

**Advancing Translational Cancer Research:
A Vision for Transitioning into the Future**

**Final Report of the BSA/NCAB SPORE Evaluation
Working Group**

June 8, 2016

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EXECUTIVE SUMMARY

Translational research has long been recognized as a key component of the bench to bedside research continuum. As such, the National Cancer Institute (NCI) launched the Specialized Programs of Research Excellence (SPORE) Program in 1992 to promote and support translational cancer research at the laboratory-clinic and laboratory-community interface. With its emphasis on translating cancer research to benefit patients, the SPORE Program has had a transformational impact on cancer research in the United States by helping to move the most important discoveries from these research sites into early phase human studies, clinical trials, and interventions.

Much of what is now considered the heart of 21st century cancer research was revolutionary at the beginning of the SPORE Program. Twenty-three years later, translational cancer research is an important component in many aspects of research involving the prevention, diagnosis, and treatment of cancer. This is reflected in the NCI's portfolio of translational research, which has expanded beyond the SPORE Program and now includes the NCI Clinical Trials Network (NCTN) and NCI Experimental Therapeutics (NExT) among many translational programs. Because opportunities at the intersection of cancer and cancer medicine continue and the potential for science-driven clinical impact is growing, continued investment by the NCI in translational research remains critical to assure that the most important scientific discoveries directly impact and benefit cancer patients, thereby reducing cancer incidence, mortality, and disparity in our nation.

Former NCI Director Dr. Harold Varmus charged the SPORE Evaluation Working Group (hereafter the Working Group) in December 2014 with reassessing the ways in which the NCI should support translational science in the future, and, with determining whether the SPORE Program was the most suitable funding mechanism for fulfilling those needs in the context of the NCI research portfolio. This charge was restated by the current Acting Director, Douglas Lowy, at a subsequent meeting. The Working Group is comprised of National Cancer Advisory Board (NCAB), Board of Scientific Advisors (BSA), Clinical Trials Advisory Committee (CTAC) and several *ad hoc* members, including Directors of NCI-designated Cancer Centers (hereafter Cancer Centers), SPORE principal investigators (PIs), and a patient advocate involved with SPORES, the NCTN and several NCI-sponsored working groups. The Working Group met three times in person and also communicated electronically from December 2014 through June 2016.

The Working Group considered historical and current perspectives of the SPORE program, its relation to the overall NCI budget, its interaction and synergies with the NCI Cancer Centers program, and an advocate's perspective; recognized changes that were made to the SPORE Program in response to reviews by other evaluation groups; and focused on formulating a series of recommendations in response to its charge. The Working Group noted that changes were made to the SPORE Program in response to a review by the SPORE Evaluation Group in 2014. As such, this Working Group is providing a larger vision that accounts for and incorporates the work of the 2014 SPORE Evaluation Group.

The Working Group recognizes that translational research does not exist in a vacuum. Rather, it depends on a robust basic research discovery pipeline and integration with clinical research, frequently conducted at Cancer Centers. Cancer Centers have scientific infrastructures which

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can be leveraged as part of an integrated translational research program. In addition, translational research needs differ by cancer site, reflecting a need to develop a mechanism to identify critical questions facing different sites.

Recommendations offered by the Working Group seek to address these needs by:

- development and implementation of a “SPORE Successor” Program, as described in this document, and
- development of a more integrated translational research effort that spans multiple NCI and extramural programs.

The recommendations are intended to provide a framework that will allow NCI to support translational research critical to patient outcomes, across all cancer sites. The Working Group realizes that these recommendations have many far-reaching implications and that translational research requires collaboration, flexibility and input from multiple stakeholders, including the advocacy community and industry. Thus, it is expected that a vigorous discussion in the extramural community to move forward will be required.

