Physical Sciences in Oncology Center Program External Review
February 2013

A panel of external reviewers was invited to evaluate the progress of the PS-OC Program in November 2012 based on internal materials and reports provided by the OPSO program staff. The panel was asked to focus the evaluation on six questions listed below:

1) To what extent have the Program's objectives and priorities been met by progress to date? Overall, does the panel believe the PS-OC Program is on track to meet its goals?
2) How did the Program design (e.g. U54 mechanism, pilot projects, role of PI as a physical scientist) facilitate achieving the objectives? Are Centers considered to be the appropriate infrastructure to achieve the Program's priorities and objectives? Have there been issues with the implementation of the Centers to date? Would inclusion of mechanisms in addition to Centers increase the Program's ability to meet its objectives?"
3) How do the scientific aims of the PS-OC Program compare with most science occurring elsewhere, specifically with respect to innovation and transdisciplinary research?
4) To what extent do the relationships between physical scientists and cancer researchers appear to be appropriately collaborative, with both groups making substantive contributions to the research? To what extent are such collaborations occurring at institutions that are not participating in the PS-OC Program?
5) How do training opportunities available through the PS-OC Program differ from training opportunities available elsewhere?
6) How would you recommend the Program's priorities be changed based upon the Program's progress to date? Does the panel believe that the potential for future progress merits continued investment by NCI in the PS-OC Program?

During the evaluation and review process questions arose among the panel members that did not fit into the six questions provided above. The panel believed that those questions, comments and/or concerns merited inclusion in the report. In constructing the report it was decided that the additional information should be included in the background section as well as be placed in the final section as recommendations to consider in moving forward.

The greatest challenge for the review committee in conducting the requested evaluation was the lack of information in the provided materials about how some of the factors used in the quantitative analysis were defined. It was very difficult for the panel to be thorough in answering the questions provided without a clear understanding, for example, of the criteria for assigning "accomplishments" to the PS-OC. This led the panel to question the interpretations made in the progress report that the data and statistics indicate, for example "a significant increase," or that new theories and hypotheses are truly "new and innovative". In addition the time frame given to perform the review was very limited and the expectation among reviewers was that all information required to perform a comprehensive scientific and

programmatic review would have been provided.

In no way does the review panel want to negate the accomplishments and progress the PSOC Program has made to date, which clearly deserve credit. However the panel does want to provide some cautions with respect to how the available data is interpreted.

The Committee commends the Program on establishing metrics in advance of the program and using appropriate quantitative methods to assess scientific progress, program integration, and transdisciplinarity. At the same time the panel cautions the NCI to not use the data to overstate the contributions of the program to the state of the science in the cancer research field. Each of the above questions is treated in its own section in this report. The conclusions from each of those sections are:

1. *Overall Goals:* The PS-OC program is demonstrating some early successes and appears to be on track. However, the accomplishments of the program should not be overstated.
2. *Mechanism:* The U54 mechanism is flexible and provides the NCI Program staff the ability to make adjustments to PS-OC program components
3. *Innovation:* The PS-OC program has begun to make some contributions. These contributions should not be overstated.
4. *Interdisciplinarity:* Interdisciplinary efforts are being formed. Currently there seems to be an imbalance with the physical sciences contributing more to the biologic sciences than the other way around. Collaborations take much effort to develop and sustain. This component of the effort is on track and requires time and nurturing in order to flourish.
5. *Training and Education:* The PS-OC program did an excellent job in identifying training activities that had been successfully utilized by various NIH U54 programs and offering them as a package to the PS-OC trainees.
6. *Future:* Initial program accomplishments are promising. Some areas of consideration for the PS-OC program are presented including, but not limited to defining PSO, sharing, reciprocity of interdisciplinarity, and diversity.

In response to the Panel's question to program staff about what they viewed as the major challenges they have faced in the implementation of the program, they reported the following challenges, which are more fully described in Appendix 1:

1. Bringing physical sciences in oncology to the mainstream of the cancer research community
2. Integration across projects within a Center
3. Providing opportunities in the area of physical sciences in oncology to those not funded directly by the program

4. Focusing on specific issues or questions given that the program covers a broad range of scientific topics

The Program staff are taking a range of appropriate steps to addressing these issues, for example through the pilot studies program and during site visits, in annual reports, annual meetings, and retreats, the program staff continually push investigators to integrate concepts and results across their PS-OC.

The PS-OC program has the same challenges and successes as many NCI special programs that have as a goal the fostering of integration, networking, and collaboration across disparate institutions and disciplines to address an important emerging area of science. The PS-OC staff has gained considerable experience n applying current methods and tools to evaluate success of NCI and investigators' efforts to integration of scientific fields, promote transdisciplinary and research, and support team science. It would be valuable to NCI if they partnered with other Divisions that have used these and various other evaluation methods to improve the capacity of NCI extramural programs to conduct these evaluations and to do so in ways that are efficient, inexpensive, and minimize staff time and NCI resources.

In addition to the steps the PS-OC staff is taking to address the challenges mentioned to the Panel, the Panel encourages the staff to:

1. Consider ways to integrate the PS-OC Program with other integrative programs such as the Integrative Cancer Biology Program. For example, one way might include hosting a small retreat of senior leaders from the various Centers.
2. Find ways at the NCI Program staff level to benefit from the experience of and share their experiences with other integrative programs that NCI is currently managing.

In future reports, including "limitations" sections would be very benefited review panels as they consider the various elements of the overall program.

Section 1

To what extent have the Program's objectives and priorities been met by progress to date? Overall, does the panel believe the PS-OC Program is on track to meet its goals?

