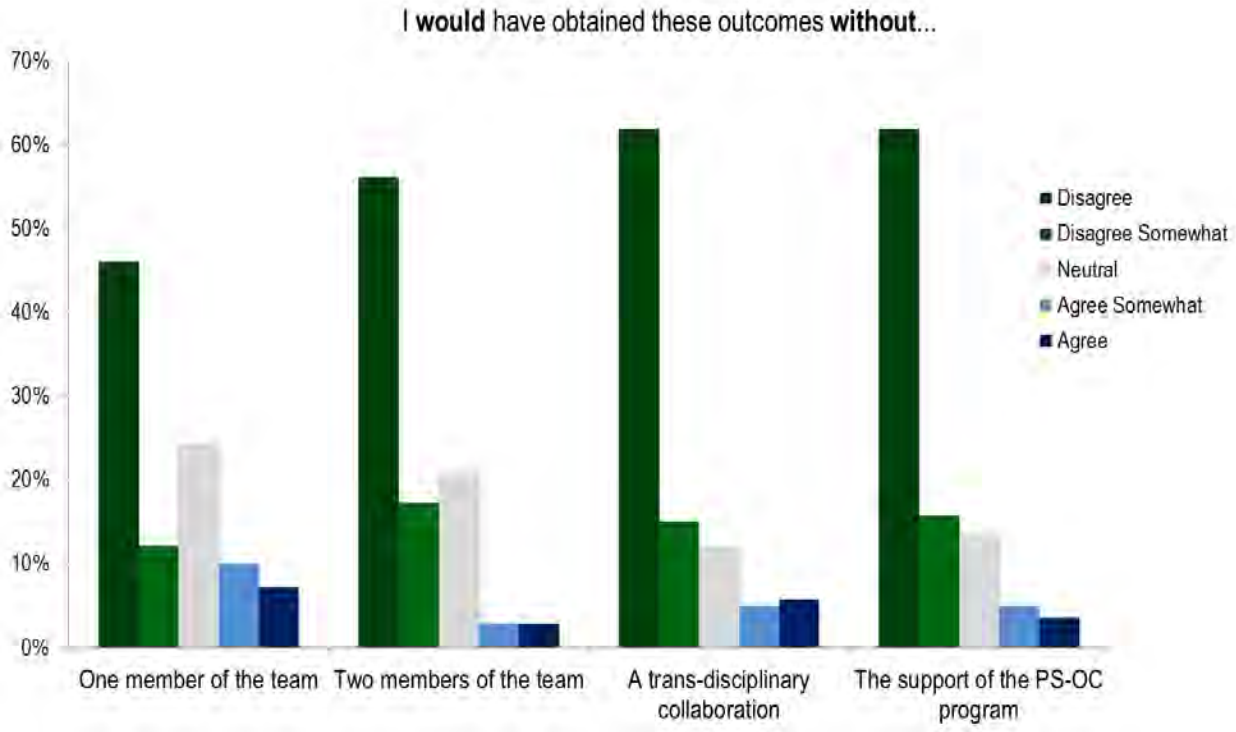


Figure 6.6. PS-OC collaborations produce outcomes that would not be possible in the absence of the transdisciplinary collaboration. Participants responded to survey questions assessing (A) the outcomes of PS-OC transdisciplinary collaborations and (B) what components of the collaboration were essential for success. In B, green bars represent disagree, blue bars represents neutral, and red bars represent agree.

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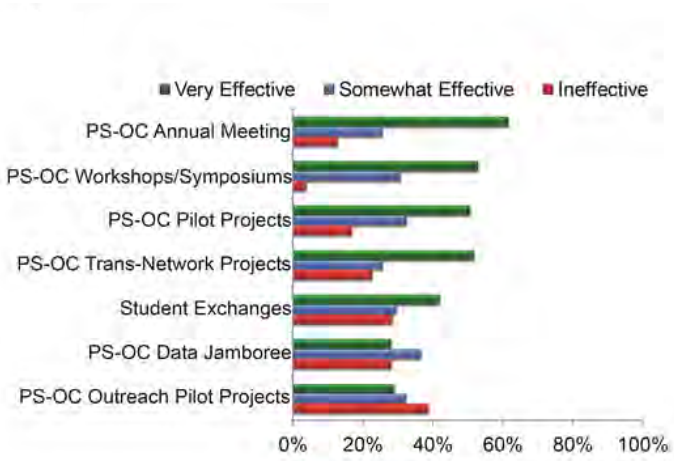


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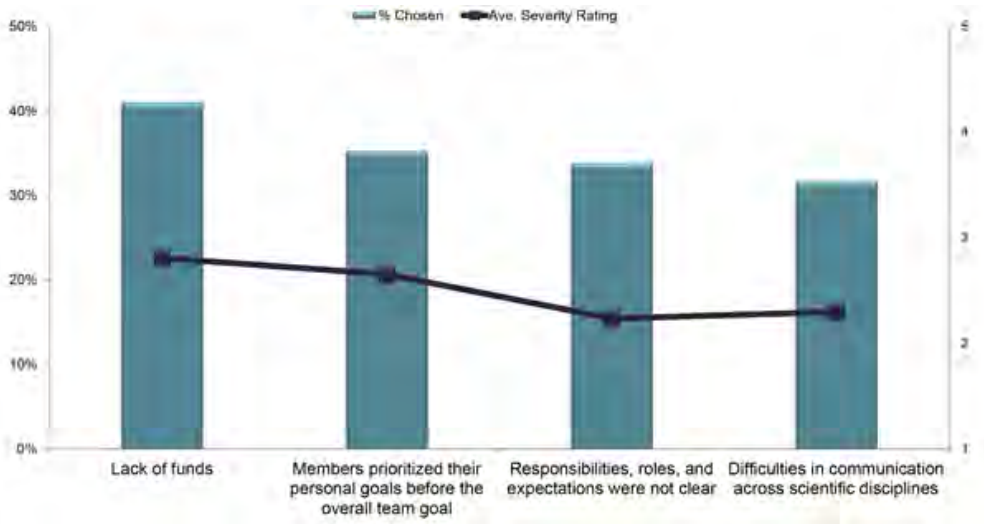



**Figure 6.7.** PS-OC Program activities and infrastructure promote the formation of effective transdisciplinary collaborations. Participants responded to survey questions assessing (A) the role of a variety of PS-OC Program components in facilitating the formation of transdisciplinary collaborations and (B) major challenges that impact the formation of effective collaborations and the severity of these collaborations. In A, green bars represent very effective, blue bars represent somewhat effective, and red bars represent ineffective. In B, blue bars represent the frequency that a challenge was indicated, and the dark blue line represents the average severity rating for that challenge.

# 7. Infrastructure Built Within and Outside the PS-OC Network

Progress toward the PS-OC Program's goals has been facilitated by the building of new infrastructure by each Center, often with the assistance of OPSO program officials. This section discusses the strategies and activities implemented at the Centers to build infrastructure that supports the achievement of the program goals, including new leveraged funding and new physical infrastructure. It also discusses identifiable results to date using information provided by progress reports and a survey completed in the spring of 2012 to measure the impact of new infrastructure toward PS-OC Program goals, the impact of PS-OC funding on new infrastructure and resources, and the need for the continued support of infrastructure in the field of physical sciences in oncology.

## 7.1 New Leveraged Funding

The PS-OC Program has generated leveraged funding by all 12 Centers over the past three years. The total amount of reported leveraged funding to date is more than $200 million, which includes awards from various sources including federal and state agencies, private foundations, and industrial partners (Figure 7.1). Most funds will support new research projects and technology development in the area of physical sciences and oncology. One education-specific award, a T32, was awarded to DFCI to support a "Physical Science Oncology Center Training Program." Major funding awarded to PS-OC investigators is listed below.

### Biomedical Advanced Research and Development Authority (BARDA)

- Shan Wang (USC PS-OC), Stanford Center for Magnetic Nanotechnology, $38M, 2009-2014, The major goal of this consortium contract proposal is to develop point-of-care (POC) and high-throughput (HT) triaging tools for rapid and accurate proteomic index dosimetry (RAPID) in a nuclear or radiological event

### National Institutes of Health

- Peter Searson and Martin Pomper (JHU PS-OC), $13.8M, 2010-2015
- Vadim Backman (Northwestern PS-OC), $3.7M 2011
- Denis Wirtz, Greg Longmore (JHU PS-OC), $2.7M, 2012-2017
- Cynthia Reinhart-King (Cornell PS-OC), $2.5M, 2012-2017
- Eric Holland, Franziska Michor (DFCI PS-OC), $114K, 2012

### Leukemia & Lymphoma Society

- Jonathan Licht (Northwestern PS-OC), $6.1M, 2012-2017, Chromatin Mechanisms and Epigenetic Targeting in Hematological Malignancies

Trans-Network and Pilot Projects were also successfully used to generate leveraged funding. The projects listed below were developed on the basis of preliminary data and were funded through these PS-OC mechanisms:

- Cynthia Reinhart-King (Cornell PS-OC). PLIER award (NSF/NCI): In vitro Models of Metastatic Collagen Microtracks, $400,000, 2012-2015
- Xiaozhang Wang (Northwestern PS-OC). R21 (NCI): Regulation of MicroRNA Silencing by Tumor Suppressor PTEN in Stem Cells, $201,623, 2012-2014.
- Thea Tlsty (Princeton PS-OC) and Elliot Botvinick. PLIER award (NSF/NCI): Regulation of Mammary Epithelial Signaling by Local Matrix Stiffness, $520,000, 2012-2014.
- Robert Austin (Princeton PS-OC) and Ariosto Silva (Moffitt PS-OC). R21 (NCI): A Translational Model of Evolution of Myeloma Adhesion Mediated Drug Resistance, $80,375, 2012-2014

# 7.2 New Infrastructure Built

## 7.2.1 New Physical Infrastructure Built at Institutions

### *Research Infrastructure*

PS-OC Program funding has made possible the building of new infrastructure. Most of the awardees have established Core Facilities that provide critical resources and expertise to scientists at their Centers, and in some cases, Centers across the Network. The PS-OC Core Facilities provide a range of resources such as micro- and nano-fabrication (Cornell, JHU, MIT, and Princeton PS-OCs); genomic sequencing/epigenomics analysis (Cornell, Northwestern, and Princeton PS-OCs); cell and tissue samples (ASU, Princeton, and Scripps PS-OCs); mathematical simulation/computational physics (TMHRI PS-OC); bioinformatics (Northwestern PS-OC); imaging ([JHU PS-OC], advanced intravital microscopy [TMHRI PS-OC], small animal imaging [Moffitt PS-OC]); and quantitative single-cell analysis (DFCI and MIT PS-OCs).

### *Infrastructure Supporting Transdisciplinary Collaborations*

Several Centers (TMHRI, DFCI, and Northwestern PS-OCs) have established journal clubs where physical scientists and cancer biologists convene to discuss recent advances in the scientific literature pertinent to their areas of investigation. In January 2010, the NU PS-OC had a PS-OC Science Jam with several PS-OC speakers to promote collaboration and review progress. The outcomes of the Northwestern PS-OC Science Jam were increased collaboration and the creation of a virtual journal club. The ASU PS-OC has supported transdisciplinary collaborations by organizing an ongoing series of workshops to explore questions at the interface of the physical sciences and oncology. These workshops bring together leaders from inside and outside the PS-OCs and have led to a number of fruitful collaborations.

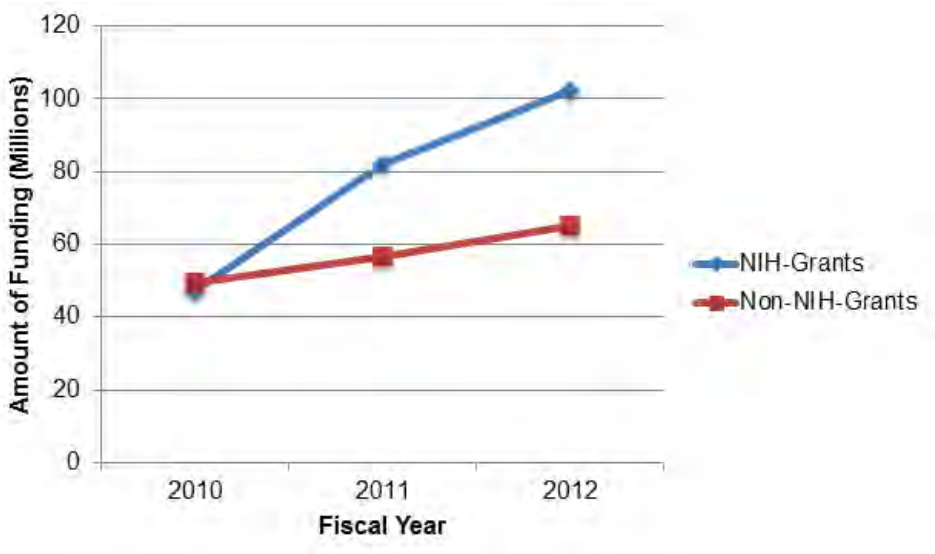



Figure 7.1. New leveraged funding accumulated by PS-OC investigators in the first three years of the PS-OC Program. Data shown are a cumulative amount of dollars broken down by NIH grants and non-NIH grants.

### *Infrastructure Supporting Transdisciplinary Education and Training*

More than 55 courses and training workshops were taught or developed with the PS-OCs to support transdisciplinary education and training. The scope of the courses ranged from individual lectures and mini-courses or modules within larger courses, to full-length graduate and undergraduate courses. A more detailed discussion of these courses is provided in Section 8.

## 7.2.2 Implementation of NCI-Recommended Activites to Build a Productive Center Infrastructure

The NCI recommended several activities to the PS-OCs to help facilitate the building of new infrastructure. Recommendations included the following:

- Strategic planning such as setting milestones, monitoring progress, and seeking advisory or community input
- Daily management and communications within the Centers
- Promoting multidisciplinary collaborations among PS-OCs
- Offering PS-OC research training programs

Nearly 90 percent of the survey respondents (PI/SIs, n=17) are fully promoting multidisciplinary collaborations among PS-OCs (Figure 7.2), consistent with the goal of building a nationwide Network of Centers. More than 70 percent of survey respondents are offering PS-OC research training programs, and more than 60 percent are conducting daily management and communications within their Centers. It appears, though, that multidisciplinary collaborations are not being promoted within the Centers, probably because these collaborations were established at the time of award and have not been emphasized in the post-award period.

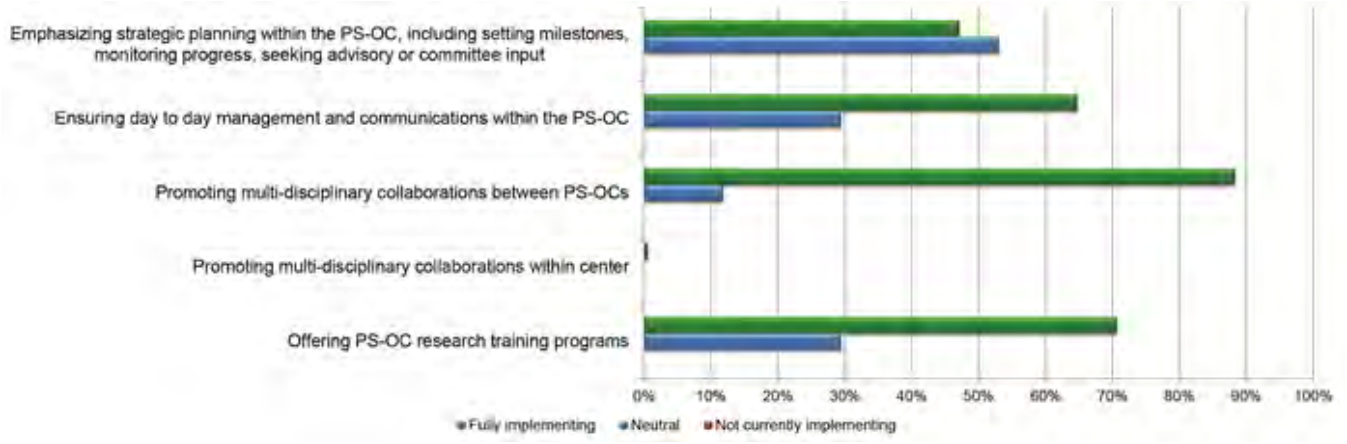



Figure 7.2. Implementation of Recommended Activities. PIs and SIs were asked, "To what extent is your Center implementing the following activities recommended by the NCI?" (n=17).

## 7.2.3 New Infrastructure Built Across the PS-OC Network

The PS-OC Network as a whole places particular emphasis on combining the strengths and infrastructure of all the PS-OCs to tackle "Big Questions" in cancer, develop new theories, integrate orthogonal datasets to gain new insights, and disseminate knowledge to the scientific community through joint workshops and seminars. Since the program's initiation, there have been a number of different projects and activities designed to enable these collaborations, including the PS-OC Annual Meeting,

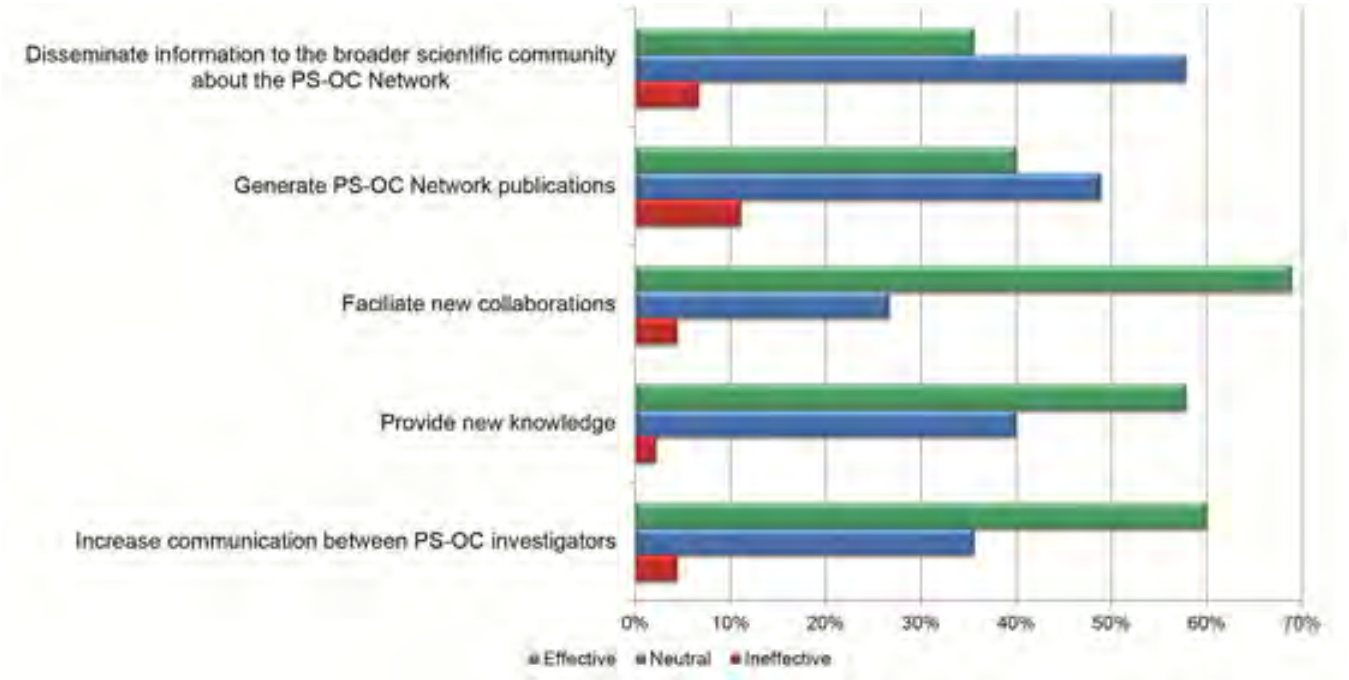



Figure 7.3. Effectiveness of Working Groups. PIs, SIs, and project investigators were asked to rate the "Effectiveness of Working Groups and Exercises in Achieving Goals" (n=64).

trans-Network projects, the Cell Line Pilot Study, PS-OC working groups, and a PS-OC investigator retreat. These activities are all supported through interactions between OPSO program officials and PS-OC investigators and have resulted in successful collaborations and innovative scientific progress.