The Working Group endorsed the following recommendations for NCI senior leadership’s consideration:

- **Ensure that the first priority for funding is to support the highest quality science (whether basic, translational, population science, or clinical), addressing the most important problems, and ensure that such projects are adequately resourced for success.**
- **Maintain or increase the current level of NCI funding support for patient-centered translational research at all stages.**
- **Develop incentives that will encourage collaborations with other academic institutions and industry.**
- **Increase integration, leveraging, and interfacing of NCI currently funded translational programs (such as the NCI SPORE, NCI Cancer Centers, NCTN, NCORP, intramural programs, the Center for Cancer Research, SEER, and Frederick National Laboratories), with the biopharmaceutical industry, advocacy groups and other funding agencies to accelerate translation of scientific advances to the bedside.**
- **Continue the current policy of funding incentives to incorporate population scientists into SPORE/TREX programs. Develop incentives to focus on cancer disparities.**
- **Create a standing NCI Translational Research Strategy Subcommittee (NTRS). The subcommittee should be comprised of extramural investigators representing the full spectrum of translational cancer research, as well as representatives from pharmaceutical, biotechnology, computational and advocacy organization(s). The**

charge of the NTRS will be to identify the most important opportunities to benefit patients, so as to serve as an integrated guide for NCI's translational investments. The NTRS should be aligned with the NCI's Board of Scientific Advisors.

- **Re-brand the SPORE Program as the Translational Research Excellence (TREX) Program, providing investigators with increased flexibility on how best to structure their research programs (ranging from small, focused projects to large-scale, team-based projects).**

Translational Research Excellence (TREX) Program specific recommendations (referred to within body of report as "SPORE Successor" Program):

- **Effective involvement of research advocates with a collective patient perspective should continue to be an integral component of the "SPORE Successor" Program.**
- **Strongly encourage impactful research projects that bring investigators from multiple institutions together. The Program should prioritize collaborative projects addressing both the most important questions within organ sites as well as "cross cancer" initiatives that focus on targeting commonly mutated genes (pathways) or cancer public health challenges. Elimination of the requirement for a minimum number of projects within each TREX will facilitate the development of both small focused projects and large scale team based projects.**
- **Each individual research project should continue to include a clinical investigator and other disciplinary based principal investigator.**
- **Where appropriate, projects can include a population scientist investigator with an relevant research aim.**
- **At least one – but not all – translational research projects within the TREX program must incorporate a defined clinical endpoint.**
- **While the WG suggests enhanced coordination of the TREX Program with NCI-designated Cancer Centers, the WG recommends that the TREX Program PI retains full autonomy so as to fulfill the Program's stated goals.**
- **Development of and adoption of community consensus standards for clinical and biological metadata, including data security, should be key components of the TREX Program.**
- **A TREX Program should encourage and value properly managed exchange of data between TREX Programs and with the larger cancer community and should encourage adoption of community data standards as they emerge.**
- **A TREX program should encourage development of a program-wide consent process that would inform patients about the: 1) risks and rewards of participating**

in a TREX program, and 2) possibility that some data may be made available to private sector collaborator that would enable use of individual patient information in research that is not envisioned at the time of consent.

- **A TREX program should contribute to the development of a functional data commons that will organize functional data being generated throughout the NCI research community in ways that will allow it to be readily accessed by research and clinical investigators in order to facilitate identification of causal relationships and that will contribute to the development of clinical decision support tools.**
- **Informative laboratory models of important aspects of cancer should be encouraged and supported (i.e., collection of primary tumor specimens to generate patient derived xenografts (PDX) and organoids, paired germline samples, engineered tissues, etc.).**
- **The TREX Program should be open to establishing translational research cores that fill broad institutional infrastructure gaps, such as tissue acquisition, informatics, and emerging technologies. Importantly, these efforts should utilize existing cores within Cancer Centers and other institutional facilities wherever feasible. A core to support collection of tumor specimens is optional. TREX tissue cores are expected to deploy novel expertise or methodologies to support impactful research, and not overlap with existing institutional cores.**
- **The Career Development component should be continued in the TREX Program to support the development of new translational investigators.**

This report contends that the SPORE Program has had a transformational impact on NCI-designated Cancer Centers. The creation of the Program provided the impetus and opportunity for Cancer Centers to: 1) develop translational research as an important strategic research focus; 2) enhance collaborations between basic, clinical, and population scientists; and 3) build translational research capacity and infrastructure for the conduct of tumor or disease-focused research, including tumor-focused research programs, tumor-focused multi-disciplinary clinical Working Groups, shared resources, and early phase clinical research and clinical trials.