The PS-OC Program has five stated objectives as listed below.

- Establish an unprecedented Network of Centers 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

Based on the materials provided to the reviewers, there is excellent evidence that the program is not only meeting its stated goals, but exceeding them. It is clear that a network infrastructure has been created that facilitates intra- as well as inter-center interactions and collaborations. While four major theme areas provide an intellectual basis for scientific questions, the resources provided to the centers appear to be catalyzing collaborations through direct funding of trans-center projects and the establishment of core facilities. Enticing experts in the physical sciences to join cancer researchers certainly broadens the perspectives with which nagging questions in cancer research can be addressed and provides distinct training opportunities wherein students and fellows can increase their knowledge base, expand their networks, and bring or develop new technologies to solve complex problems. And impressively, the program is already seeing the conduct of clinical trials among various centers. From the materials provided, it was anticipated that this would be a future goal – and a very pleasant surprise that clinically focused work was being done so early in the program's existence.

The review panel was particularly impressed with the progress made in terms of publications attributed to the program, including the return on investment presented as number of publications per dollars invested by center. Phrases such as "the program hit the ground running", "how are they doing this?" and "astonishing" were captured from the review panel during their discussions about the program.

However, the review panel was not able to determine from the written documentation provided, how publications, clinical trials and patents are being attributed to this granting mechanism. Is the same approach being taken for this program as for other NCI funded programs? It is also not clear from the materials provided to what the program attributes its astonishing metrics of success achieved in only 3 years of existence. What are the tangible and concrete factors that contribute to this level of accomplishment? In general, there was

difficulty in being able to dig deep into aspects of the program given the fairly high-level and general reporting approach taken. This will be addressed further in Section 3.

The presentation of such outstanding data in the context of an extremely well polished and expertly created report led the review panel to ask several questions including how resources were being spent in the context of this program. There was general agreement that the program was "too well presented". The report provided was extremely self-laudatory, had a public relations quality, and lacked sections devoted to challenges, problems, or lessons learned during the course of the initial three years of the program. Upon the request of the review panel the PSOC Program staff set up a teleconference in order to provide some information about challenges faced (Appendix 1). The reviewers were neither provided with data regarding the overall PSOC budget nor asked to consider it. Some pieces of budget information can be found in the report. Based on the materials provided to this review panel and the associated text describing the contributions, efforts and activities of the support staff and contractors supporting the administrative side of the PS-OC it could only be concluded that a substantial percentage of the overall budget is dedicated to administering the program. We will return to this point in Section 6.

One cautionary note is the description of an *"unprecedented Network of Centers and transdisciplinary teams focused on solving cancer problems"* found throughout the report. While this is true in the strict sense of the phrase in that these exact centers have not been put together before, there are other efforts utilizing these types of teams at both a multi-PI R01 level and a center level. One example is NCI's Integrative Cancer Biology Program (ICBP), which predates the PSOC and is composed of similar teams. In fact, at various times more than half of the key personnel in the ICBP were from the physical science community (Physicist, Engineers, and Mathematicians).

The review panel, again, wants to recognize that there are many successes of the program to date. There would great value in sharing information about how this was done more broadly, not just across NCI, but also with the broader NIH and other funding agencies. Such information could provide valuable guidance for how to successfully launch a program of high priority for a funding agency.

It may benefit the program to clearly articulate their definition of "unprecedented" and what criteria are used in that characterization. In the panel's experience this term is often used when stating a vision – a desired future state. If the program had used this term to describe its vision for the future and then articulated a mission and goals to achieve it, that probably would have worked. It does not work as a stated accomplishment.

Section 2

How did the Program design (e.g. U54 mechanism, pilot projects, role of PI as a physical scientist) facilitate achieving the objectives? Are Centers considered to be the appropriate infrastructure to achieve the Program's priorities and objectives? Have there been issues with the implementation of the Centers to date? Would inclusion of mechanisms in addition to Centers increase the Program's ability to meet its objectives?

The design of the PS-OC program appears to have enabled excellent progress towards the Program's objectives. Likely important contributors to success were requirements and provisions set out in the design by NCI staff to promote cooperative and collaborative efforts. These features included the requirement that the PI be a physical scientist and that there be a Senior Investigator from cancer basic/clinical sciences; availability of trans-network pilot funding; funding for training; strong NCI Extramural staff involvement; potential for cores that could service more than one center; a Steering Committee that included the PIs and NCI staff; and an annual meeting of NCI staff and the Centers' leadership teams.

Centers appear to be the appropriate infrastructure to achieve the Program's priorities and objectives for two reasons. First, the U54 mechanism enables a host of research and support activities by multiple awardees to address complex scientific problems such as how the physical sciences can be employed to accelerate progress in cancer and oncology (see end of this document for the definition of the U54 mechanism). Second, it allows strong and continuous input by NIH extramural staff to ensure integration of the projects and collaboration among the awardees.

While the very structure of these centers mandated by the RFA guaranteed a transdisciplinary aspect to the research, mandating this structure is not the same as achieving it in practice and this is always challenging. The program through many activities and oversight from NCI staff appears to have done an excellent job in achieving this goal. Researcher feedback suggests that this has been more effective in activities within the "network" of centers than in broader outreach activities (Figure 5.7, pg49). This could reflect the lack of maturity of many of the centers where the first priority is to develop collaborations locally.

The implementation of the Program appears to have occurred as planned. Annual meetings and meetings of the Steering Committee meetings have occurred regularly. Interactions between and among the centers and the NCI are clearly occurring based on evidence from the network analysis and analysis of authorship of scientific papers. Core facilities were established, pilot programs developed, training programs developed and offered, research was successfully undertaken, and outreach and dissemination are occurring.