### *Working Groups Initiate Communication and Collaborations*

The working groups and exercises led by OPSO program officials have been most successful (>50 percent of the respondents indicate as effective) in facilitating new collaborations, providing new knowledge, and increasing communication between PS-OC investigators (Figure 7.3). As discussed in Section 6, the PS-OC Annual Meeting and the Trans-Network and Pilot Projects were the most effective activities for encouraging investigators to find collaborators and start collaborations (Figure 6.7A).

### *PS-OC Network Activities Generate Innovative Scientific Ideas*

The most effective PS-OC-supported activities for encouraging investigators to generate innovative scientific ideas are the Annual Meeting and the Pilot Projects (more than 60 percent of respondents find these efforts to be effective; Figure 7.4). Other activities such as student exchanges, Outreach Pilot Projects, and Young Investigator Trans-Network Projects were not deemed to be as effective by the survey respondents.

When surveying trainees only, the activities that best encouraged them to generate innovative scientific ideas were the PS-OC annual meeting and the PS-OC related workshops, bootcamps, and symposia (data not shown).

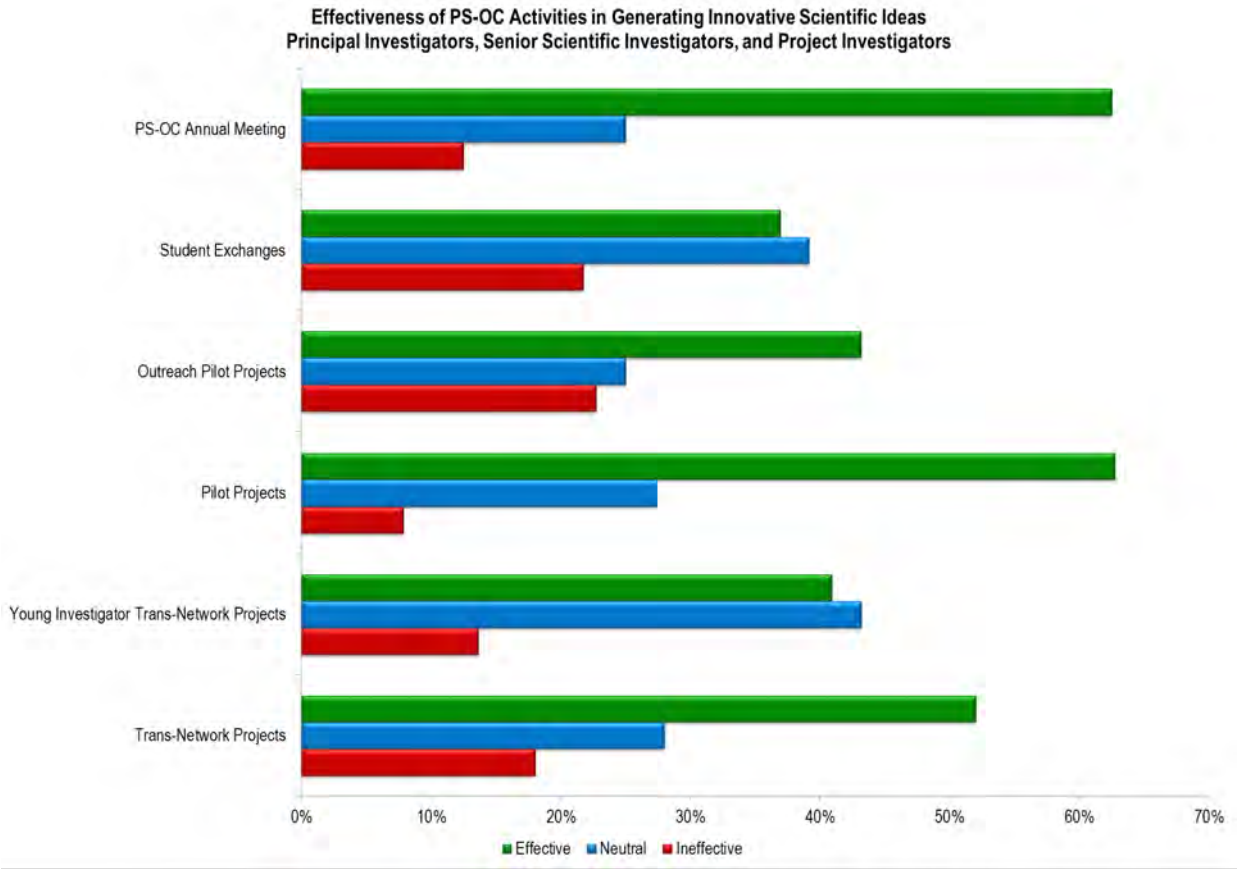



Figure 7.4. Effectiveness of PS-OC Activities in Generating Innovative Scientific Ideas. PIs, SIs, and project investigators were asked, "How effective have the following PS-OC opportunities been in encouraging you to generate innovative scientific ideas?"

### 7.2.4 Effectiveness of PS-OC Program in Building New Infrastrucutre

#### *PS-OC Funding Support*

The PS-OC Program offered resources to PS-OC investigators that would not have been available without PS-OC support. From the survey, it was apparent that the PS-OC Program helped facilitate access to this equipment and infrastructure for PS-OC researchers beyond what would have been available otherwise, as shown by the 82 percent positive response in the survey; Figure 7.5.

#### *PS-OC Program Staff*

The U54 mechanism used for PS-OC awards requires substantive involvement by PS-OC program staff, and the survey was also used to determine how effective the program staff were in fulfilling this mandate (Figure 7.6). The staff were deemed most effective in terms of facilitating interactions between PS-OC investigators, advancing research, and guiding strategic decisions, with between 60 percent and 65 percent of respondents indicating that the program officials were effective in achieving these goals. Additionally, according to at least 40 percent of the respondents, the staff is effective at communicating funding opportunities and resources, coordinating working group teleconferences, and answering questions about PS-OC and NCI guidelines and procedures (Figure 6.6). In all of the categories surveyed that concerned the effectiveness of PS-OC program staff, fewer than 5 percent of survey respondents rated the staff as ineffective.

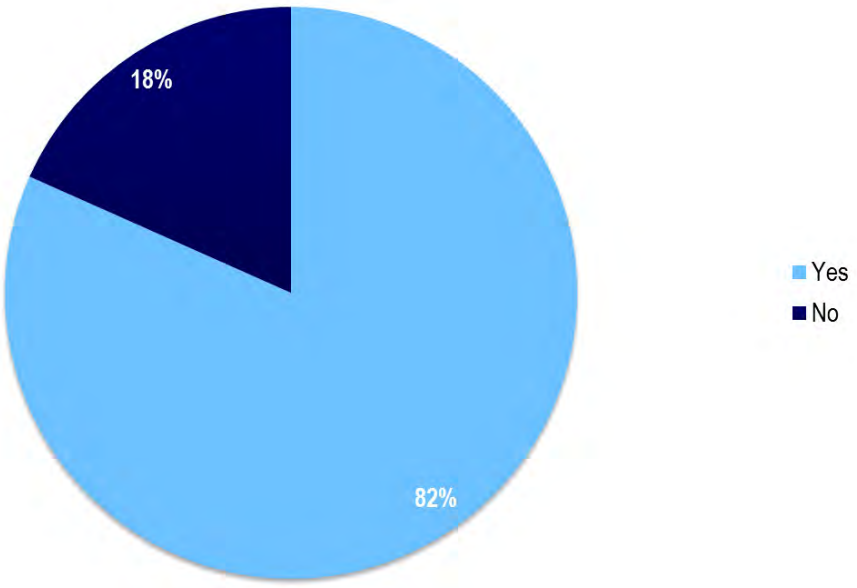



Figure 7.5. Access to equipment and infrastructure. External Scientists, PIs, SIs, and project investigators were asked, "Did the PS-OC facilitate access to equipment and infrastructure for PS-OC researchers beyond what would have been available otherwise?" (n=156).

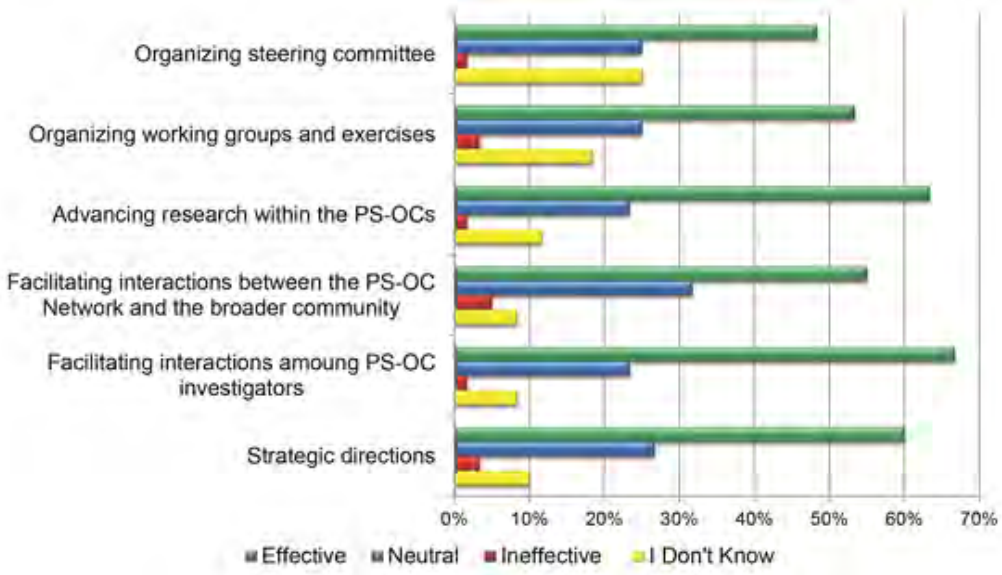



Figure 7.6. Effectiveness of PS-OC Program Staff. PIs, SIs, and project investigators were asked to rate, "How effectively have the PS-OC program staff performed the following roles in the management and direction of the PS-OC Program?" (n=60).

## 7.3 Continued Support of PS-OC Infrastructure

The PS-OC Program was established with the purpose of bringing new types of scientists with new perspectives to cancer research and build infrastructure to support collaborative team science at the interface of the physical and life sciences. Preliminary assessments of the Program indicate that new infrastructure has been established at the PS-OCs to support research, education, and collaborations. However, it unclear whether this infrastructure is sustainable and will support continued progress in this area in the absence of further PS-OC funding. To address this question, the survey included questions about other funding sources for physical sciences in oncology research. Additionally, NIH databases were queried to determine the level of NIH funding through other mechanisms. The results of both investigations indicate that this area of science is still maturing and more support is warranted to ensure continued progress in this area.

### Other Support at Institutions

Is there other support for PS-OC investigators at their institutions? From a total of 60 PIs, SIs, and project investigators, only 37 percent responded that they receive support outside of the PS-OC Program for physical sciences in oncology, clearly indicating that most institutions do not provide support for the convergence of these disciplines (Figure 7.7) outside of the PS-OC Program. Of those who do receive institutional support, greater than 80 percent directly receive funding, and/or collaborate with other researchers who receive funding, and/or use equipment, materials, or infrastructure supported by the institution (Figure 7.8).

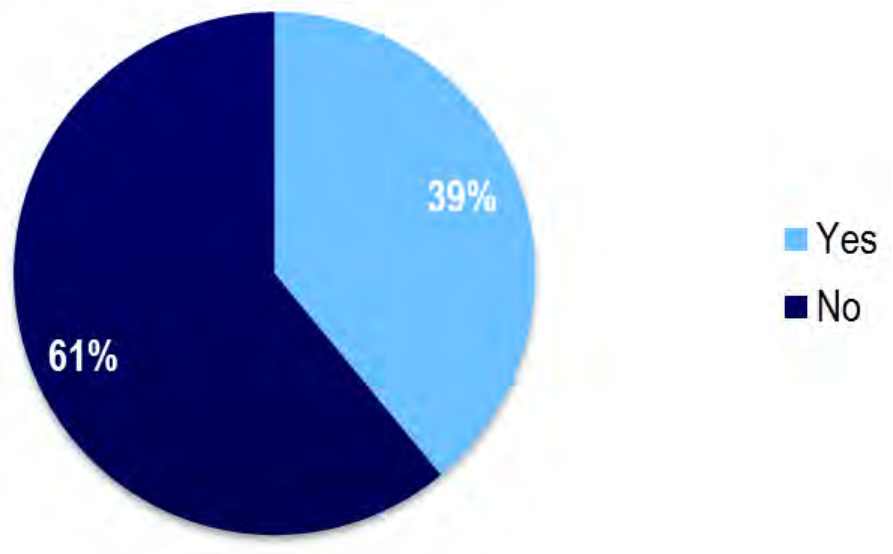



Figure 7.7. Sources of Support for Physical Sciences in Oncology Research Outside of PS-OC. Investigators were asked the question in the survey, "Do any sources of support exist for physical sciences in oncology research at your Institution outside of the PS-OC?"

Are institutions starting to implement strategies to promote convergence of physical sciences and oncology? Based on the response to the survey of PS-OC investigators and external scientists to the PS-OC, it appears that the majority of research institutions do not have a strategy in place to support research and education in this area. Only 34 percent of PS-OC respondents (n=60) and 30 percent of external scientists (n=96) are at institutions that have an overall strategy or mechanism for converging the fields of physical sciences and oncology. It is expected that this number will grow as the PS-OC Program continues to mature due to increased success in the field.

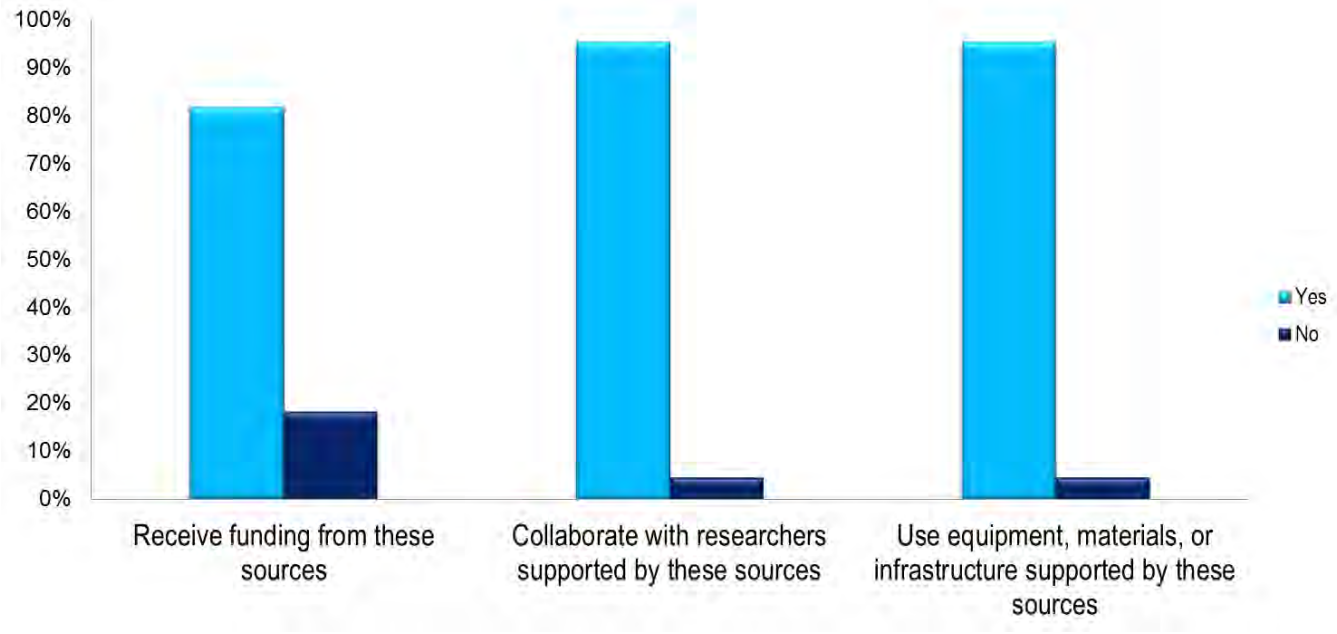



Figure 7.8. Support outside of the PS-OC Program for physical sciences in oncology.

## Other Support from the NIH

Within the PS-OC Program, five of the current PIs have never been funded by any institute at the NIH, and another three have never been funded by the NCI. These statistics clearly show that this program is supporting new investigators in cancer research. In order for the field of physical sciences in oncology to continue beyond the PS-OC Program, investigators will need to obtain funding through the general R01 mechanism or other types of support. Using NIH grant databases, the grant history of 96 physical scientists affiliated with the PS-OC Program (PIs and Project leaders) was examined. In FY 2012, the physical scientists affiliated with the PS-OC Program (PIs and project leaders, 96 investigators) only had 5 R01 applications funded (Figure 7.10). This number has been similar for the last four years, even with a spike in the number of applications submitted in 2012.

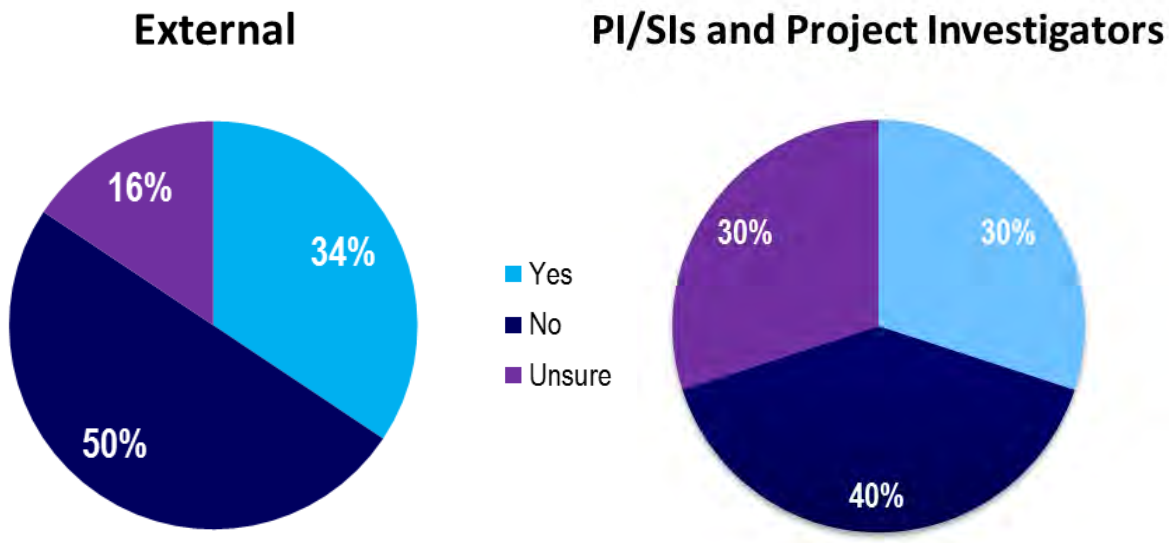



Figure 7.9. Strategy for converging physical sciences and oncology. External Scientists (A), PIs, SIs, and project investigators (B) were asked, "Does your Institution have an overall strategy for converging physical sciences and oncology?" (n=156).