A survey of the PIs and Senior Investigators indicated that almost 90% were promoting multi-disciplinary collaborations between PS-OCs, but lagging was implementation of promotion of multi-disciplinary collaborations within centers, and less than half of the PIs and Senior Investigators were emphasizing strategic planning in their centers. The Working Groups appear good at promoting collaborations, new knowledge and increased communication among investigators. PIs and Senior Investigators rated NCI Program Staff as good to very good in effectively performing their roles in management and direction of the program (the NCI staff received ratings of 40-60 "effective" in the various activity categories). (Note: It might have been better had the survey used a scale with at least 5 categories (e.g., very effective, effective, neutral, etc instead of effective, neutral, not effective) because many respondents used the "neutral" category, which is hard to interpret).

Chapter 7 of the Year 3 Evaluation Report addresses the infrastructure built by the network. Figure 7.1 shows that PS-OC investigators have been awarded new grants since the program inception, especially from NIH, but it is not clear whether these grants grew out of or relate in any way to using physical sciences to solve cancer/oncology questions.

Overall, all the component parts of the Program are functioning very well; all of the major pieces of the infrastructure called for in the RFA (training programs, pilot studies processes) are in place and appear to have helped the investigators to achieve great success.

Challenges such as the small number of physical scientists in the PS-OC who held funded R01s in 2012 is to be expected in an initiative in its third year. To address this challenge, it is suggested that Program staff emphasize to the PS-OC investigators that NIH's multi-PI mechanism may work well for PS-OC investigators applying for NIH grants as it allows scientists from different disciplines to have leadership roles. NCI program staff could also work with Study Section SROs to identify a cadre of physical sciences scientists who could serve in the future as ad hoc reviewers for PS-OC type NIH grant applications.

There does not appear to be a need for inclusion of mechanisms in addition to Centers to meet the program objectives. No specific deficiencies related to the mechanism were noted in the report, and the U54 mechanism is flexible and provides the NCI Program staff the ability to make adjustments to PS-OC program components.

> ***Description of the U54 Specialized Center – Cooperative Agreements Mechanism:*** *To support any part of the full range of research and development from very basic to clinical; may involve ancillary supportive activities such as protracted patient care necessary to the primary research or R&D effort. The spectrum of activities comprises a multidisciplinary attack on a specific disease entity or biomedical*

problem area. These differ from program project in that they are usually developed in response to an announcement of the programmatic needs of an Institute or Division and subsequently receive continuous attention from its staff. Centers may also serve as regional or national resources for special research purposes, with funding component staff helping to identify appropriate priority needs.

Section 3

How did the scientific aims of the PS-OC Program compare with the most science occurring elsewhere, specifically with respect to innovation and transdisciplinary research?

The scientific aims of this program are broad, spanning fundamental biological understanding and physical properties to more abstract theories of cancer. The goals are identified in four major thematic areas:

- **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 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 prediction of viable pathways to develop novel interventions.

In addition to these four scientific areas the program also had goals to develop innovative approaches in a trans-disciplinary environment.

In conducting this review certain considerations have to be made as to the scope of both the broad scientific areas identified and comparable research efforts. Therefore, the review reflects selected areas of science as well as representative scientific programs and not *"most science occurring elsewhere"* (the phrasing of question 3 provided to the review panel) as this is too broad for this report. This is reflected primarily by the current literature and

reviewers experiences about other NCI programs. Due to limited time and resources the review was primarily based on the OPSO own draft report "PS-OC Program Metrics-Year 3 Update Fall 2012". This report, herein referred to as the "PSOC report", was quite detailed and included many novel metrics to try and assess abstract concepts such as "innovation" and "multi-disciplinary" research.

Another challenging aspect of this review was identifying and describing specifically the unique areas of science listed in the four scientific themes as these frequently overlap and are based on well-established research efforts. Certain jargon and vocabulary associated with cancer biology terms, such as the inclusion of words as "physics", "forces", "mathematics", "dynamics", etc. do not necessitate a new field or area of research. However, it is also true that these may indeed reflect emerging areas of research utilizing physical science concepts to develop new theories of cancer and research fields.

The PSOC report clearly shows that the centers have been very productive in the generation of both manuscripts and other key metrics such as inventions and training. Accessing scientific accomplishments as related to the field published papers is the primary metric used both by the PSOC report and this review. The sheer volume of manuscripts generated is quite impressive and, one could even conclude based on the numbers reported, better than comparable NCI U54 programs as reported in section 12 of the PSOC report.

However, there were a couple of concerns regarding the assumptions made in this section. First, it is not always correct that the level of funding should directly correlate with the number of publications resulting from that funding. Second, certain types of research take longer to develop and may not have the capacity for multiple publications but that does not diminish the importance of the work. For example, clinical trials, animal studies, and epidemiology studies are very expensive as compared to more computational and cell line studies. Frequently these studies take additional time to conclude.

Another example is large projects such as the TCGA which frequently result in a large publication with many authors reflecting the scope of the project and the real value is the generation of the data which provides fuel for the research community. Another interesting comparison would be to see if the papers attributed to the PSOC centers cited papers from the other programs and R01s included in the study, which would reflect the building of science in related fields and the challenges of developing a field. One last point in regard to PSOC contribution to the NCI portfolio as compared to NIH funding is curious. Figure 11.4 (p122) clearly shows that while the PSOC has made a significant contribution to the four PSOC cancer related themes, it is a relatively minor component when compared to that of the whole NIH. In other words, there is currently significant support for these cancer fields outside of the PSOCs.

As mentioned earlier, it is always difficult to identify let alone assign attribution to innovative, transdisciplinary research or impact of new research areas. The PSOC report has helped by identifying a number of "Potential Breakthrough Publications" (Section 4.3 p30) as well as identifying "New Knowledge" using some proprietary metrics developed for this report by a contractor (Section 5 p39). It clear that many of the papers listed have had a significant impact on the field and could even be described as innovative in the field of cancer biology integrating many of the themes defining the PSOCs. In section 4.3, five such papers are cited on page 31.

One point that is overlooked in section 4.3 as well as throughout the PSOC report is the diversity of the attribution of the cited work or group of investigators. As with most transdisciplinary research it is difficult to "lay sole claim" to a specific paper or area of research as suggested throughout this report. Specifically:

- Paper # 1 Fraley *et al.* describing a role of focal adhesion proteins in cell motility is actually supported by 4 NIH grants, one from DCB, NCI; 2 from NIGMS; and the PSOC grant. All apparently contributed to this work as cited from the original manuscript. It is also apparent that some of these grants predate the PSOC center suggesting a pre-PSOC initiation of the work.
- Paper #2 by Polo *et al.* on stem cells seems to have been performed without PSOC support according to the acknowledgement section of the paper.
- Paper # 3 is a review with no acknowledgements.
- Papers #4 and #5 are again supported by a variety of grants with the last paper (Mukherji *et al.*) showing a large percentage of non-PSOC support including a long-standing program project.

While this recognition doesn't disregard or discount the PSOC contribution to these important papers, it does highlight the difficulties of trying to attribute research to a specific program in a very sophisticated and complex research field. This is especially true when crossing disciplines and should be recognized. The same analysis was not performed on sections 4.5-Patents and 4.6-Clinical Trials, but it appears that the PSOC centers have been very active in these areas. Of particular note is the large amount of patents and new technology emanating from the centers.

As mentioned earlier the PSOC report and identified contractors utilized unique metrics to identify innovation and new knowledge areas spawned from the PSOCs. This is a difficult task and the report is commended for tackling this in both conventional and novel ways. The datasets described in section 5.2 (p40) are indeed novel and have potential to be used in many studies across the cancer research community. Section 5.3 (p49) describes innovation through the development of "New Theories and Hypotheses" a major goal of the PSOCs.

Four new "theories" are described and these are indeed new and emerging areas for cancer research but at least for the first three areas, it is difficult to see these broad topics as originating or created exclusively by the PSOCs. For example, much work has been done on chromatin architecture and its functional role on transcription and DNA alterations such as translocations. Of particular note is the work of the NCI intramural researcher, Tom Mistelli. Cancer heterogeneity is a very developed and active area of research. The microenvironment has clearly been shown to impact this heterogeneity. Mathematical models have even been developed to help explain this phenomenon. The PSOC has played a role in these developments of late but to varying degrees, these are established research questions supported by a number of programs.

Probably the most abstract analysis is in section 5.4 (p54) using "bursty" topics on specific double word combinations to uncover "emerging" topics from the PSOC centers. These word combinations were chosen to describe common research clusters across over 600 PSOC attributed publications and progress reports. Sixty-eight such clusters were identified and compared pre- and post- PSOC to identify new topics emerging in the PSOC arena. While potentially instructive, one question is the real scientific basis or context for the word combination other than their appearance in a document. Out of the 68 topic clusters they identified 3 rather broad "thematic areas with burst co-occurrence during the PS-OC Program years". These are cell forces, evolutionary dynamics, and stochastic single-cell dynamics. While these do appear to be emerging areas, it is hard to suggest PSOC providence in these areas.

One area of particular interest is the cell force theme, which is composed of cell migration, cell-cell adhesion, and the extracellular matrix. These three areas have a rich history and there is one NCI program that predates the PSOC that extensively focuses on these areas, the Tumor Microenvironment Network (TMEN). Again many of the references listed can be attributed to TMEN and other programs.

It is important to point out that there is a rich history of fundamental research being performed on the basic biology of normal cell growth, development, and functioning that has routinely integrated physical science approaches, including but not limited to, computations, physics, and engineering. One could argue that the PSOC report data suggests that the surge correlates with the PSOCs, but one must also caution that using double word occurrence may not reflect the broader area of research that frequently undergoes various semantic evolutions and incarnations during the emergence of a field.

In summary, the PSOC program and centers have overall been very active in developing and working in some of the more exciting and potentially promising areas of cancer research.

They have achieved this by forming well-organized and managed transdisciplinary centers for research. The PSOC report has been very helpful in identifying the strengths of the centers. As mentioned throughout this review one concern and difficulty is accessing the PSOC contribution versus "most science occurring elsewhere" as phrased in the driving review question. In this regard it appears that the contribution of the PSOC, while noteworthy, is at times overstated. It should be noted that this review used representative examples taken from the PSOC report and is not a detailed analysis of all of the advances and activities.

Section 4

To what extent do the relationships between physical scientists and cancer researchers appear to be appropriately collaborative, with both groups making substantive contributions to the research? To what extent are such collaborations occurring at institutions that are not participating in the PS-OC Program?

The short answers to the above are: to some extent and not as much as one would like. But in fact the questions posed all are asking the panel to judge how successful the PS-OC program has been to date. The short answer to that question is that the PS-OC "experiment" appears encouraging but that it is clearly too early to tell how successful it will be. The review panel is confident that the experiment will not fail, but how successful it will eventually be is not yet known. And whether this was the optimal approach to foster an interest in oncology by those trained in the physical sciences will likely never be answered.