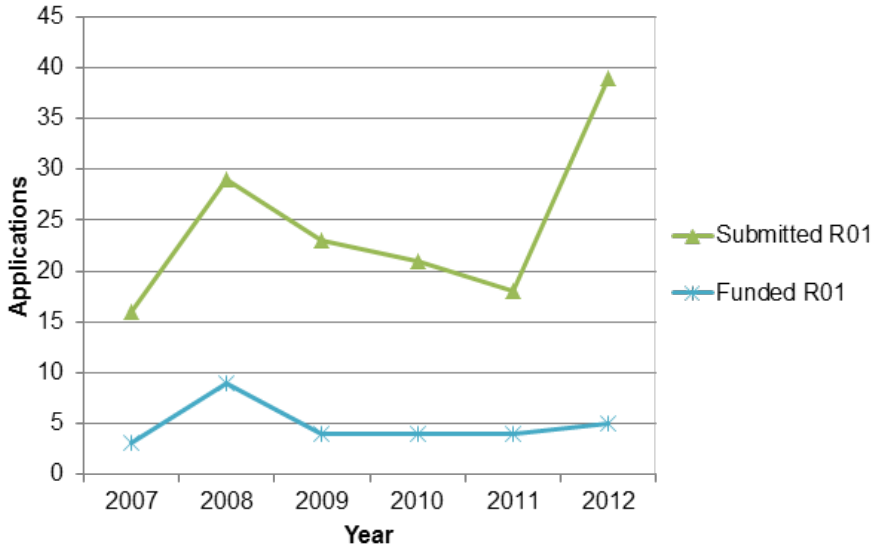



Figure 7.10. R01 applications (funded and submitted) from PS-OC-affiliated physical scientists over the past five years.

Summary statements and scores are a good indication of feedback that physical scientists are receiving on their grant applications. Overall, in the past three years approximately 65 percent of R01 applications were scored, with an average score around 35. These figures have fluctuated up and down with no observable trends. Summary statements were reviewed to identify feedback from peer reviewers. In most cases, the reviewers scored the proposals high in innovation and made positive comments on the interdisciplinary methods and teams included in the proposals. But many comments questioned the clinical relevance of the physical science-based approaches (e.g., predictive models or physical property measurements) and often describe the proposals as being overly ambitious.

In addition to the NIH databases, there was a survey question posed to PS-OC investigators and external scientists about feedback that they have received on grant applications to the NIH. The information gathered by the survey confirms our observations of the summary statements. Over one-quarter of investigators, 26 percent stated that their applications are

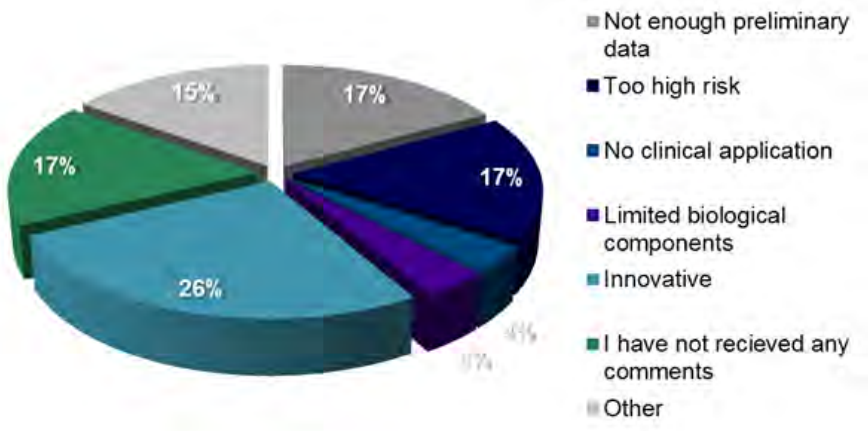



Figure 7.11. Feedback on NIH applications. External Scientists, PIs, SIs, and project investigators were asked, "What comments have you received on the grants submitted to NIH?" (n=156).

considered innovative by peer reviewers. And 17 percent of investigators have never received comments suggesting that their applications were not discussed. The most frequent negative comments appeared to be "not enough preliminary data" and "too high risk," identified by 17 percent of respondents. A small number of respondents, 4 percent, selected "no clinical application" or "limited biological components" as feedback received on NIH applications (Figure 7.11). In general, the PS-OC investigators indicate that they believe there is a lack of expertise in the study sections to effectively review and critique their applications.

## 7.4 Summary

The formation of a new physical sciences in oncology field requires support and infrastructure to develop and remain sustainable long term. In three years of operation, the PS-OC Program has built physical infrastructure, developed transdisciplinary courses, and initiated new journal clubs and seminar series to support the convergence of physical sciences and oncology. Additionally, through the cooperative agreement mechanism, the OPSO has supported PS-OC efforts by organizing program activities, such as working groups and the Annual PS-OC Network Investigators' Meeting. Based on survey results, the infrastructure built by the PS-OCs and the OPSO has been successful in promoting innovation and transdisciplinary collaborations. Unfortunately, the support for the field appears to be hindering on the funding from the PS-OC Program. Only a few institutions or other Program are supporting convergence of these two fields outside of the PS-OC Program. While established NIH investigators have been able to leverage other funding sources for PS-OC-type research, many of the PS-OC investigators with physical sciences backgrounds still have low success rates for R01-type grant applications. Based on these findings, there appears to be a need for continued investment in the PS-OC Program in order to strengthen infrastructure to support convergence of physical sciences and oncology post-PS-OC Program.

# 8. Training

One of the primary aims of the PS-OC Network is to, "Train a new generation of transdisciplinary scientists in the area of physical sciences in oncology." Toward this end, the NCI has placed a strong emphasis on equipping the graduate students and post-doctoral fellows within the PS-OC Network to successfully work in transdisciplinary teams at the interface between the physical sciences and the life sciences. This section examines the following questions:

i. How many trainees are in the Network, and how has this changed over time?

ii. What are the academic backgrounds and areas of expertise of the trainees?

iii. How involved have the trainees been in PS-OC Program activities?

iv. How do the trainees rate the Education and Training activities?

v. How many trainee exchanges occurred, and did these benefit the trainees?

vi. How many new courses have been developed by the PS-OC Network?

vii. Where have trainees gone after completing their training in the PS-OC Program?

viii. Do trainees plan to continue in the field of physical sciences in oncology?

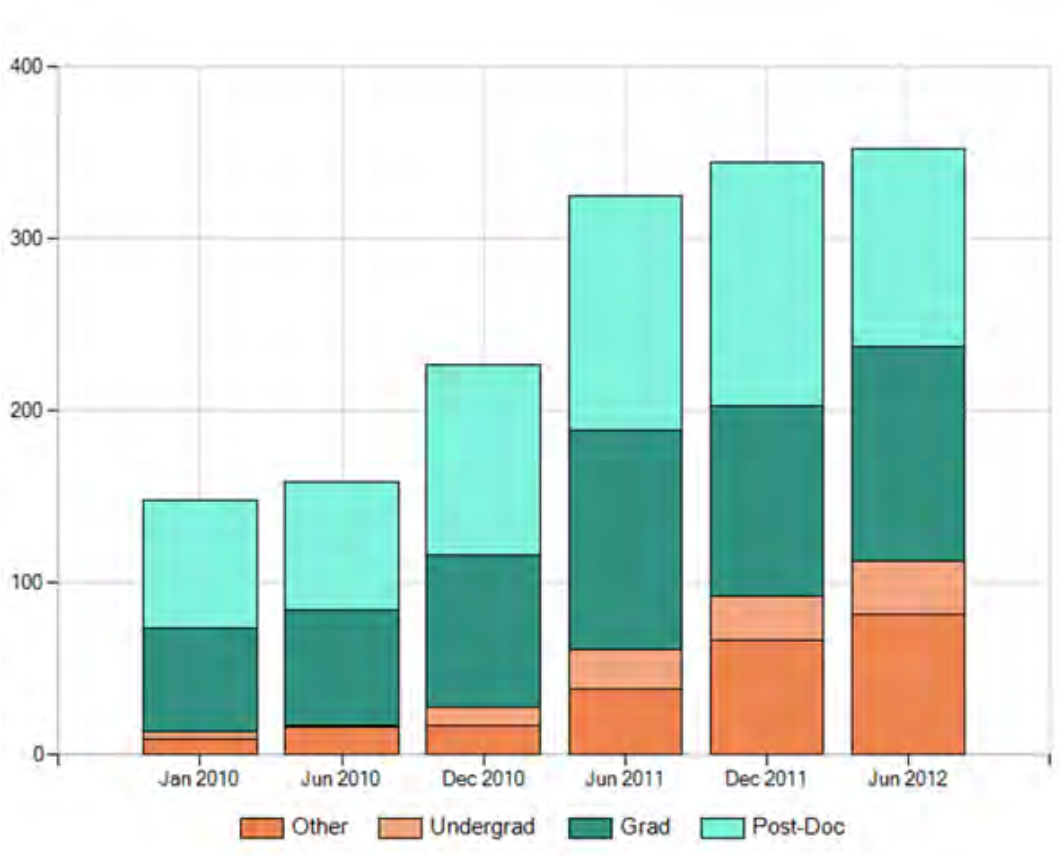



Figure 8.1. Growth of Trainees in the PS-OC Network by Category. The bar charts show the number of undergraduate, graduate, and post-doctoral trainees across the entire Network. The data for this chart were derived from the semi-annual progress reports. Individuals listed as trainees but not classified into the groups listed above were coded as "Other" for this analysis.

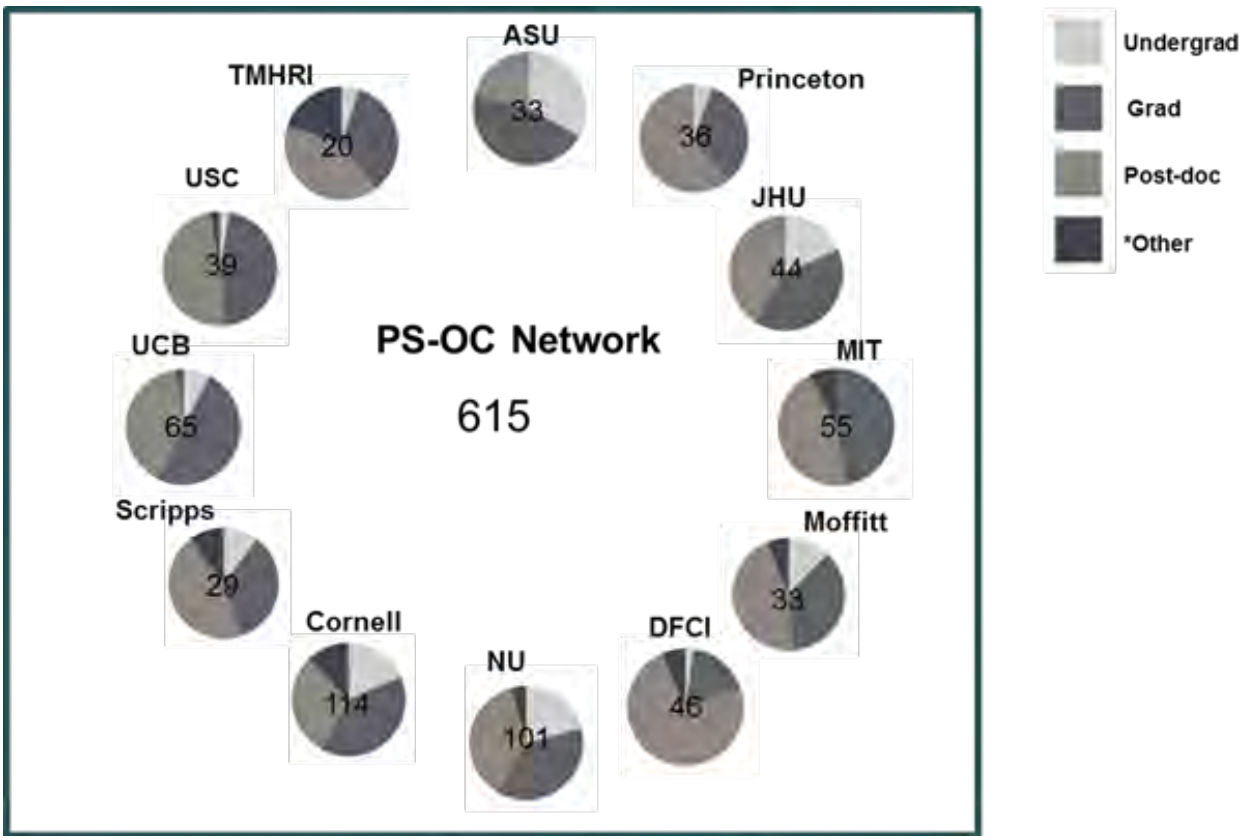



Figure 8.2. Composition of trainees by Center. The pie charts show the cumulative totals for undergraduate, graduate, post-doctoral fellows and other trainees at the individual PS-OCs from the start of the Program to the present. Data are derived from the semi-annual progress reports.

To answer these questions, this report draws on information provided by progress reports and a survey that the trainees completed in the spring of 2012. The survey was sent out to all the trainees in the PS-OC Network, and 75 responses were received.

## 8.1 Breakdown of Students and Fellows Supported

### How many trainees are in the Network, and how has this changed over time?

From the start of the Program in September 2009 to June 2012, the number of graduate students involved in projects at the Centers has more than doubled, from 60 to 124 (Figure 8.1). Similarly, the number of post-doctoral fellows involved has also approximately doubled, from 74 to a peak of 141 in December 2011. The mission of the PS-OC Program to train new leaders in the area of physical sciences in oncology has also included undergraduate students. Typically, these trainees have worked parttime in PS-OC-funded laboratories or as part of summer internships. The involvement of this group of trainees has also increased over time. Five undergraduate students were recorded in the first progress report, and this has grown steadily to 31 students in the June 2012 report. The PS-OCs also included trainees who were not categorized into either of the groups discussed above ("Other"). The trainees included in this group are reported as medical students, research associates, research specialists, research technicians, or fellows. As of June 2012, 82 trainees fell into this category compared to 9 in Jan 2010.

All 12 Centers have contributed to educating and training students over the course of the Program. In total, 615 trainees have been involved with the PS-OC Network and have been reported through the Education and Training Unit in the progress

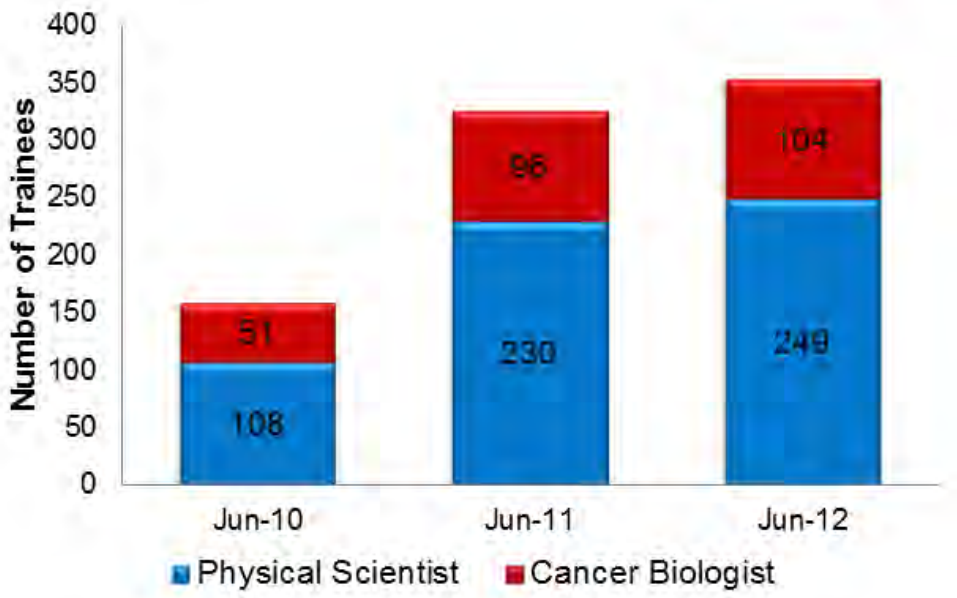



Figure 8.3. Breakdown of trainees by academic background. Data from the annual progress reports were used to categorize the expertise of the trainees as either physical scientists or cancer biologists based on the academic degrees held.

reports. Each Center is comprised of a different ratio of trainees categorized into undergraduate, graduate, post-doctoral, and "other," which demonstrates the diversity that each Center brings to the Network (Figure 8.2).

### What are the academic backgrounds and areas of expertise of the trainees?

The PS-OC Network consists of transdisciplinary teams that are approaching cancer research at the interface of the life and the physical sciences. Thus, knowing the academic backgrounds of the trainees is an important piece of information for understanding how well the Program is working in bringing together these two groups of researchers. To address this question, the progress reports collected information on the academic degrees held by the trainees, and this information was used to categorize them as either "physical scientists" or "cancer biologists" (Figure 8.3). This data shows that since the start of the Program, about two-thirds of the trainees have a background in the physical sciences. This is consistent with the mission of the PS-OC Program, and although the number of trainees has grown through the course of the initiative, this proportion has remained steady.