This question asks about the extent of collaborations and indirectly the productivity and publication record of the collaborations. Consistent with the overall program design, it is inherently collaboratively. Those involved in the program recognize that this is the defining characteristic of this program and they would be foolish to not pursue collaborations and pursue them aggressively. Thus collaborations are clearly occurring and they are occurring often – and these appear most of the time to be within one center – an outcome that should not be viewed as less than optimal, but quite possibly as optimal.

The PS-OC program will be most successful and its full potential realized when the exchange of ideas becomes a "two-way" street. At the present time it appears, that in most cases physical scientists are working to take the biology further. This is progress and it is valuable. We are only seeing the beginning of oncologists pursuing ideas developed by physical scientists. This too is progress and it is valuable. But it is too early for the stream of ideas from physical scientists to oncologist to be other than in the infancy in which it finds itself.

Can the panel be critical of the PS-OC program assessment and the metrics utilized? It can, recognizing that designing such metrics was a difficult if not an impossible task. The panel can also be critical of the use of baseline measurements that were clearly wanting. The PS-OC program was designed to further catalyze transdisciplinary collaborations. But because in fact such metrics are far from perfect, one must be cautious in how they are interpreted. It is here that the 3-year update is left wanting. Specific examples include the following:

1. The iTRAQR network analysis tool was used to examine the evolution of the PS-OC network-wide collaboration landscape and in the first three years collaborations accumulated. So too did the "network density", especially when "reported and authorship collaboration" are measured. The metrics summary concludes, "The collaboration data illustrates that collaborative teams have become more integrated at both the center and the network level". The goal will be to see if this level of collaboration can increase or at least be sustained over time.

2. The conclusion is reached that the "PS-OC Program has 'specifically' promoted the formation of trans-disciplinary collaborations. Here again the report documents "striking" increases in trans-disciplinary collaborations. Compared to baseline there has clearly been an increase. However, it is not clear that 12.6% should be considered a "striking" increase. It must be recognized that it takes time to establish such collaborations, generate hypotheses to be tested, conduct the necessary experiments and undergo peer review that will likely require additional experiments before publication. Very few such new collaborations will have had time to fully mature during this initial period. Consequently it is premature to judge the trajectory at this time, although the trend is clearly positive. But rather than to focus on the increase seen in these first three years, which as is noted, was anticipated, one wants to see not only a continued rise in this value in the coming years but evidence that the collaborative efforts are being sustained over time. Ideally in the future the majority of publications from this program will reflect transdisciplinary collaborations.

3. Similarly the report concludes the "PS-OC Program promotes the development of essential and productive collaborations", but this too can be challenged. The surveys lead to the conclusions that PS-OC participants are forming large trans-disciplinary collaborative teams. This seems indeed to be the case. But it's too early to conclude as the report does that these are teams where "individuals have defined roles and teams are productive and working together". For the latter the data captured did not address these aspects and the conclusions are therefore not founded on the data presented. It must also be recognized the data does not allow one to judge the optimal size of a collaborative team. It may be that smaller teams are more effective and more

adaptable to change, or that the optimal size of a team depends on the project at hand. In short lacking the data to reach the conclusions reached one must be more circumspect and also recognize that the goal ought not to be to promote larger and larger groups but rather optimally sized groups that can truly work in an integrated fashion.

4. From the questionnaires the report also concludes "these are high quality collaborations that would not be possible in the absence of the trans-disciplinary collaboration". Again the data gathered did not address this and certainly did not address the aspect of high quality. One can simply ask how is high quality defined and what measures of this were in the survey? The answers are it has not been defined and it was therefore not measured in the survey. While one can surmise these to be high quality collaborations in fact there is no data to reach such a conclusion. As for the conclusion that they would not be possible in the absence of the trans-disciplinary collaboration, this is likely accurate. But whether such collaborations could have been achieved by other means remains unknown.

The summary (Section 6.4 pg77) correctly concludes (*when words are crossed out for conclusions not supported by data*) that:

1. (~~Significant~~) Progress toward the milestone of ***establishing a~~n~~ (~~unprecedented~~) Network of Centers and transdisciplinary teams focused on solving cancer problems*** has been made.
2. Over the first three years of the PS-OC Program, individual Centers have become more integrated and grown to include new disciplines and collaborators and the broader PS-OC Network has become more connected.
3. There has been an (~~significant~~) increase in cross-disciplinary publications by PS-OC investigators compared to the years preceding the PS-OC Program (*an observation that as noted was predictable).*
4. Investigators are forming strong trans-disciplinary collaborative teams that have allowed them to make progress addressing important scientific questions (~~that would not have otherwise been possible)~~.

To date the program appears to be achieving what it hoped for. Further time is needed to properly evaluate it. It is then that we will begin to know if efforts to determine "*a stochastic Markov chain model to describe lung cancer growth and metastasis*" or to establish "*optimality in the development of intestinal crypts*" result in a paradigm change sufficient to impact our understanding of cancer and to yield better therapies.

Section 5

How do training opportunities available through the PS-OC Program differ from training opportunities available elsewhere?

One of the five primary program goals of the PS-OC is to "train a new generation of transdisciplinary scientists in the area of physical sciences in oncology". The program has allocated a significant amount of resources toward this goal, which enabled the establishment of training/education infrastructure at the PS-OC Program Office and funded PS-OC centers, and arrays of training/education activities. The PS-OC Program Office gathered large amount training outcome information from biannual progress reports submitted by the PS-OC centers.

Each of the 12 PS-OC centers has a set-aside budget of $100,000/yr for training/education-related activities. An Education and Training Core is supported in each of the 12 PS-OC centers and a Project Manager at the PS-OC Program Office is designed to lead an Education and Training Working Group that coordinate program-wide training/education-related activities.

In addition to playing critical roles in research and attending research-focused activities such as PS-OC annual meetings and research seminars, PS-OC trainees participated in a number of training activities that include:

- *Courses/Boot camps/Workshops*: a total of 110 courses have been developed and taught, which cover topics ranging from Cell Culture Techniques to Mathematic Modeling of Cancer.
- *Trainee exchange*: half of the Training/Education budget is designed to support trainees from one Center to go to a different Center to learn new skills. Up to this point, 113 trainees have participated in this program.
- *Young Investigator Awards*: an internal competitive funding mechanism was established to encourage collaborations between trainees from different PS-OC centers. Up to this point, 12 such grants have been awarded.

A total of 615 trainees have participated in the program since its inception. About 70% of them came with a background primarily in physical sciences, and 30% of them in biology-cancer research. Most of the trainees are either graduate students or postdoctoral fellows (~ 35% each), while others include undergraduate students, medical students, and research associates/staff scientists.

The majority of the graduate students trained in the PS-OC Program (70%) have gone on to postdoctoral fellowships, while two of them have already moved into faculty positions. Six postdoctoral fellows trained in the PS-OC Program have moved into faculty positions, while others have moved into industrial positions or new postdoctoral fellowships.

A unique feature of the PS-OC Program is that it has allocated resources designed for training and education activities, and supports training/education infrastructures at the Program Office and Centers with designated staff. These measures ensured that training-related issues are always on the agenda in program functions such as annual meetings, and that large arrays of training activities are continuously available for the trainees.

The PS-OC program did an excellent job in identifying training activities that had been successfully utilized by various NIH U54 programs and offering them as a package to the PS-OC trainees. The large number of courses (110) appears to be critical for training students with background in either physical sciences or biology for transdisciplinary research. However, a few potential concerns exist including the fact that the overall participation rates seem low and it is not clear how effective the courses are, or whether they will continue to be taught.

The Trainee exchange and Young Investigator Awards programs are innovative in that they specifically emphasize trainee-initiated cross-disciplinary collaborations. If the program is re-funded this would be an area that could be enhanced and strengthened.

A large number of trainees (615) have been involved in the Program in only three years. Given that the total investment is roughly $90M in three years, it translates to 6.6 trainees trained for $1M invested. It appears that the program has been effective in attracting young scientists to the area of research. It is re-assuring that 70% of the graduate students trained in the PS-OC Program entered postdoctoral fellowships. It will be interesting to know how many of their fellowships remain in the PS-OC research areas. It is also interesting to know how many of these fellows had primarily a physical science background initially.

As a measurement of the trainees' development as investigators, it will be important to have information on how many of them have tried and/or succeeded in applying for Fellowships and/or Career Development Awards.

The rate of participation of various training activities, levels of trainee satisfaction of the various training activities, and interest level to stay in PS-OC research areas after the training are critical measurements of the effectiveness of the training activities offered by the PS-OC Program. The PS-OC Program made a serious effort to gather information on these measurements through a survey. Unfortunately, only 75 out of the 615 trainees responded to

the survey. A future survey with improved trainee participation will provide data for a creditable evaluation on these important measurements.

Section 6

How would you recommend the Program's priorities be changed based upon the Program's progress to date? Does the panel believe that the potential for future progress merits continued investment by NCI in the PS-OC Program?

This final question provided the review panel an opportunity to consider the program as a whole, in the context of the various goals and theme areas. It also provided the panel members to further consider questions and/or concerns that emerged for them in the course of this review.

In general, the panel is encouraged by the initial successes of the program and another funding cycle has the potential to yield additional successes. The challenges with measuring success have already been discussed. A number of themes emerged from the discussions of the panel with respect to future efforts. Those are presented in the theme areas that follow.

Defining PSO

Perhaps the most challenging question that came up for the review panel was "What is the definition of PSO?" Even after reviewing all the materials provided by the PS-OC Program Staff the external reviewers were not able to answer this question.

It appears to the review panel that regular Strategic Planning is missing from the governance activities. It is recommended that the Program consider Strategic Planning as a dynamic process and to engage in an annual exercise to clearly review and redefine, as needed, short and long-term goals. This will provide an opportunity to determine whether the existing objectives are relevant and leading the program in the direction of achieving the goals.

How is success defined for this program overall? And where is it headed? The program appears to have a strong focus on developing a new research field. However, much of the material provided reads as though it is being "forced". Clearly there are new tools and approaches being used and developed for investigations into the challenges of understanding and managing cancer.

However, there are definitely areas of basic biology exploration and discovery that are already heavily intertwined with the physical sciences – areas of research for whom these approaches would not necessarily be novel or surprising. What does the PSO Program want

to accomplish with this program? How will the NCI know when it has been successful? Or when it is time to redeploy resources to new efforts?

Metrics of Success

Numerous metrics of success of the program were presented in the report. It may be worthwhile to also consider watching Major Scientific Association Meeting Agendas to determine whether special sessions are being devoted to cancer/physical sciences as well as who is being invited to do the speaking. This would be important for both the Cancer focused meetings as well as some those focused in the physical sciences.

Another metric of success imagined by the review committee is that the receipt of R01 type grants with a physical science and oncology focus would be readily accepted and reviewed by the NIH grants administration and review boards. Reemphasizing a point made earlier in this report, utilization by scientists of different disciplinary backgrounds of the co-PI RO1 mechanism would also demonstrate success in catalyzing transdisciplinary relationships.