## 8.2 Trainee Involvement in the PS-OC Program

### How involved have the trainees been in PS-OC Program activities?

In keeping with the mission to train the next generation of scientists working in the area of physical sciences in oncology, the Network has offered a variety of hands-on and interactive training opportunities as well as more traditional courses. To determine how involved the trainees have been with the Program, trainees were asked in a survey to select the activities in which they had participated while part of the PS-OC Program. The most common activities are shown in the chart below (Figure 8.4)

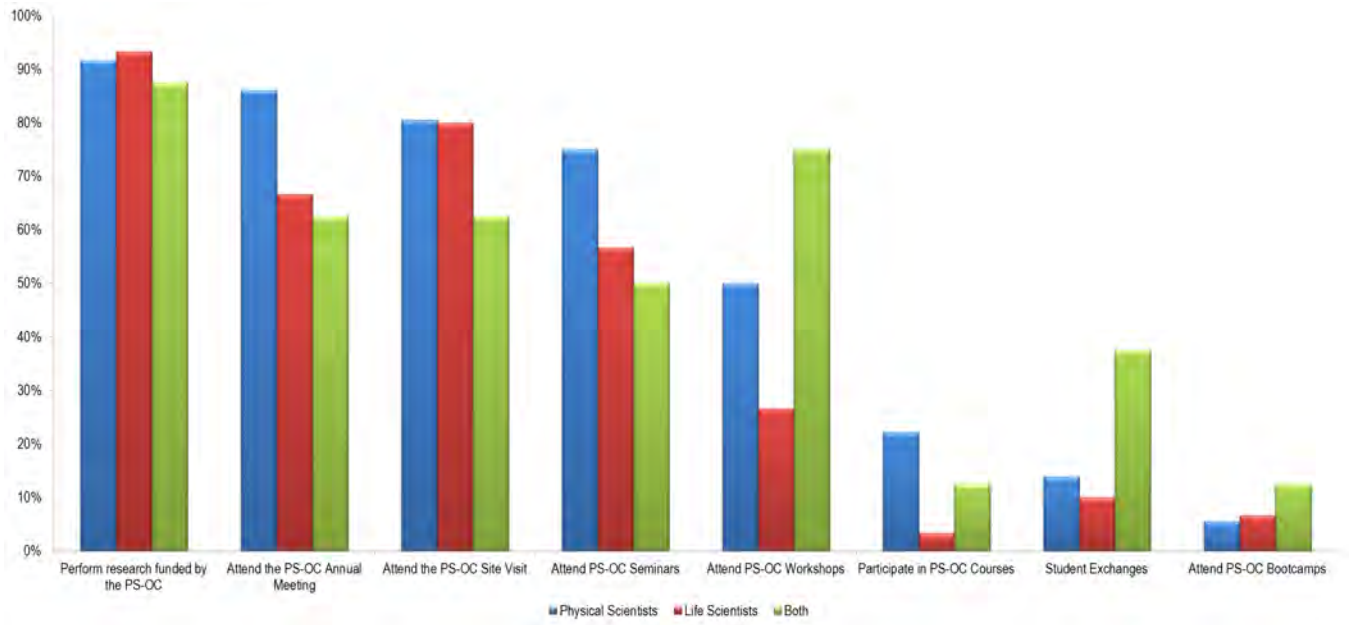



Figure 8.4. Trainee involvement in the PS-OC Program. Trainees were asked in a survey to select the activities in which they have participated as part of the PS-OC Program. The respondents were also asked to select the areas of expertise, and this information was used to classify the trainees as physical scientists, life scientists, or both if they had extensive crossdisciplinary skills.

The survey results indicate that outside of their research, there have been high levels of involvement by the trainees in the Annual Network Investigators' Meeting and in attending site visits by NCI program officials, seminars, and workshops. The results also suggest that PS-OC-designed courses have, to a large extent, reached trainees outside of the Network.

## How do the trainees rate the Education and Training activities?

The trainees were also asked in the survey about how effective the PS-OC training activities had been in meeting the Program goals of (1) initiating training in the new field of physical sciences in oncology; (2) facilitating mentor-mentee relationships; (3) facilitating career development; (4) bringing new knowledge to trainees; (5) teaching new skills; and (6) facilitating the interaction and sharing of ideas among trainees (Figure 8.5). Overall, the trainees responded positively to these questions. Excluding respondents who answered "I don't know," the remainder of the surveyed trainees all thought that the PS-OC Program was doing a good job of facilitating the sharing of ideas among trainees. For the other questions, respondents indicated that the Program was doing either a "fair" or "good" job at meeting the specified goals.

The trainees were also asked to rate how useful the Education and Training Units had been in helping trainees: (1) gain experience in the field of physical sciences in oncology; (2) establish new contacts; (3) provide trainees with access to new resources and equipment; (4) develop new skills; and (5) participate in unfamiliar research activities (Figure 8.6). About 75 percent of those surveyed thought the PS-OC Education and Training Units were either "wseful" or "fairly useful." The remaining 25 percent were neutral regarding these questions. For establishing new contacts, half the respondents thought that the Education and Training Units were "useful" in this regard, while the other respondents were neutral.

The next sections evaluate specific components of the Education and Training activities that have been implemented by the Program.

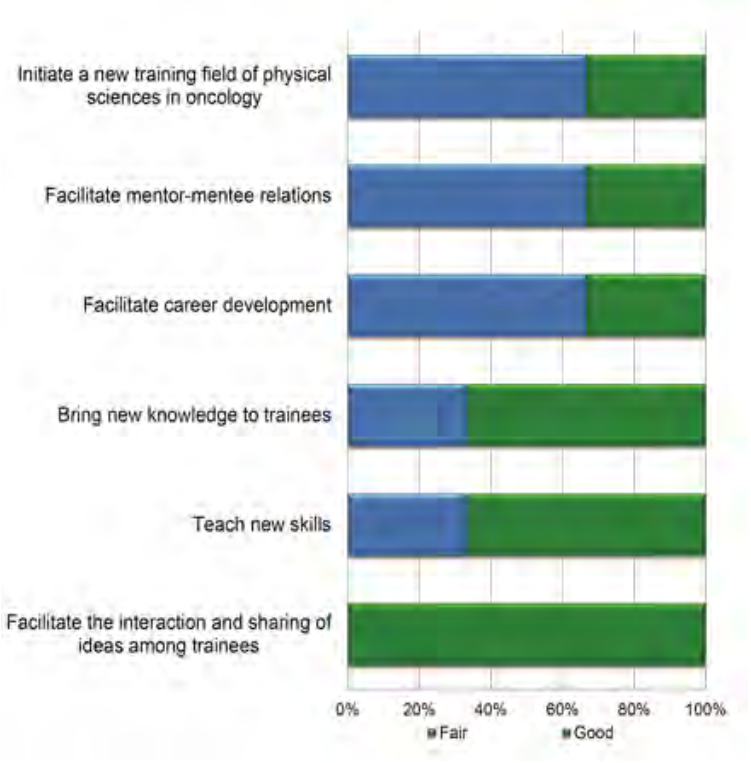



Figure 8.5. Trainee response to the effectiveness of PS-OC training activities. Trainees were asked to rate how well the PS-OC training program is meeting the goals listed above. The survey used a five-point scale ranging from very poor to very good and allowed the option of "I don't know."

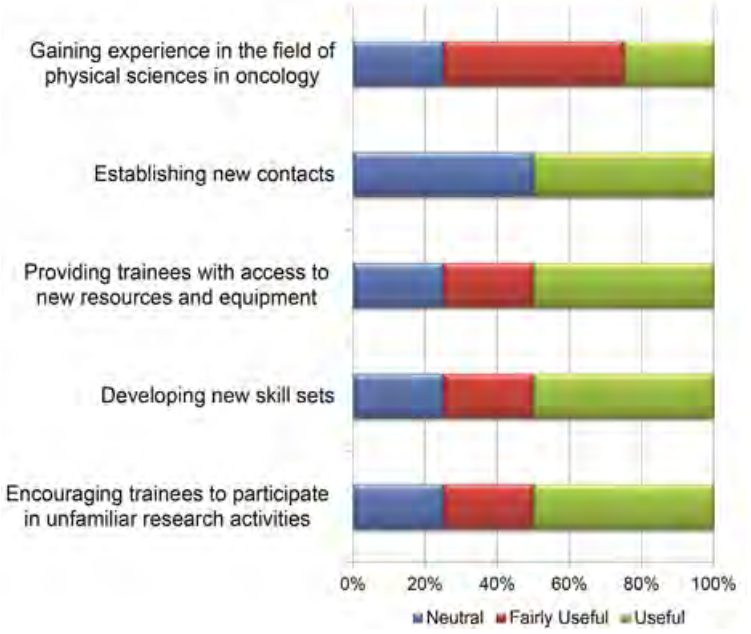



Figure 8.6. Trainee response to the effectiveness of the Education and Training Units. Trainees were asked to rate how useful the PS-OC Education and Training Units had been for the trainees in meeting the goals listed above. The survey used a five-point scale ranging from very poor to very useful and allowed the option of "I don't know."

## 8.3 Trainee Exchanges

### How many trainee exchanges occurred, and did these benefit the trainees?

Exchanges of trainees between Centers in the PS-OC Network are a key component of the training activities supported by the PS-OC Program. The exchanges encourage the cross-fertilization of ideas between Centers and facilitate the collaborations that are vital to the work of this Program. Since June 2010, there have been approximately 40 trainee exchanges reported each year (Figure 8.7) and a total of 113 since the PS-OC Program began.

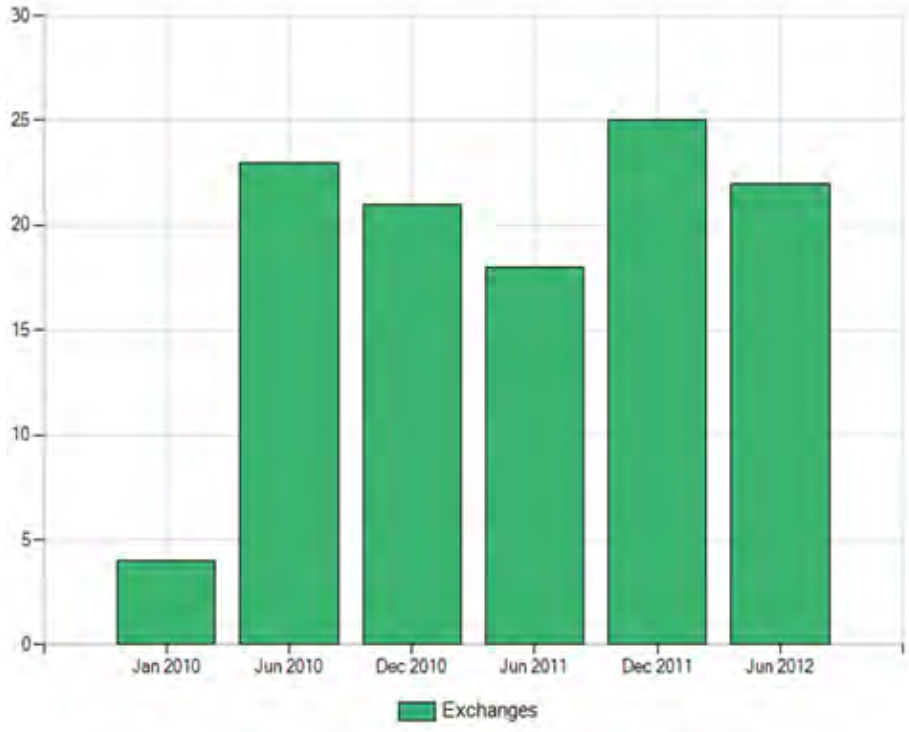



Figure 8.7. Number of exchanges between PS-OCs. The chart shows the number of new exchanges listed in the progress reports submitted on the indicated dates for all of the Centers.

The exchanges have benefitted physical scientists and cancer biologists. For example, a post-doctoral fellow with a computer science background visited the lab of Scott Lowe to learn first-hand about the mouse model of Burkitt's lymphoma developed by that lab. This animal model has since been adopted by the University of Southern California PS-OC to study using computational techniques. As an example of an exchange of trainees with a background in cancer biology, two post-doctoral fellows from the Tlsty cancer biology lab at the University of California, San Francisco, worked in the Austin lab at the Princeton PS-OC to learn how they could apply the tools and approaches of physical sciences, such as microfluidic chips, to their research.

In order to assess the value of the exchanges that have been facilitated by the PS-OC Program, trainees were asked in the survey what they thought was the overall usefulness of the exchanges and whether they thought the exchanges could have occurred without the PS-OC Program (Figure 8.8).

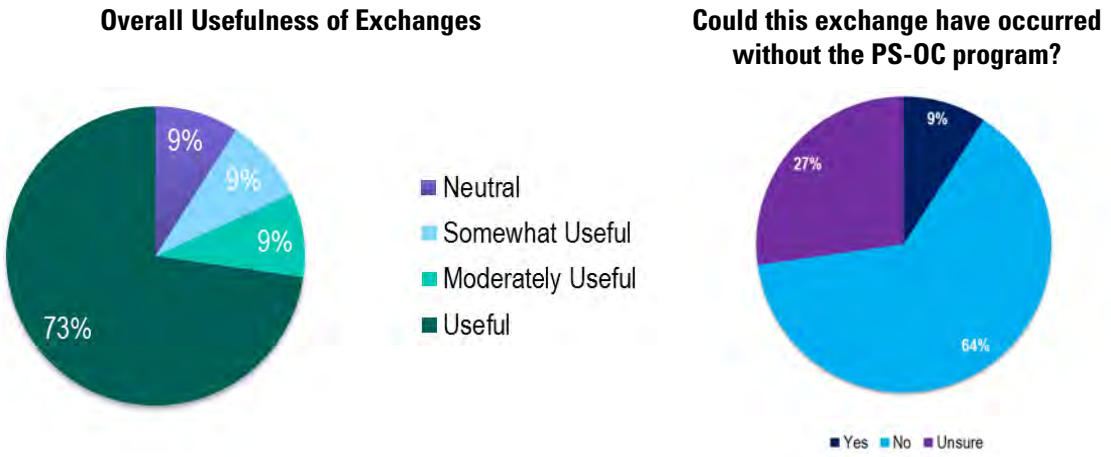



Figure 8.8. Trainee response to usefulness of exchanges. Trainees who had participated in exchanges within the PS-OC Network were asked to rate the overall usefulness of the exchanges (left panel) on a five-point scale from extremely not useful to very useful and were asked for their opinion on whether the exchanges could have occurred without the PS-OC Program (right panel).

Eighty-two percent of the trainees who had participated in an exchange answered that the exchanges were "useful." Sixty-four percent of the trainees who had participated in an exchange also thought that the exchanges could not have occurred without the PS-OC Program. The exchanges have been particularly helpful in the context of Trans-Network Projects, which is discussed further in Section 8.5.

## 8.4 Course Materials and Training Modules Created

### How many new courses have been developed by the PS-OC Network?

Developing new courses for both undergraduate and graduate students has been one of the most effective mechanisms for training the next generation of transdisciplinary scientists working at the interface of cancer biology and the physical sciences. Courses have a lasting impact that extends beyond the trainees who are directly part of the Network and fulfill two key roles: breaking down the barriers such as terminology that impede collaboration between physical scientists and life scientists and meeting the specific needs of trainees to work in multidisciplinary teams. In addition, courses often have a broader reach by including out-of-Network trainees. The progress reports show that between 13 and 26 new courses were developed between each reporting period. Since the inception of the PS-OC Program, a total of 55 courses have been taught or developed across the 12 Centers (Figure 8.9).

The scope of the courses ranged from individual lectures and mini-courses or modules within larger courses to full-length graduate and undergraduate courses. A full list of the courses is provided in the Appendix. The courses developed by the PS-OC Network have helped to expose physical scientists to cancer research and taught them lab skills. For example, the OPSO has arranged a training course on mammalian cell culture techniques, the Scripps PS-OC conducted a Bootcamp in Tumor Pathology, and the UCB PS-OC taught a full course on breast oncology. Other courses have been designed to meet the needs of cancer biologists and have helped to equip them with quantitative skills and an understanding of techniques such as designing microfluidic devices to help them approach cancer research from a PSP. For example, the DFCI PS-OC has taught courses on the mathematical modeling of cancer and the evolutionary systems biology of cancer, and the UCB has taught courses on tissue mechanobiology and most notably has been able to redesign the undergraduate "Math for Biologists" course to be based around examples from cancer biology. This highlights the quantitative and physical sciences-based approaches that are used in the PS-OC Network.

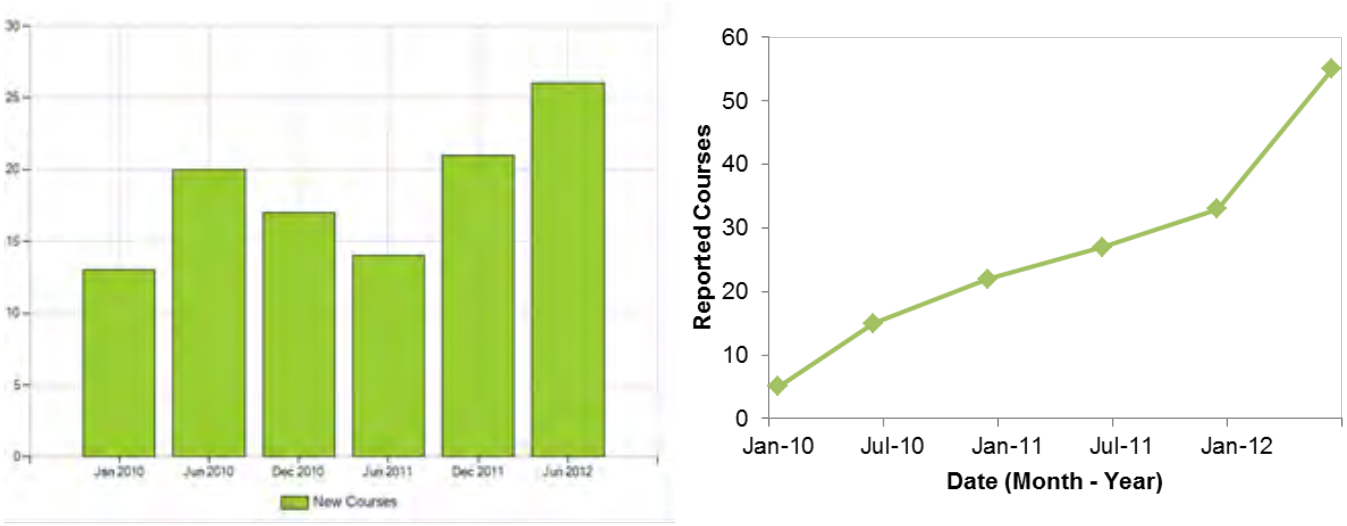



Figure 8.9. New courses developed and taught by the PS-OCs. The left panel shows the number of new courses that were listed in the indicated progress reports. The right panel shows the cumulative total of new courses over time from January 2010 to June 2012.

## 8.5 Young Investigator Trans-Network Awards

To promote collaborations among trainees within the PS-OC Network, the NCI and the PS-OC Steering Committee established an internal funding mechanism to support collaborative research projects between two or more Centers. This mechanism is referred to as the Young Investigator Trans-Network Awards. To date, 12 projects have received funding through this mechanism. The size of the awards has ranged from about $10,000 to $27,000 in total costs, and the awards are announced at the Annual PS-OC Network Investigator's Meeting. To apply for this award, trainees put together a short proposal that is reviewed by a committee of senior PS-OC investigators, NCI program officials, and trainees. In addition to funding innovative collaborations between trainees, this award program affords trainees the opportunity to gain experience in grant writing and reviewing. The survey results strongly support the Young-Investigator Trans-Network Award program; about 80 percent of the respondents indicated that these awards successfully increase discussions among trainees and promote collaborations. A list of the awards to date is shown in Table 8.1.