Sharing

There are largely two types of sharing that take place across the Centers and/or pushed out from the Centers. These include programmatic information about the centers and their missions in general, for example, how they are functioning, their scientific accomplishments, the training programs and opportunities as well as others. The other type of sharing that is required involves that of scientific information gathered from experiments and trans-Center collaborations.

Based on the data provided, it is not clear whether the web site developed by the PS-OC program staff to facilitate interactions among the various centers has really taken off or is serving the role(s) intended. Given the number of people associated with the program the statistics on web site use do not look that encouraging. It is also clear that at least some, if not all the centers, have developed their own web presences to help disseminate information about their program and activities. This is in keeping with the directives of the program under the communication and outreach efforts.

Given the immense amount of resources dedicated to the program there may be resources and programmatic information that would be valuable to share across centers as well as beyond the centers including but not limited to education, training, programmatic information and core facility operations (e.g. course syllabi, interdisciplinary graduate requirements, lecture videos, evaluation criteria for funding interdisciplinary projects, and agreements for sharing reagents, credit, etc…).

In addition, with the creation of a data repository for the Centers it will be important to determine who will have access to the information stored. Will this data be accessible only to Center members? Or as part of the overall plan to extend the reach of the PS-OC would this include providing others outside the centers with opportunities to mine collected information and data? Clearly these are challenging questions to address but answering them now may inform the infrastructure that is established to support them. What can be done to maximize, expand, and leverage the investment to benefit the maximum number of people?

The NCI Division of Cancer Control and Population Studies (DCCPS) strategically invested resources into the development of the "Team Science Toolkit". From their website *"The Team Science Toolkit is a user-generated collection of information and resources that support the practice and study of team science. The Toolkit connects professionals from many disciplines, providing a forum for sharing knowledge and tools to maximize the efficiency and effectiveness of team science initiatives."* Given this is an NCI developed tool for catalyzing and supporting interdisciplinary work, it would be extremely powerful to have the PS-OC funded centers contributing their knowledge for the benefit of others interested in how to successfully conduct transdisciplinary work.

Engaging Physical Scientists to work on cancer – are Oncologists developing an appreciation for the hard sciences?

One of the goals of the PS-OC program was to create interdisciplinary approaches to tackling questions about cancer. As described in the report, the intent was to incentivize partnerships between cancer researchers and physical scientists. That is, they could learn and gain from the other so as to expand their own disciplinary field perspectives in new directions. From the materials presented to the reviewers, and as described in Section 4 above, there seems to be a very strong trend toward the physical scientists being folded into the cancer research realm as evidenced by information collected about where collaborative work is being published (journals cancer researchers largely look to when publishing) and which students (cancer biology vs. physical scientists) are taking advantage of opportunities to learn more about the other's discipline. While the external review panel was pleased to see a engineering, physics, and mathematical terms being used when considering publications resulting from the funding of the PS-OCs, it is not clear that there is similar reciprocity with respect to what the biologists are bringing to the physical sciences as would be reflected in publications within those disciplines. Is this level of reciprocity a desired outcome of this program?

It is worth considering that, in general, the physical sciences have been very successful in evaluating individual success in the context of a team when it pertains to evaluation during tenure and promotion. Could this be contributing to the willingness of the physical scientists to more readily expand into the biological arena and publish in new journals without the apparent sharing of credit in the other direction? For interdisciplinary research to be truly

successful the reviews and rewards for participation need to be clear and explicit. It would be valuable for the centers to explicitly share the criteria they are using to review tenure track and early career investigators participating in the PS-OC program. Creating environments where transdisciplinary work of early career investigators is supported by the institution, as evidenced by policies and procedures, would be one measure of success for this program.

Diversity:
Given the current emphasis of the NIH on increasing the diversity of the scientific workforce and providing opportunities for talented underrepresented minorities to enter careers as researchers there seems to be little explicit encouragement from this program to assure each of the centers has a program to open its doors for and to identify such students. Northwestern University was one institution featured in the report that has created such an opportunity. Moving forward it is recommended that the PS-OC program encourage the funded centers to expand their reaches, perhaps through specific programs or partnerships with HSBUs and/or local colleges and high schools.

Trans-NCI Program Integration
It is recommended that the PSOC Program integrate as much as possible with other NCI programs that have a physical sciences component. These would include, but is not limited to the NCI Nanotechology Alliance in Cancer and the Proteomics Program efforts. Performing an environmental scan of the goals of both NCI and NIH programs would help determine where opportunities exist for leveraging this program in the context of other NIH investments.

Long Term Plan for Program Administration
Clearly tremendous credit can be given to the program staff in creating, launching, nurturing and maintaining the overall PS-OC Program. The investment of time, effort, and resources has played a key role in the early successes. While this investment may be critical in the early stages of the program, the review panel suggests that the extremely high level of administrative support may not need to be sustained at similar levels in out years of the program. Of course the review panel was not explicity asked to comment on the budget and was not provided that information and so this comment is knowingly made without the full budgetary context. With the caveat that the review panel does not have knowledge of how funds are being spent across the program, it recommends that the PS-OC program develop a program administration plan articulating the long-term plan for the administrative investment into the program, especially if the investment in PS-OCs will continue with a renewed funding cycle.

Summary

In summary, the panel is impressed with the early successes of the PS-OC Program. As is clear from the overall review, the program appears to be on track by catalyzing interactions between cancer researchers and physical scientists and helping prepare emerging leaders for working across traditional disciplinary boundaries using a robust funding mechanism that provides guidance and support while still offering flexibility and freedom for pursing challenging ideas. The program should be proud, yet realistic, about the successes and accomplishments to date.