Table 8.1. List of the Titles and PS-OCs of the Young Investigator Trans-Network Awards Funded to Date.

| Title | PS-OCs |
|---|---|
| Probing Transcriptional Response as a Function of Spatial Organization of Signaling Complexes Across Length Scales | UCB & MIT |
| Identification and Characterization of Circulating Tumor Cells by Partial Wave Spectroscopy | Scripps & NU |
| Tracking the Intracellular Mechanics of Cancer in Living Subjects using Nanorheology | JHU & USC |
| Synergistic Effects of Hypoxia and Substrate Stiffness on Cancer Cell Force Generation and Hypoxia-Mediated Protein Expression | Cornell & JHU |
| Using Tumor Genomic Diversity as a Prognostic Marker for Metastasis | MIT & DFCI |
| Towards a Predictive Theory of Driver Mutations in Cancer | DFCI & MIT |
| Identification of Tumor-Initiating Cells using an Integrated Physics Approach | TMHRI & USC |
| Nuclear Architecture Reflects Functional Links Between Cellular Metabolism and Tension | ASU & UCB |
| Understanding the Formation of Circulating Tumor Cell Clusters | Scripps & DFCI |
| Control of EGRF Pathways via aAplitude-Modulated Low-Frequency Electric-Field Modulation | TMHRI & Moffitt |
| Identifying the Impact of Nuclear Architecture in the Regulation of Metabolic Pathways | NU & DFCI |
| The Role of the 3D Mechanical Environment in Regulating Angiogenesis | Cornell & Moffitt |

## 8.6 Trainee Career Development

### Where have trainees gone after completing their training in the PS-OC Program?

Although the PS-OC Program has been in existance for only about three years, a significant number of trainees have already left the Network as new ones enter. Thus, one way to evaluate whether the Program has contributed to training a new generation of scientists in the field of physical sciences in oncology is to examine what happens to trainees when they leave the Program. Based on the progress reports, 100 trainees have left the Program since its inception. Table 8.2 shows the reported career transitions of graduate students and post-doctoral fellows.

Table 8.2. List of Career Transitions Made by Trainees Who Participated in the PS-OC Network. The information on trainee career transitions was obtained from the semi-annual progress reports.

| Transition | Number |
|---|---|
| Grad Student - Faculty | 2 |
| Grad Student - MD | 1 |
| Grad Student - Staff Scientist | 3 |
| Grad Student - Postdoc | 14 |
| Postdoc - Faculty | 6 |
| Postdoc - Corporate | 6 |
| Postdoc - Staff Scientist | 6 |
| Postdoc - Postdoc | 14 |

Encouragingly, the majority of the graduate students left to continue their training through post-doctoral fellowships (70 percent). Of the post-doctoral fellows, 44 percent left to do another fellowship and 19 percent secured permanent staff scientist positions. It was also positive to observe that 19 percent of the post-doctoral fellows were able to obtain junior faculty positions. Finally, the remainder of the fellows for whom we have data left for corporate positions, including high-level positions: One became a company Chief Executive Officer, two joined companies in managerial positions, and one transitioned to become a Vice President of Research.

### Do trainees plan to continue in the field of physical sciences in oncology?

As another measure of the impact of the PS-OC Program in training a new generation of scientists in the field of physical sciences in oncology, trainees were surveyed about whether they planned to continue conducting research in this field after completing their training (Figure 8.10). Out of all the trainees, 58 percent indicated that they planned to stay in the field, while 37 percent remained unsure. Only 5 percent of the trainees plan on leaving the field. The trainees were also asked for their opinion on whether they thought it would be difficult to obtain funding for PS-OC-type research if the PS-OC Program did not exist; 75 percent thought that in the absence of the PS-OC Program, funding for this type of work would be difficult to obtain, while the remainder were unsure.

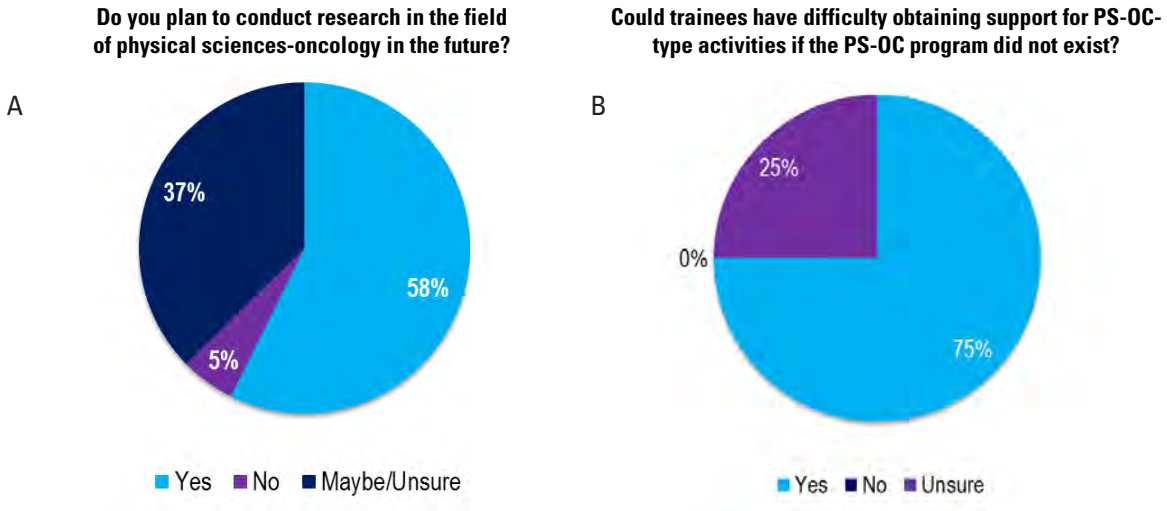



Figure 8.10. Trainee response to continued research in physical sciences in oncology field. Trainees were asked whether they planned to conduct research in the field of physical sciences in oncology (A) and whether they thought that support for PS-OC-type activities would be difficult if the PS-OC Program did not exist (B).

## 8.7 Summary

Training a new generation of transdisciplinary scientists in the area of physical sciences in oncology is a key goal of the PS-OC Program. Although the Program has been running only for about three years, progress has been made. The trainees (students and post-doctoral fellows) have typically participated in a range of training activities offered by the PS-OC Network. Exchanges have been of particular value to the trainees by helping to establish trans-Network collaborations and stimulate the exchange of ideas. The PS-OCs have also developed courses aimed either at trainees in the Network or more broadly to undergraduate and graduate students outside the Network. While it is too early to evaluate the success of these efforts, the survey results indicate that the majority of trainees plan on staying in this new field of research, and the progress reports show that a number of trainees have made successful career transitions that are consistent with these aims.

# 9. Convergence of Physical Sciences and Oncology

The PS-OC Program emphasizes the convergence of physical sciences and oncology fields through team science to support new and innovative approaches and theories in cancer research. As described in Section 5, indicators of collaborations have been collected through progress reports and surveys to reflect the increase in connectivity among investigators. However, measuring the impact of the PS-OC Program on the convergence of two disparate fields to form a new physical sciences in oncology field is a unique challenge, and it is one that has become a focus of the PS-OC Program staff through Program performance monitoring. To date, most metrics have focused on extant data such as publication activity (Porter and Youtie, 2009; Hall et al., 2012). Other measurement efforts have incorporated qualitative and quantitative interactions among team members (Rhoten, 2004); and recently, some systems have been developed that allow researchers to document their collaborative activity (Gewin, 2010; Mitchell, 2011). These approaches are powerful but are typically applied post hoc. In the current study, we describe the development of indicators for transdisciplinary activity using data from multiple modalities and methods for collection of these data on an ongoing basis for real-time assessment of programmatic outputs and outcomes. The PS-OC Program Staff worked with contractors to design a novel indicator for monitoring the convergence of these fields based on scientific output.

## 9.1 Measuring Field Convergence

The Web of Science database identifies each journal by scientific category. Using this classification, several journals were identified as containing physical sciences- or oncology-related publications. From each of these two categories of journals, 100,000 publications were randomly selected. All titles and abstracts from these 200,000 publications were mined for words, removing common English words and then stemming words, which is how all possible variants of a word are searched to yield more comprehensive search results. This process resulted in more than 65,000 single-word terms identified for each category—physical sciences or oncology. Additional criteria were imposed on these lists of terms to identify unique and relevant terms for each category.

Criteria for physical science terms:

- Must occur in greater than 70 percent of physical sciences publications and less than 30 percent of biology or oncology publications
- Identified as a strong descriptive single-word term by manual selection

Criteria for oncology terms:

- Must occur in greater than 90 percent of oncology publications
- Must be part of a medical subject headings (MESH) term (MESH terms are the most specific set of terms that describe the content of an article)

The final list of unique terms included 1,643 physical sciences terms and 571 oncology terms. Each paper published by a PS-OC investigator was classified into a type of publication based on these terms. If the publication contained only physical sciences terms or only oncology terms, it was considered a physical sciences publication or an oncology publication, respectively. If the publication contained terms from both categories, it was considered to be a physical sciences in oncology publication, but if the publication did not contain any of these terms it was placed in the "other" category.

Publications from PS-OC investigators were identified from five years prior to the award of the PS-OC Program to use as a baseline for monitoring the convergence of these fields through post-award publications.

## 9.2 Evidence of Field Convergence in the PS-OC Network

PS-OC Program staff developed a novel indicator to examine the convergence of the physical sciences and oncology fields in publications as a way to monitor the performance of the PS-OC Program. Using Web of Science journal categories, 1,647 unique physical science terms and 571 unique oncology terms were identified and used to classify PS-OC investigator publications since 2004. These sets of specific terms allow Program staff to monitor the convergence of the Network's scientific outputs and to establish the impact of the PS-OC Program on increasing the number of publications with both physical sciences and oncology terms. An increase in publications incorporating both types of terms was expected as collaborations matured between physical scientists and cancer researchers.

To date, the PS-OC Program has observed a 20 percent increase in the percentage of PS-OC investigator publications that converge the physical sciences and oncology fields (Figure 9.1). Currently, 40 percent of all investigator publications contain terms from both the physical sciences and oncology. The percentage of oncology-specific publications has remained constant since the start of the PS-OC Program, but the percentage of publications classified in the physical sciences has decreased. If the results are broken down by investigator discipline, it was observed that the increase in convergence is due to physical scientists publishing more oncology-relevant publications (Figure 9.2A). Cancer researchers have shown a slight increase in the number of physical science publications since the grant was initiated in 2009 (Figure 9.2B).

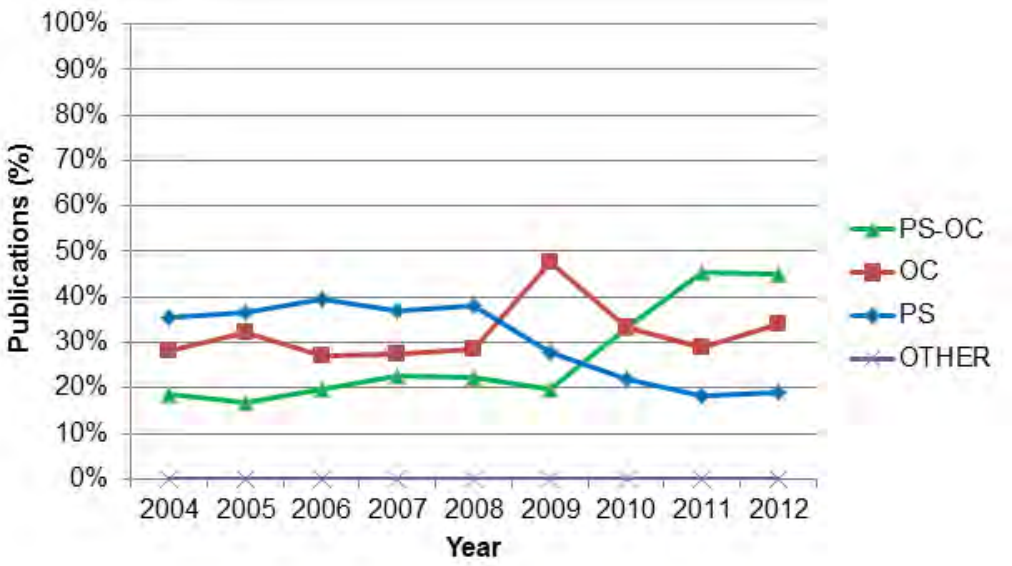



Figure 9.1. Classification of PS-OC Investigator publications by discipline from 2004 to the present. Unique terms were used to classify publications before and after PS-OC funding (award in 2009 indicated by the dashed line). Publications were classified in the physical sciences (PS; blue), oncology (OC; red), physical sciences-oncology (PS-OC; green), or other (OTHER; purple). The percentage of publications with both physical sciences and oncology terms has increased from below 20 percent to more than 40 percent of all publications since the program was initiated in 2009.

A breakdown view of each Center displays the range of convergence across the PS-OC Network (Figure 9.3). All PS-OCs have increased the percentage of transdisciplinary publications as a result of the PS-OC Program support since 2009. The increase in transdisciplinary publications from pre-grant years to post-grant years ranges between 5 percent and 40 percent across the Network.

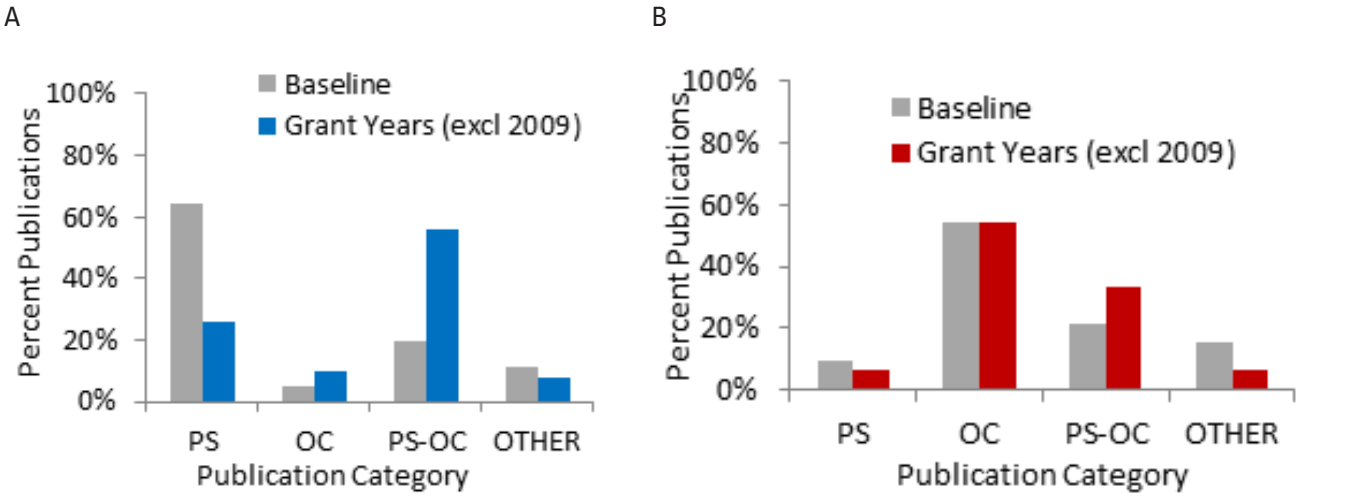



Figure 9.2. The breakdown of publication types based on investigator discipline. The percentage of publications classified as physical sciences (PS), oncology (OC), physical sciences-oncology (PS-OC), or other (OTHER) that were published by PS-OC Network investigators identified as physical scientists (A) or oncologists/cancer biologists (B) during the baseline (gray bars; five years pre-award), or during the grant years (blue and red bars, respectively; excluding 2009).

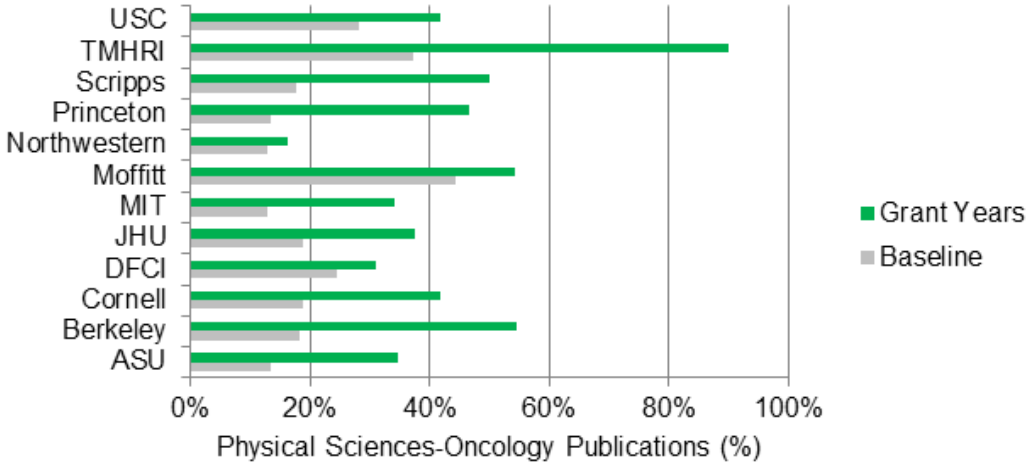
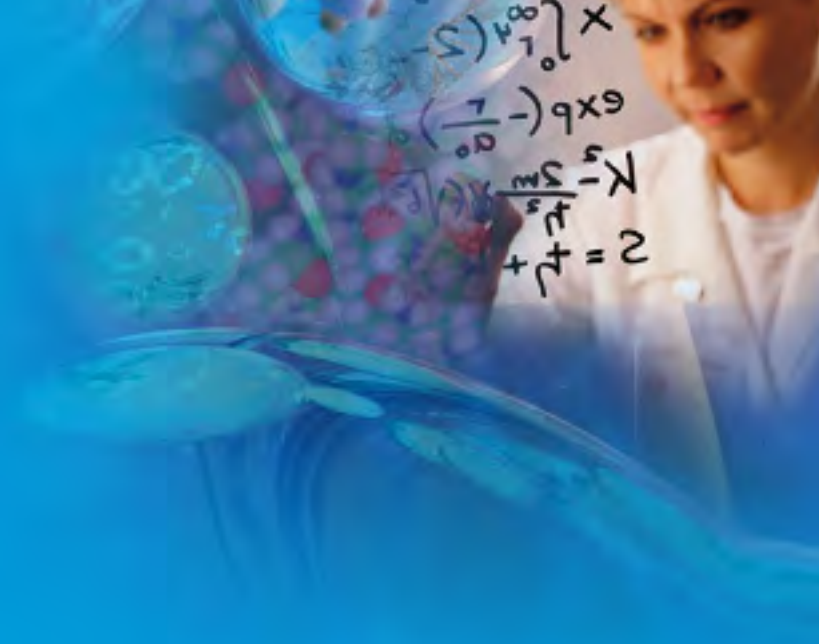



Figure 9.3. The percentage of physical sciences-oncology publications before and after PS-OC funding. Of the total publications by each of the PS-OC investigators, the percentage of physical sciences-oncology publications that are indicative of convergence of the two fields are shown for either the baseline (gray bars; five years pre-award) or the grant years (green bars). Each PS-OC displays an increase in the percentage of transdisciplinary publications during the grant years.

Program staff anticipate the percentage of transdisciplinary publications to grow as collaborations mature. In addition, it is expected that more physical scientists will continue to expand their knowledge and publish more oncology-related papers. The impact of the PS-OC Program on the convergence of disciplines as measured by its publications appears to be substantial, and it is anticipated that the positive impact will continue to grow over time.

## 9.3 Summary

The PS-OC Program is focused on converging physical sciences and oncology fields to generate new knowledge in cancer research. The OPSO has developed an indicator to monitor the convergence of physical sciences and oncology in PS-OC investigator-affiliated publications. After three years of operation, 40 percent of all publications generated by the PS-OC Network are categorized as transdisciplinary. This represents a 20 percent increase in the number of transdisciplinary publications produced by PS-OC investigators since the start of the PS-OC Program. Based on these results, the PS-OC Program appears to have made progress in generating transdisciplinary publications. The number of transdisciplinary publications is expected to increase as collaborations among investigators result in more publications.