The program directors clearly worked extremely hard to launch the program and set it up for success. In addition it is clear they are very committed to sustaining the program and improving it.

The concern of the review panel lies in what is an inherently challenging thing to do for interdisciplinary work. That is to measure its success. The committee commends the program for trying to define metrics of success of for interdisciplinary and transdisciplinary work. However the panel found the report provided for the evaluation of the program lacked sufficient data, over interpreted data, or failed to provide descriptions of the limitations of the analysis performed. As such the panel concluded that the data provided did not fully support the claims made in the program report.

Respectively Submitted

Invited Review Panel

L. Michelle Bennett, PhD, Deputy Scientific Director, NHLBI (Chair)

Antonio “Tito” Fojo, MD, PhD, Senior Investigator, CCR, NCI

Daniel Gallahan, PhD, Deputy Director, DCB, NCI

Ming Lei, PhD, Deputy Director, Center for Cancer Training, NCI

Deborah M. Winn, PhD, Deputy Director, DCCPS, NCI

Appendix 1.

PS-OC Program Review Panel

Wednesday, November 28, 2012

2:00 pm – 2:30 pm ET

Meeting Minutes

Attendees: Dr. Michelle Bennett (Panel Chair), Dr. Debbie Winn, Dr. Tito Fojo, Dr. Dan Gallahan, Dr. Larry Nagahara, Dr. Nicole Moore

Summary:

- The panel asked Larry and Nicole to summarize some of the challenges of the PS-OC Program in the first three years. (Dr. Winn, 3 min)
- Nicole and Larry discussed four challenges that the program has faced and answered a couple additional questions from the panel (Dr. Moore)

Challenges

5. **Bringing physical sciences in oncology to the mainstream in the cancer research community**
    - This is an overarching challenge for the PS-OC Program
    - Program staff are not seeing the field of 'physical sciences in oncology' taking off at cancer specific meetings, cancer specific journals, or cancer centers as quickly as they are seeing advances in the science.
    - There are new symposiums emphasizing 'physical sciences in oncology' at conferences for biomedical engineering and cell biology. But, we have not yet seen a large push for this research at cancer specific conferences.
    - PS-OC investigators tell us they have had difficulties publishing their trans-disciplinary research within cancer specific journals. Research is primarily being published in journals such as PNAS or Plos One.

6. **Integration across projects within a center**
    - Investigators are comfortable with R01s – U54 is different mechanism and it has taken a couple years for the investigators to grasp the advantages of the U54 and integrate across projects.
    - During site visits, in annual reports, annual meetings, and retreats the program staff continually push investigators to integrate concepts and results across their PS-OC
    - Program staff are starting to see integration slowly come out at the PS-OCs – but there are still some investigators that seem more comfortable in their individual silos.

- Pilot project set aside funds have been a great way for people across projects to work together (explore ideas)

7. Providing opportunities in the area of physical sciences in oncology to those not funded directly by the program

- PS-OC program wants to build a scientific community of investigators in the area of physical sciences in oncology
- Program staff want to include as many as people as possible outside the PS-OC in this scientific area to create a broader community and also see projects in this area funded through the general R01 mechanisms
- Two mechanisms were put in place to try to expand the community:
  - Pilot Project - outreach set aside funds – 50K to fund work with someone outside their PS-OC (taking time for them to figure out how to do this and make it effective)
  - Outreach Unit (about 50K) to support symposium, workshops, training, … to try to make the "field" more accessible to others (depending on center, this is more/less effective – some have trouble distinguishing this $ from the education set-aside)
- Have not seen increase in success of the physical scientists in study sections (yet) – how can we get more scientists associated with PS-OCs into study sections

Question from panel: Are you thinking about reducing the number of restrictions associated with the funding?

A: Yes, this may be effective – since all centers have their own strengths/weaknesses this would provide them needed flexibility to align with their strengths

A: PS-OC Program has a unique structure. PIs/Centers are learning how to implement this new funding mechanism.

8. The program covers a broad range of scientific topics making it a challenge to focus on specific issues or questions

- The PS-OC program cast a very wide net: the benefit at the time was that we received lots of ideas and now have a very diverse portfolio of research effort across the Centers – but we cannot focus on a specific problem
- Could we have them address a specific topic? Specific problem? In cancer Research?
- The program staff are looking at ways to make the program more specific in the next phase.

Question form panel: Any unevenness among the Centers? Are you happy with all they are doing? (Not all are evenly funded – and don't have equivalent staff)

A: Centers are all different sizes and it is difficult to measure productivity and impact this early. At some centers some researchers have long histories of working together – so they got off to a faster start – those that did not are having a little more difficulty getting off the ground but have just as much potential to produce high impact innovative science in a couple years. Communication barriers between the physical scientists and cancer researcher have resulted in some delays at centers. Roles and responsibilities differ among the centers as well which leads to different types of collaborations between projects and may lead to difference in the impact of the Centers.

Question from panel: It appears that the PS-OC program staff are trying to put together a data sharing forum on their website. What is the status of this?
A: The process of putting together a data sharing forum has occurred in several stages. For the cell line exercise pilot project the program staff started an intranet site on the PS-OC website for all investigators to drop data and results. This is now transition to a more formal system hosted by the University of Tenessee that will have a user interface and database and should be complete next year.

A: We have also used the intranet site for the formation of proposals ideas for trans-Network projects. All the proposals and ideas were posted on the intranet for several weeks and open to feedback from all investigators in the Network.