# 10. Research Dissemination

One of the goals of the PS-OC Program is to collaboratively disseminate information to the cancer research communities and the public about the research taking place at the intersection of physical sciences and oncology. The convergence of the physical sciences and oncology is unique to the PS-OC Program. Dissemination of PS-OC Program ideas to the broader research community is essential for continued growth and success of the field. Therefore, it is important for the PS-OCs to "tell their story" to promote the impact of a PSP in cancer research. As part of the PS-OC Program infrastructure, each Center is engaged in active communications with the cancer research communities and the public through advocacy, workshops, media interviews, publications, scientific conferences, and a bi-annual newsletter. PS-OC Program staff have also actively engaged the scientific community through various scientific conferences, websites, Nature special issues, editorials, and symposiums. As part of the PS-OC Program evaluation plan, information was collected on PS-OC outreach activities and a survey of external scientists was conducted to assess the impact of these activities.

## 10.1 PS-OC Seminars and Workshops

Most of the PS-OCs have an Outreach and Dissemination Unit dedicated to communicating information about the PS-OC to the broader scientific community and the public. Each Center disseminates information differently based on the Center infrastructure. But most PS-OCs host seminars and workshops to disseminate information on physical sciences in oncology. In three years of operation, the PS-OCs have organized more than 300 workshops and seminars (Figure 10.1). A complete list of these workshops can be found in the Appendix, and some are highlighted in Section 7 of the PS-OC Program Update Section 7. The target audience for these workshops is mixed. Some workshops are dedicated to educating the disparate fields (physical scientists or oncologists/cancer biologists) about current research findings in the specific fields, and others are focused on dissemination of PS-OC specific research at the intersection of the two fields. Both types of workshops have included investigators from inside and outside the PS-OC Network.

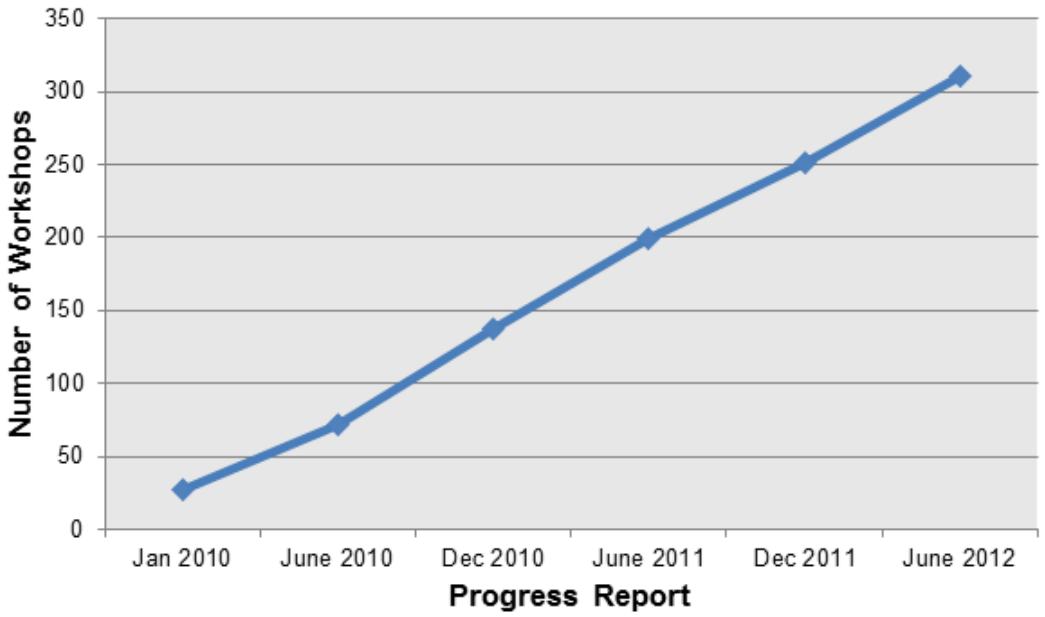



Figure 10.1. Cumulative number of workshops. The graph shows the cumulative number of workshops listed in the progress reports submitted on the indicated dates for all of the Centers.

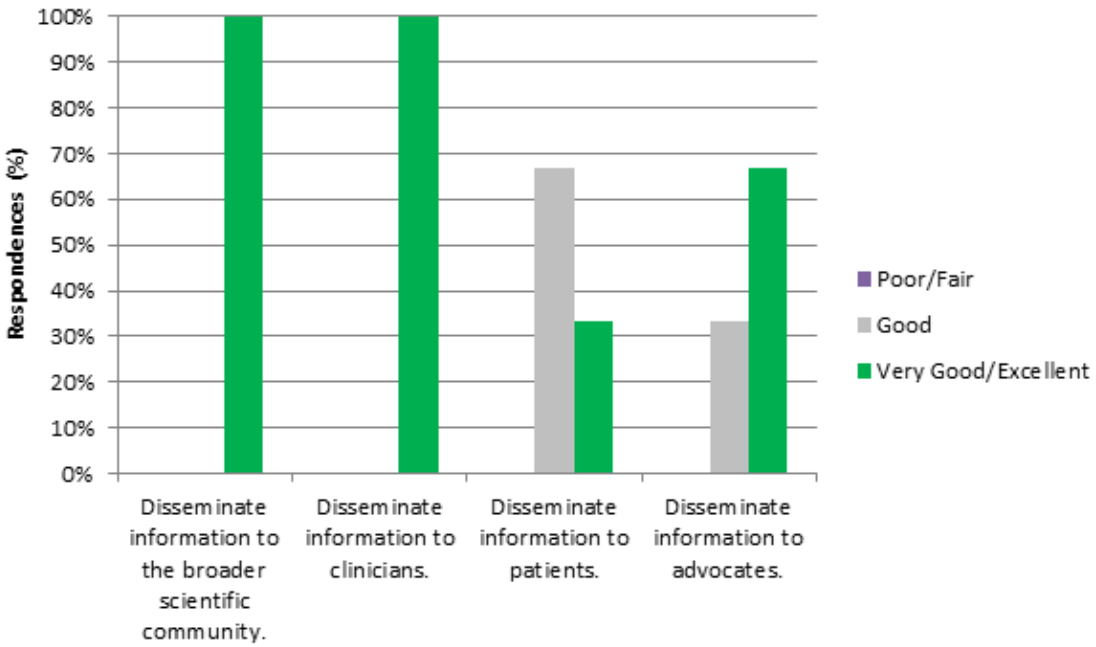



Figure 10.2. Dissemination of PS-OC information to the scientific community and the public. PS-OC Outreach and Dissemination Unit coordinators were asked to rate the success of the Unit in the dissemination of PS-OC information to four different groups (scientists, clinicians, patients, and advocates).

As of January 2010, the PS-OCs organized a total of 27 workshops. This number expanded to 137 workshops by the end of 2010 and continued to increase to a total of 311 workshops by June 2012 (Figure 10.1). These workshops included symposia that targeted oncologists and cancer biologists. Others were geared toward physical scientists, mathematicians, and engineers. The PS-OCs also organized workshops and technology Bootcamps for graduate, undergraduate, and high school students, since they are the future researchers that can move this field forward.

In the PS-OC Program survey, the Outreach and Dissemination Unit coordinators were asked to rate the overall ability of the PS-OC Outreach and Dissemination Unit to disseminate information to the broader scientific community, clinicians, patients, and advocates. Reponses from the survey suggest that the PS-OCs believe they are successful in disseminating information to scientists and clinicians. But they state that there could be improved dissemination to patients and advocates (Figure 10.2).

Over the last year, the PS-OC Program has tried to engage the advocate community more effectively. PS-OC Program advocate, Dr. Carole Baas, has initiated a goal within the PS-OC Program for every PS-OC to have an advocate involved in its Center. For many of the physical scientists, this has been the first time they have worked with an advocate. As of June 2012, seven advocates were associated with the PS-OC Program. These advocates were surveyed about their roles in the Program. PS-OC advocates have participated in PS-OC workshops and in the PS-OC Annual Meeting and also appear to be participating in scientific discussions within the PS-OC (Figure 10.3).

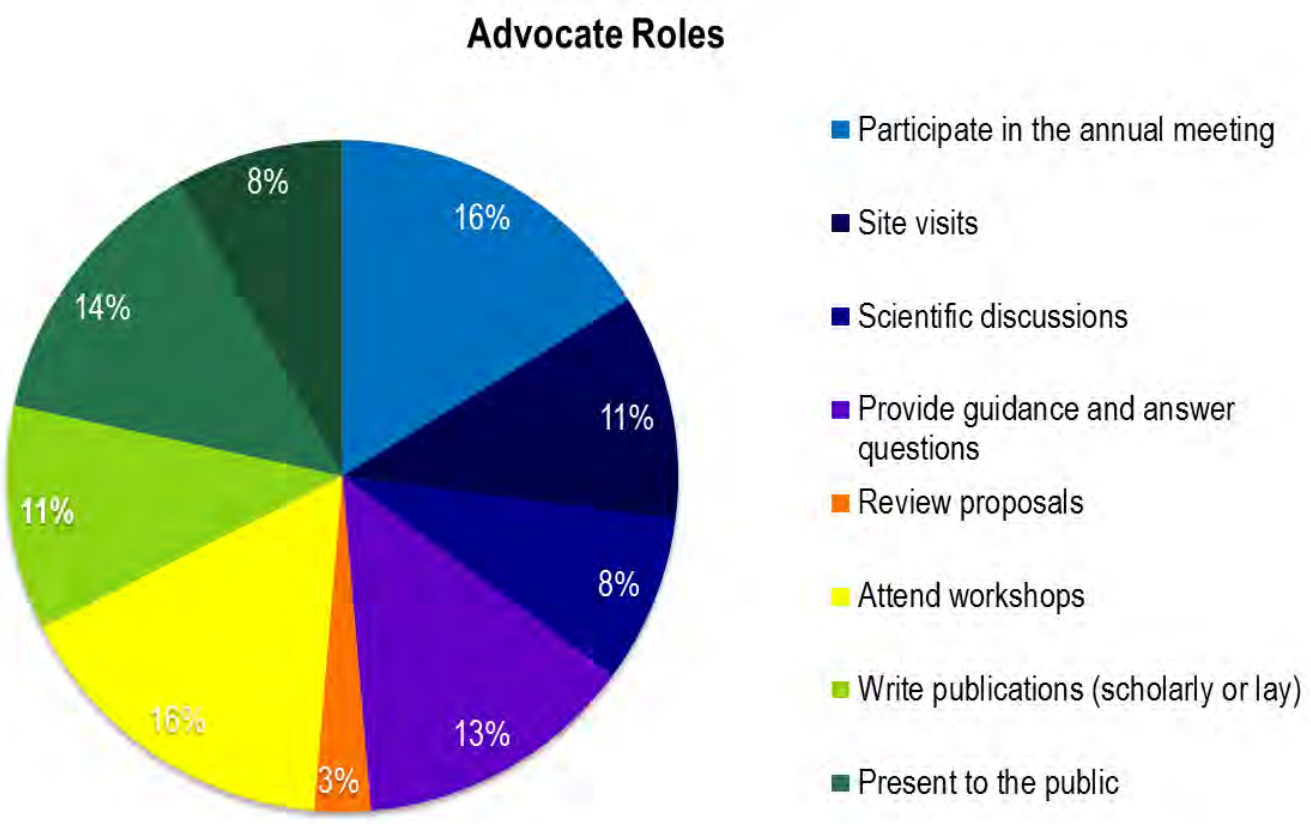



**Figure 10.3.** The roles of advocates in the PS-OC Program. The PS-OC advocates were asked about their roles in the PS-OC Program.

## 10.2 PS-OC Investigators Presenting at Meetings

All PS-OC investigators are encouraged to collectively disseminate their PS-OC research at scientific conferences and seminars and in publications. In the PS-OC Program survey, the investigators were asked how they disseminate their research results to the scientific community and the public. More than 75 percent of respondents indicated that disseminate results through conference presentations, publications, and invited presentations. This was followed at a distant second by websites, e-mails, and radio or newspaper sources of communication. Only three percent stated that they have not disseminated information about the PS-OC Program (Table 10.1).

These survey results have been validated with information collected in the PS-OC progress reports. As highlighted in Section 4, the PS-OC investigators have published 601 manuscripts and books as of June 2012 in more than 210 different journals. Through these publications, the investigators have reached a diverse group of scientists from various disciplines. In addition to these publications, PS-OC investigators have reported more than 3,000 presentations of their research at more than 300 different scientific meetings and seminars over the last three years (Figure 10.4). This averages approximately two to three presentations per person per grant year. PS-OC investigators have presented across the United States (38 of 50 states), with the most presentations in California (Figure 10.5). In addition, they presented their work at conferences in Canada, China, Japan, Taiwan, Indonesia, India, Australia, and Brazil and at 78 conferences across Europe (Figure 10.6).

Table 10.1. Response Rate of PI/SIs and Project Investigators on How They Disseminate Information About the PS-OC Network.

| Dissemination of PS-OC Program Information (PI/SIs and Project Investigators) | Response Percent |
|---|---|
| Presentation at conferences/scientific meetings | 88% |
| Publications | 87% |
| Invited talks | 78% |
| Webpage | 42% |
| Email | 42% |
| Newspaper or radio | 17% |
| I have not disseminated information about the PS-OC | 3% |
| Other | 3% |

The PS-OC Program aims to reach out to a broad range of scientists outside of the PS-OC Network, including both traditional cancer researchers and physical scientists. The PS-OC survey asked the investigators to identify the types of scientists in the audience at their presentations. The results from the survey show that the presentations reached scientists and physicians with a broad range of scientific backgrounds. More than 50 percent of respondents have presented to biologists, oncologists, engineers, or physicists (Figure 10.7). A smaller number of PS-OC investigators have presented their research to other types physical scientists, such as chemists, information technologists, mathematicians, theorists, and radiologists.

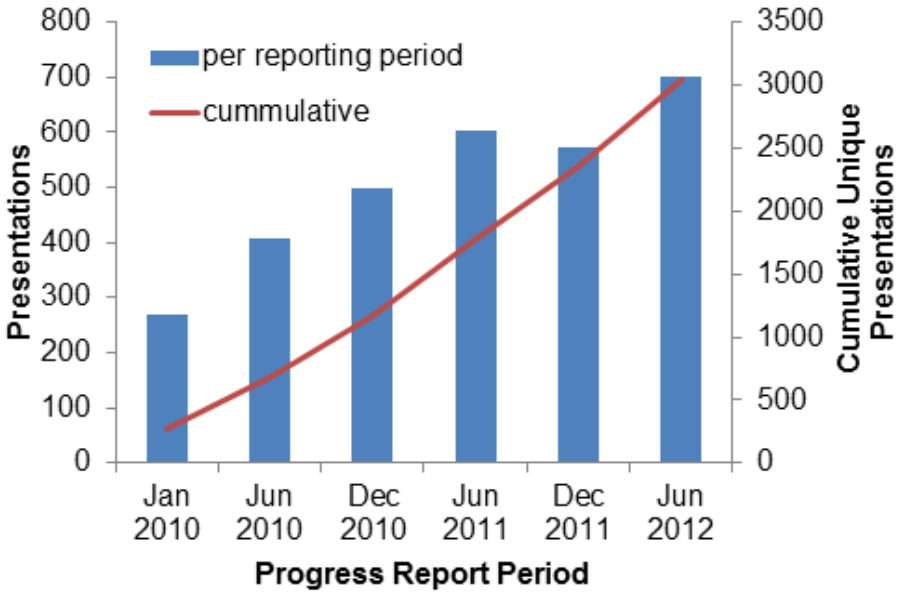



Figure 10.4. Presentations reported in the PS-OC progress reports. (Blue bars) The number of presentations reported in the PS-OC progress reports for each reporting period. These presentations may be reported in more than one reporting period. (Red line) The cumulative number of deduplicated, or unique, presentations, reported over time.

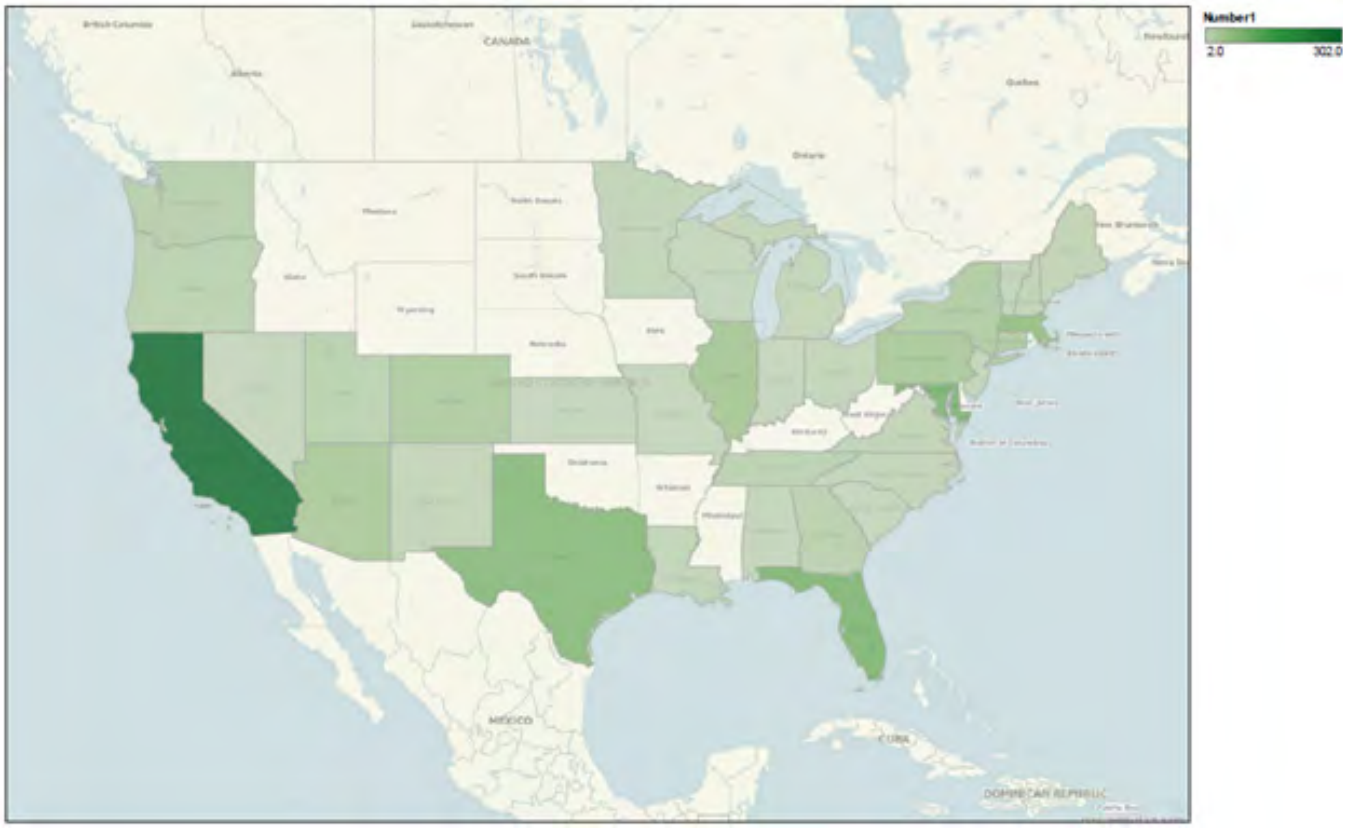



Figure 10.5. Conferences/meetings held across the United States where PS-OC investigators have presented their research findings.

## 10.3 Evidence of PS-OC Research Dissemination

The PS-OC Program evaluation used three metrics to assess the progress of PS-OC Program dissemination to the scientific community. First, the PS-OC Program staff conducted a survey of scientists external to the PS-OC Program to assess their familiarity with the PS-OC Program. Second, investigators inside and outside the PS-OC Program were surveyed about the status of the physical sciences-oncology field. Third, PS-OC Program staff performed a broad search of new programs or centers worldwide that have initiated concepts similar to the PS-OC Program.

### External Scientists Are Familiar with the PS-OC Program

The PS-OC Program staff invited approximately 300 investigators outside of the PS-OC Network to complete the PS-OC Program survey. A total of 96 investigators, 29 percent of those invited, completed the survey questions. External respondents, who varied in experience level, included assistant professors, cancer center directors, and college deans. Each investigator was asked to self-identify his or her scientific training. Approximately 40 percent identified as life scientists and 60 percent identified as physical scientists. The level of familiarity varied among respondents. About 35 percent of these investigators were involved in NCI workshops or the review of the PS-OC Program. Of the other 65 percent of respondents, only 3 percent of those polled in the survey stated that they were not familiar with the PS-OC Program (Figure 10.8). Based on comments from these respondents, most appear to have heard about the PS-OC Program based on interactions with PS-OC investigators.


Figure 10.6. Conferences/meetings held across the world where PS-OC investigators have presented their research findings.

## Formation of the New Physical Sciences-Oncology Field

When surveyed, PIs, SIs, project investigators, and external scientists to the Program agreed that they saw evidence of the formation of a new field of "physical sciences-oncology" in publications, at scientific meetings, in their current and future research plans, as well as in their institutions (Figure 10.9). Respondents included scientists within the PS-OC Network as well as 96 external scientists. Interestingly, the results show the formation of a physical sciences-onoclogy field from the bottom-up (Figure 10.8). More than 45 percent of respondents agreed that there is evidence of the formation of a new physical sciences-oncology field in publications, conferences, and their own research plans; less than 10 percent disagree with this statement. However, within the investigators' departments and institutions more than 25 percent of respondents stated that they do not see evidence of a physical sciences-oncology field within their institutions or their departments. These results suggest that the field is developing at conferences and within investigators' laboratories, but, there appears to be slower formation of a new field at the institution and department levels.

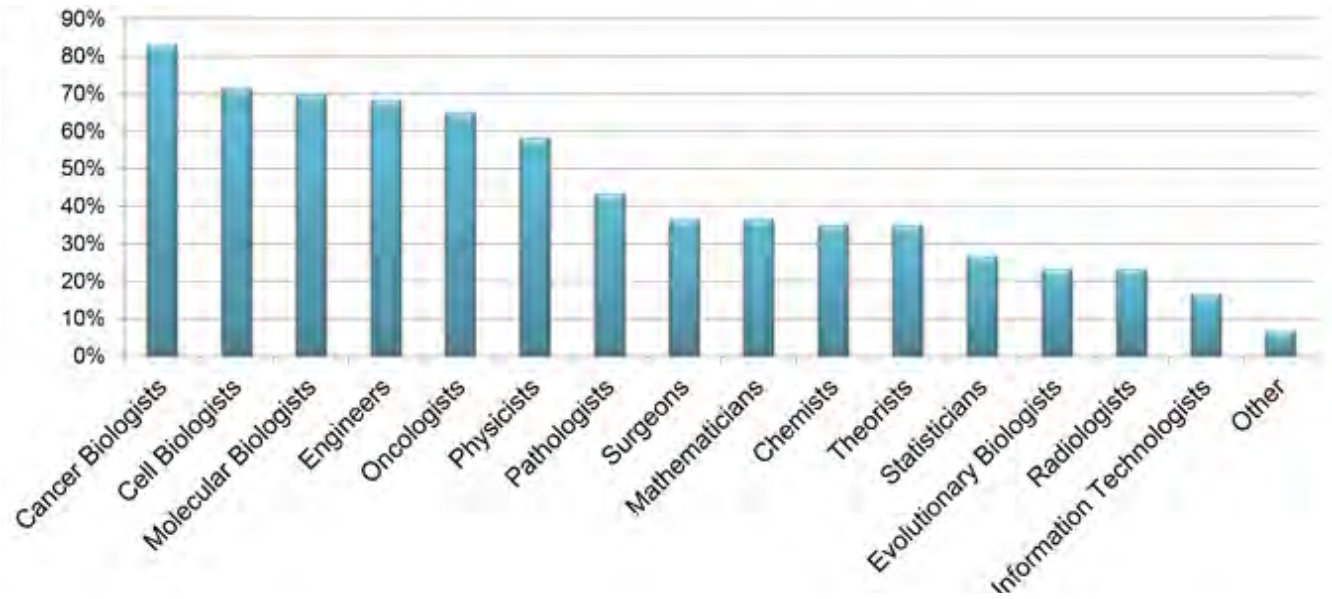



Figure 10.7. Presentation of PS-OC research to different types of scientists. PIs/SIs and project investigators responses to survey question indicating what types of scientists have been presented PS-OC research.

## Conferences and Workshops Integrating Physical Sciences and Oncology Outside of the PS-OC Program

Adding to the evidence of the emerging field of physical sciences and oncology is the increase in the number of conferences (in the United States and worldwide) dedicating entire scientific sessions to the inclusion of physical sciences oncology or biomedical sciences. Prominent examples include the following:

- The joint conference of the European Organization for Nuclear Research (CERN) and the International Conference on Translational Research in Radiation Oncology (March 2012)
- PhysCell (September 2012)
- The International Meeting of the German Society for Cell Biology (November 2012)
- The American Society for Cell Biology 2012 Annual Meeting (December 2012)
- Computational Physics Methods for Cancer, hosted by the European Center for Atomic and Molecular Calculation (CECAM) at École polytechnique fédérale de Lausanne (EPFL) (June 2012)
- Physics of Living Matter, hosted by the Center for the Physics of Medicine at University of Cambridge (September 13-14, 2012)

## New Initiatives Related to the PS-OC Program

In the United States, several organizations and agencies have been encouraging those in the field of physical sciences, mathematics, and engineering to engage more deeply in biological sciences and, more specifically, in cancer research. This is evident from the different initiatives of the NIH and the NSF and from the joint efforts of both agencies in addition to those of other research institutes. Three divisions within the NSF (Mathematical and Physical Sciences, Engineering, and Biological Sciences) are jointly funding a program to support proposals that incorporate approaches and address questions that have traditionally been the domain of the mathematical and physical sciences, engineering, or biological sciences. Since 2006, the NSF has also

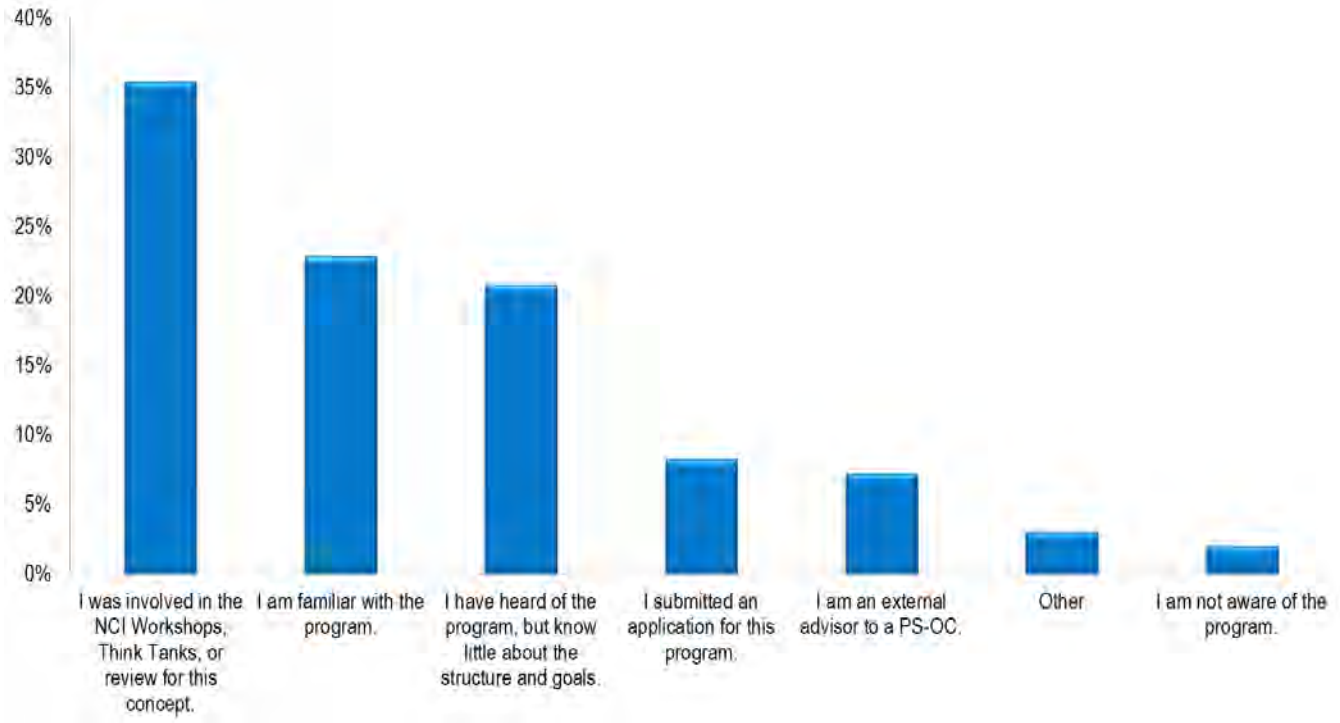



Figure 10.8: External Scientists indication of familiarity with the PS-OC Program. Survey response of 96 external scientists demonstrating awareness of the PS-OC initiative through various sources.

joined forces with the National Institute of General Medical Sciences (NIGMS) to support mathematic and statistical research of biological and biomedical sciences questions. In addition, since 2011 the OPSO itself has had ongoing collaborations with the NSF that fund the Physical/Life Sciences Early-Stage Research (PLIER), also called Physical and Engineering Sciences in Oncology (PESO). This program aims at applying perspectives from physical sciences to advance the understanding of cancer development at various scales.

Throughout Europe there is evidence that the vision of the NCI and the NSF to engage physical scientists, cancer biologists, and oncologists in working closely with one another coincides with initiatives based on similar beliefs that engagement of not only physical scientists, but the concepts and methods of physical sciences research, could benefit cancer research. One example of this type of initiative is the joint effort of the Cancer Multi-organization Thematic Institute (ITMO) and the Health Technologies ITMO of the French National Alliance for Life and Health Sciences (AVIESAN), in partnership with the French National Cancer Institute (INCa) to initiate a call for research projects in physics, mathematics, or engineering sciences related to cancer (www.eva2.inserm.fr/EVA/jsp/). New laboratories of excellence (LABEX) have also been funded in France, including CELTISPHYBIO, initiated in 2012 at the Institut Curie to establish a center for physics in cell biology. In Sweden, the Science for Life Laboratory (SciLifeLab, www.scilifelab.se), which integrates research across multiple intuitions to enable collaborations among technical universities, medicals schools, and basic science research, is one of the largest scientific investments in Swedish history. New funding programs for interdisciplinary projects at the physical science/biomedicine interface funded by the German Science Foundation (DFG) and the Max-Planck-Society are almost too numerous to list. Overall, despite the many funding constraints for science throughout the world, this area of research appears to be expanding.

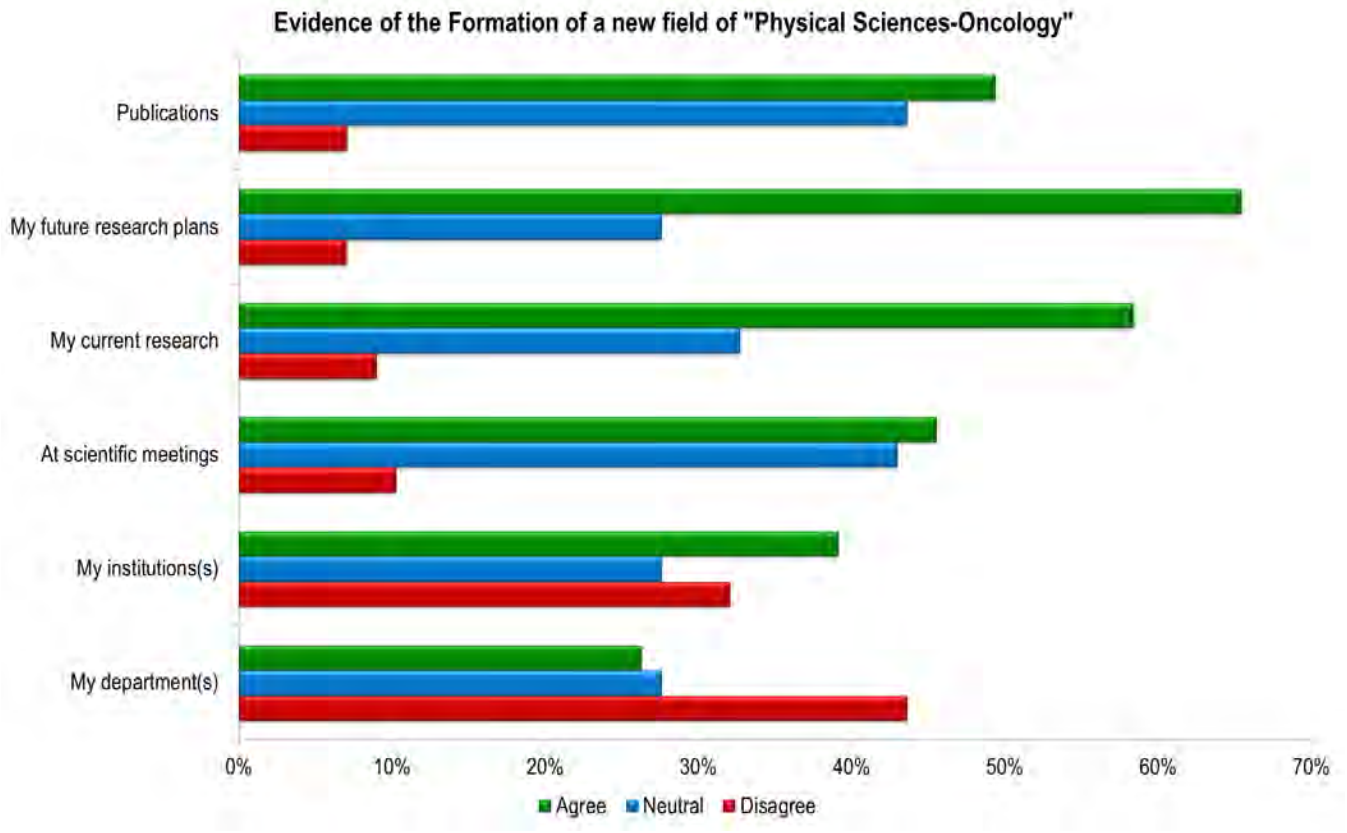



Figure 10.9. Responses to survey statement, "I have seen evidence of the formation of a new field of 'Physical Sciences-Oncology' within…". (Green bars) Respondents that agree with the statement. (Red bars) Respondents that disagree with the statement. (Blue bars) Respondents that are neutral and do not agree or disagree with the statement.

## 10.4 Summary

The PS-OC Program is focused on building scientific teams, infrastructure, and training programs to support the convergence of the physical sciences and oncology fields and bring a new perspective to cancer research. Toward this goal, the Program needs to successfully disseminate research results and experiences to the broader scientific community to encourage continued support and enthusiasm for this area of science. The PS-OCs have widely disseminated research results through workshops, seminars, conferences, and publications. To date, PS-OC investigators have presented more than 3,000 times at conferences worldwide. Additionally, the PS-OCs have engaged seven advocates to participate in the PS-OC Program to assist in dissemination of results to the public and patient communities. The evaluation of the PS-OC Program after three years highlights the emergence of physical sciences in oncology within workshops, conferences, and initiatives outside of the PS-OC and in Europe. Investigators within and outside of the PS-OC Program agree that there is evidence of the formation of a new physical sciences-oncology field emerging within publications, at scientific conferences, and within their own research laboratories. The convergence of these disparate fields within departments and institutions outside of the PS-OCs is still a work in progress and should be emphasized in the future years of the Program.

# 11. OPSO Contributions to the NCI Research Portfolio

## 11.1 Breakdown of Direct Costs for Each PS-OC

Each PS-OC is composed of projects, shared resource cores, and Education and Outreach Units that are governed by an Administrative Unit. The Centers are consistently organized into these divisions in order to effectively integrate the physical sciences and cancer biology perspectives across the Network, but each Center varies in the number of projects/cores and Outreach/Education Units according to the funding allocated. For example, the Moffitt PS-OC was originally funded under the provisions of the American Recovery and Reinvestment Act (ARRA), which allowed for three projects and one core, but not Education or Outreach Units due to reduced funding levels and limitations on restricted funds compared to those Centers supported by appropriated funds. For all the Centers, a majority of the direct funding cost contributes to the three to five major projects focused on the thematic areas. The remaining funds are distributed among the shared resource cores, the Administration Unit, and Education and Outreach Units depending on the specific needs of each Center. The breakdown of the direct costs of each Center is shown below (Figure 11.1).

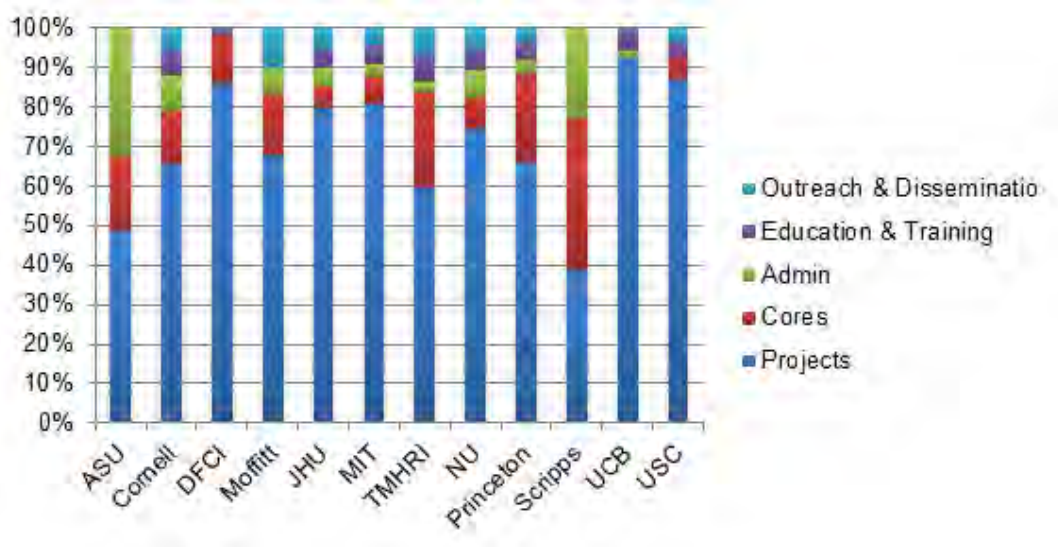



Figure 11.1.

## 11.2 Funds for PS-OC as a Percentage of All Physical Sciences Grants at NCI/NIH

At the start of the PS-OC initiative, the four major themes that emerged included physics and cancer, the evolutionary theory of cancer, information theory and cancer, and de-convoluting the complexity of cancer. A Query View Report (QVR) search was conducted to determine the PS-OC's contribution to the NCI and the NIH's entire portfolio for these four thematic areas (Figure 2). For each of the four PS-OC themes, OPSO program officials completed a QVR search for applications based on specific key terms in abstracts, aims, titles, or summary statements. The total dollar amount funded was queried in order to calculate the PS-OC proportion of the NIH and the NCI portfolios for each theme.

For two of the themes, physics and cancer and complex systems and cancer, the PS-OC initiative has substantially contributed to the NCI's portfolio, comprising more than 80 percent of the NCI's funding in 2009. The other two themes, evolution and cancer and information and cancer, also comprises more than 60 percent of the NCI's portfolio in 2009 (Figure 11.3).

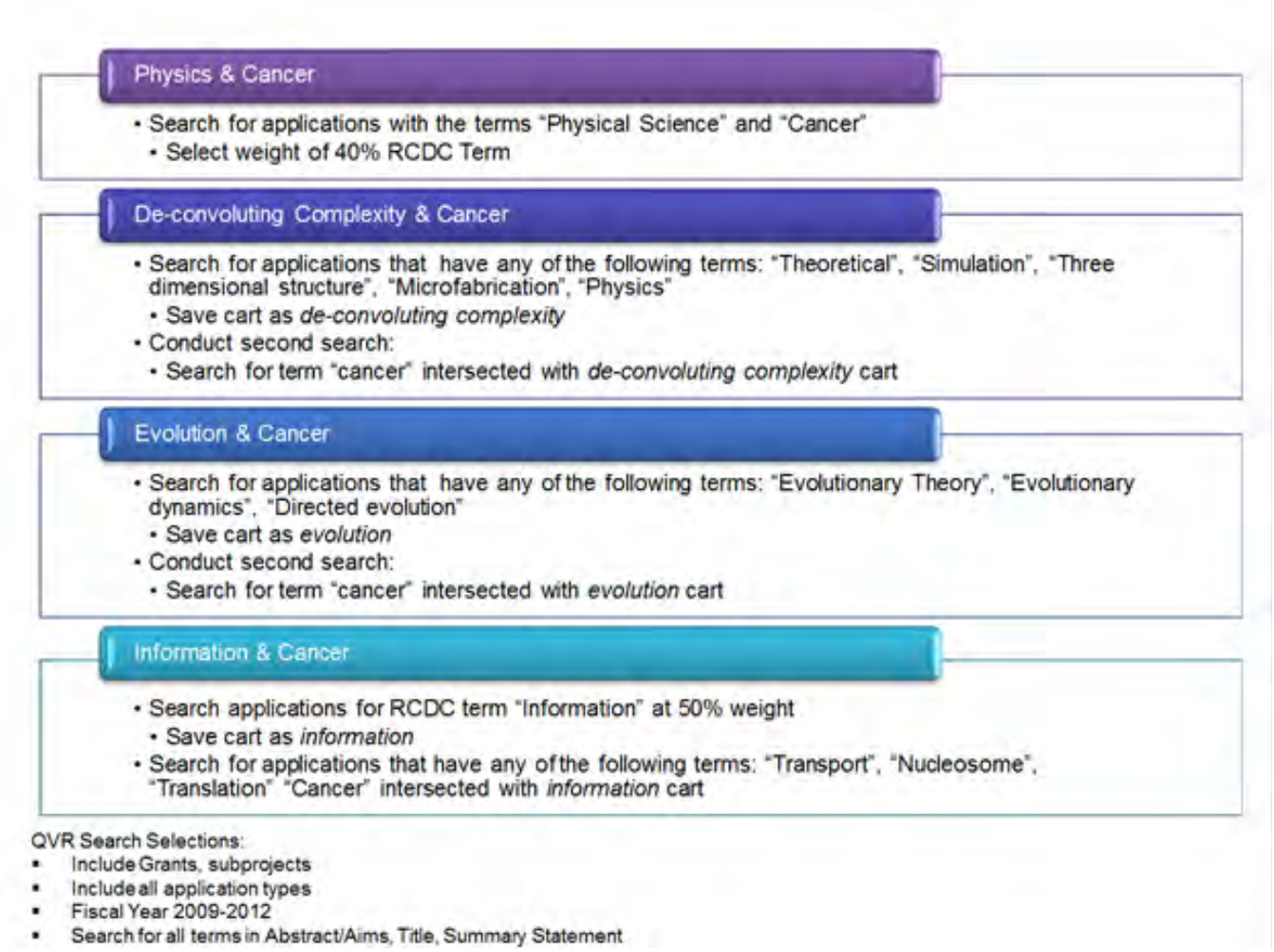



Figure 11.2. QVR Search. The NIH QVR System searched for applications related to the four thematic areas supported by the PS-OC initiative.

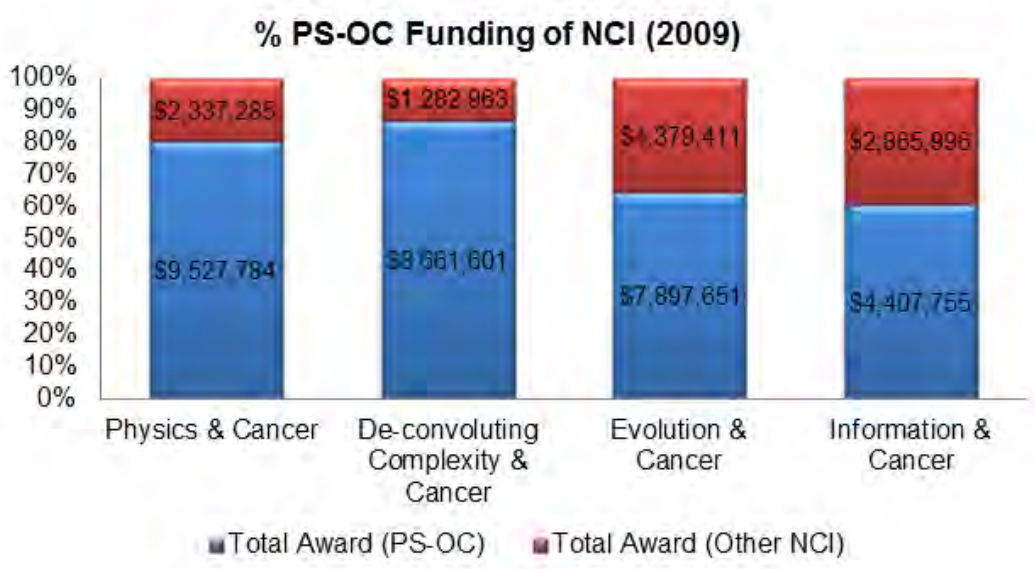



Figure 11.3. PS-OC Funding as a Percent of the NCI's Portfolio. Amount of funding that the PS-OC Program contributes to the NCI's portfolio in each thematic area.

# 12. Comparison of PS-OC Program Early Output to Other NIH Programs

## 12.1 Comparable Programs

To evaluate the relative performance and productivity of the NCI's investment in the PS-OC Program, the output of this Program was benchmarked against three comparable NCI funded U54 programs and the NIGMS funded "Glue Grants." Additionally, Type 1 R01 grants that started in 2009 (the same year as the PS-OC Program) were also included in the analysis in order to determine how the Program fared compared to research funded by this more widely used mechanism.

## 12.2 Metrics Used

The most commonly used metrics to evaluate the scientific impact of research are the number of publications, the number of citations, the journal impact factor, and the number of patents. However, to effectively compare the programs listed above, it is also necessary to account for several other variables that affect these measures, including the following:

- *Level of funding.* The greater the level of investment from funding agencies, the greater the expected output. To correct for this, the relevant metrics will be calculated on a per dollar basis.
- *Lag time for newly initiated programs.* It takes time for newly initiated research to bear fruit and start producing research for publications. To account for the fact that the other U54s being assessed began several years before the PS-OC Program, comparisons will be made over the same phase in the program life cycle – the first three years of funding.
- *Time since publication.* Articles published earlier have had more time to accumulate citations. Since the selected programs began at different times, simply counting the number of citations would not constitute a fair comparison. Instead, this analysis looks at the number of "highly cited articles" produced. For the purposes of this study, papers that ranked in the top 25th percentile for citations, based on year of publication, were classified as "highly cited."[10]

The programs were compared based on the following key evaluation metrics that were calculated over the first three years of funding. Data on total costs were retrieved from the QVR database; date on the number of publications were retrieved from the SPIRES database; and the number of citations was determined by combining the citations detected by both the eSPA and the Thompson Reuters Web of Science databases.

- Number of publications per million dollars in total costs (pub/$MM)
- Number of highly cited publications per million dollars of total costs (highly cited/$MM)
- Average journal impact factor
- Weighted impact,[11] of the pub/$MM x average journal impact factor
- Number of patent applications

[10] For the years 2005-2011, the citations for all papers with the key term "systems biology" in the Thompson Reuters Web of Science database were retrieved and entered into a database. This search returned publications that covered a broad range of PS-OC-related themes and provided a sample of between 3,000-5,000 papers each year. Publications that ranked in the top 25th percentile for citations based on the year of publication were categorized as "highly cited."

[11] In order to factor in both the number and quality of publications, a new metric termed "weighted impact" is used. This metric is calculated by multiplying Pub/$MM with the average journal impact factor.

# 12.3 Comparison of Early Output of the PS-OC Program with Other U54 Programs and Type 1 R01s

## Publications Per Million Dollars in Total Costs (PUB/$MM)

Over the time periods evaluated, the NIH database SPIRES was used to extract publication information affiliated with the PS-OC Program , comparable U54 NIH Programs, and a subset of R01 applications. Although the SPIRES database is limited in the amount of information available for each publication, it is the only available database with comparable data for each Program. According to the SPIRES database, the PS-OC Program has funded 401 publications in the first three years of operations, which translates to 4.4 papers per million dollars of total costs (pub/$MM; see Table 12.1). The comparable NCI-funded U54s ranged from 1.0 pub/$MM to 1.7 pub/$MM. Type 1 R01s that were evaluated generated a total of 3,073 publications but at a higher cost, since on average only 2.5 publications were produced per million dollars.

It should be noted that several of the publications in SPIRES cite more than one grant and in many cases more than one NIH program. Based on the SPIRES database, 41 percent of the PS-OC publications cite one grant number and are exclusively attributed to the PS-OC Program.

## Average Journal Impact Factor

The journal impact factor metric is a measure of the citation frequency expected for an average article in a specified period of time for a specific journal. It is typically used as a measure of a journal's prestige and thus also serves as an indirect measure of an article's scientific merit, although we do note that there are caveats in using the impact factor this way. Nevertheless, because it is a widely used metric, we calculated the average journal impact factor for the programs being compared based on data from SPIRES. The PS-OC Program average was second overall for the NIH Programs considered, with an average impact factor of 9.8 (Table 12.1).

Table 12.1. Bibliometric comparison of the PS-OC Program with Other U54 Programs and Selected R01 Grants. This table shows the specified metrics for the Physical Sciences-Oncology Center (PS-OC) Program, 3 different NCI U54 Program initiated in the past 10 years, and new (type 1) R01 grants starting in 2009. The data shown reflect the average performance of these grants over the first three years of funding to facilitate comparisons with the progress of the PS-OC Program. Total Funding used to calculate publications and citations per $MM.

| | Time Period | Total Publications | Publications/ $MM | Average Journal Impact Factor (IF) | "Weighted Impact (IF x Pub/$MM)" | Total Highly Cited Publications* | Highly Cited Publications/ $MM |
|---|---|---|---|---|---|---|---|
| PS-OC | '09-'12 | 401 | 4.4 | 9.8 | 43.6 | 105 | 1.3 |
| NCI (1) | '06-'09 | 41 | 1.7 | 10.9 | 18.8 | 21 | 0.9 |
| NCI (2) | '04-'07 | 49 | 1.0 | 9.4 | 9.6 | 41 | 0.7 |
| NCI (3) | '05-'08 | 148 | 1.7 | 9.8 | 17.1 | 120 | 1.2 |
| NIGMS | '00-'03 | 17 | 0.7 | 9.7 | 6.9 | n/a | n/a |
| R01s | '09-'12 | 3073 | 2.5 | 5.9 | 15.0 | n/a | n/a |
| | | Publication Metrics | | Journal Impact Metrics | | Citation Metrics | |

+Total Highly Cited Publications, 2011 is last year analyzed.

### Weighted Impact: Pub/$MM X Average Journal Impact Factor

The pub/$MM metric provides a measure of productivity in terms of publication volume per dollar spent. The average impact factor score is an indirect measure of the quality of those publications. In order to account for not only the volume of publications but also the "quality" of publications, a non-traditional metric—that will be referred to as "weighted impact"—was also evaluated. This metric is calculated by multiplying pub/$MM by the average impact factor of the journals where the papers were published. Based on this measure, the PS-OC Program also scored better than the programs it is being benchmarked against (Table 12.1). The average weighted impact score was 43.6 compared to 18.8, 9.6, 17.1, 6.4, and 17.3 for the three NCI U54 programs, the NIGMS U54 programs, and the 2009 R01 cohort, respectively (Table 12.1). The caveat of this metric is that it places an emphasis on journal impact factors. Although this is a useful measure in gauging the influence of a journal, it is an indirect measure for assessing the impact of an individual publication. To avoid these complications, publications were also evaluated based on direct citation data (see below).

### Number of Highly Cited Publications per Million Dollars of Total Costs (Highly Cited/$MM)

Citations of published research are one direct measure of a paper's influence. As discussed previously, simply counting citations will not allow for meaningful comparisons; thus, the metric of highly cited publications per million dollars of total costs (highly cited/$MM) was used since it allowed the citations to each paper to be objectively ranked and accounted for differences in the length of time since publication. The SPIRES database does not contain citation information. For this study, citation data were downloaded from eSPA and the Thompson Reuters Web of Science databases. eSPA tended to be better at detecting older citations while the Web of Science was better with more recent citations. The two lists were combined, and any duplicates removed. In the case of a discrepancy between citation numbers, the Web of Science number was used. For the purposes of this study, papers that had a number of citations to rank them in the top 25th percentile, based on year of publication, were classified as "highly cited."[12] Papers published after December 2011 were not analyzed for this study due to a limited amount of data for 2012. Because of this limitation, only PS-OC publications from 2009 to 2011 were analyzed—290 out of 401.

The PS-OC had the highest average highly cited/$MM score (1.3; see Table 12.1). Because of the large number, the average for the entire group of R01s was not calculated. A look at the individual Centers showed that while on average the PS-OC Program Centers outperformed the others, the top-performing Centers in the other NCI U54 programs had higher highly cited/$MM scores. These were 4.7, 3.4, and 4.0, respectively, compared to 2.9 for PS-OC (Figure 12.1). The top, bottom, 25th, and 75th percentile R01s were analyzed to get an idea of the range of highly cited/$MM scores for these grants. While the top-ranked R01 grant produced almost 10 highly cited articles per million dollars of total costs, the grant in the top 75th percentile produced only 1, indicating that the U54 programs on the whole were slightly better at generating highly cited work. In summary, this analysis demonstrates that the PS-OC Program was effective at producing high-impact work and was cost-effective in doing so. Finally, it should be noted that because reference citation data are only available through 2011, the scores for the PS-OC Program are an underestimate, since the publications from 2012 were not included.

[12] For the years 2005 to 2011, the citations for all papers with the key term "systems biology" in the Thompson Reuters Web of Science database were retrieved and entered into a database. This search returned publications that covered a broad range of PS-OC-related themes and provided a sample of between 3,000 to 5,000 papers each year. Publications that ranked in the top 25th percentile for citations, based on the year of publication, were categorized as "highly cited."

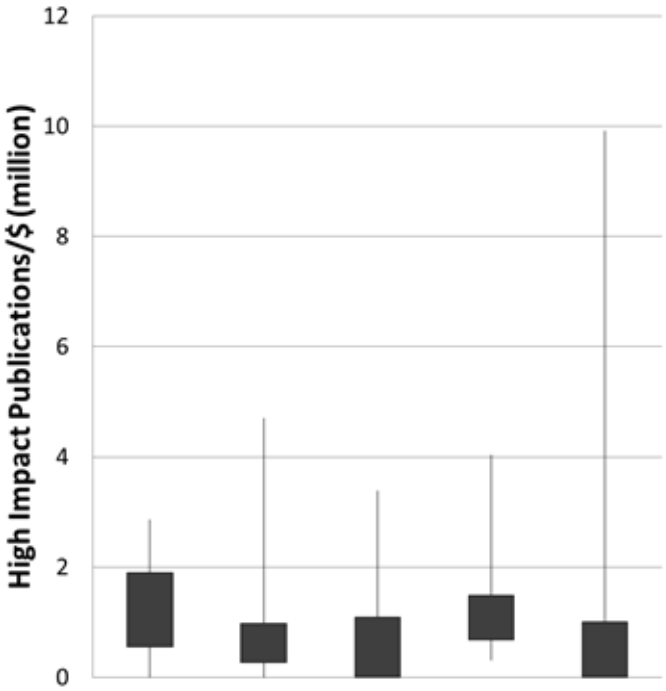



Figure 12.1. Number of High-Impact Publications per Million Dollars of Total Costs. See main text for definition of "Highly Cited Publications". Citation data was retrieved from eSPA and the Thompson Reuters Web of Science databases. Lines show the range for the highest and lowest scoring grant for each group, while the boxes show the range between the 25th and 75th percentile for each group.

## Number of Patent Applications

Information on patents filed for the other NCI U54 programs were downloaded from eSPA. Patent applications from the PS-OC Program were obtained from the latest progress reports, since they are too recent to be included in the eSPA database. Data were not collected for the R01 grants because there were too many grants to analyze in depth. The NCI program with the most patent applications had 16 according to the database, while the others had two and one respectively. However, in total, the combined number of patents for the other U54 programs in the first three years was one. This emphasizes the point that it takes time for new initiatives to bear fruit. It is difficult to conduct a direct comparison of the PS-OC Program patent disclosures to these older programs because of limitations with databases and lack of time. But, according to the progress reports, the PS-OC Program has led to 23 patents being filed in the three-year start-up period being considered. This return is potentially greater than that of the other programs, pending the final numbers.

## 12.4 Summary

Overall, the analysis indicates that when funding levels and timing are controlled for, the PS-OC Program was productive relative to other NCI U54 Programs and Type 1 R01s. The average PS-OC score for publications/$MM, weighted impact, high-impact publications/$MM, and number of patents was higher than those for the U54s and R01s evaluated. These results indicate that the investment by the NCI into the PS-OC Program is being rewarded by the generation of new knowledge, the dissemination of that knowledge through publications, and avenues for translational research through patents. The OPSO will continue to coordinate with, and learn from, other NCI Programs to improve on ways to measure the relative success of large U54 programs.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