Over the past few years, resources have been limited while opportunities have expanded with new discoveries in genetic and basic research that are ready for translation into new therapeutic approaches. A critical element to future success requires evolving the way translational research is organized at the NCI and in the TREX program. Additional resources and greater flexibility in the program organization are needed to create a more interactive environment with the NCI Cancer Centers and other research institutions to: 1) assure synergy and eliminate duplication of resources and research infrastructures in order to more rapidly and quickly move new translational discoveries into the clinical setting; and, 2) identify areas where additional basic research is needed to support translational activities. NCI needs to identify how to obtain input from the community on the most important questions in translational research and to create a collaborative environment across the scientific community, specifically, TREX awardees, NCI Cancer Centers, advocates, and other NCI programs and to encourage interactions with pharma and biotech companies.

I. INTRODUCTION

The development of science-based therapies for cancer patients has been an aspiration of the National Cancer Institute (NCI) since its inception in 1937. Unfortunately, the absence of a deep understanding of the biological basis of cancer made such clinical aspirations unrealistic for most of the 20th century. By the late 1980s, key principles in cancer biology began to emerge, and the notion of cancer as a genetic disease gained momentum. An enormous gap remained, however, between the laboratories studying cancer biology and cancer medicine and the clinics treating patients. Few projects spanned laboratory and clinic, and few investigators were “bilingual” in basic science and clinical medicine. A tremendous opportunity at the intersection of laboratory and clinic—an intersection that would come to be known as translational research—was becoming obvious.

To address this challenge, the NCI launched an ambitious initiative known as the Specialized Programs of Research Excellence (SPORE) Program in 1992. The SPORE Program, which began as an appropriation of Congress and is now in its 23rd year, represented a first-ever effort to invest in making translational cancer research feasible. It created mechanisms for clinicians, basic scientists, and population scientists to work together at a time when such interactions seemed foreign. It created infrastructure, such as tissue banking, at a time when the study of primary human tumors was far from routine. Most importantly, the SPORE Program 1) created a home for disease-based translational cancer research that at the time was non-existent, even at the largest NCI-designated Cancer Centers (hereafter Cancer Centers); and, 2) illustrated the need for academic–private sector collaborations as a key part of translational research.

The SPORE Program catalyzed an entire field of translational cancer research to improve treatment for patients with cancer. It created disease-based intersections of science and medicine that became models for modern cancer research as well as translational research infrastructure that became the model for integrative cancer research at most Cancer Centers. Projects funded under the SPORE mechanism contributed to the development of transformative new approaches, some of which are now the standard of care for cancer patients. Through Career Development awards, the SPORE mechanism also served as a way to ensure that the next generation of translational cancer researchers was trained and nurtured. Much of what is now considered the heart of 21st century cancer research was revolutionary at the beginning of the SPORE Program 23 years ago. The NCI portfolio of translational research now extends well beyond the SPORE Program. For example, intense efforts to define the genomic and epigenomic landscape of tumors and to elucidate the role of the tumor microenvironment and host immunity in cancer pathogenesis and epidemiology are beginning to transform treatment paradigms that are resulting in improved clinical outcomes for cancer patients.

Although translational cancer research now may be more the rule than the exception, much work remains to be done. The opportunities at the intersection of cancer biology and cancer medicine have never been greater, and the potential for science-driven clinical impact is growing exponentially. Additionally, the application of modern omic technologies has illustrated the complexity of the task and highlights the need for even closer basic-translational interaction coupled with support from “Big data” analytics. If we are to really achieve precision medicine goals, the latter needs to be a part of next generation translational research. Continued investment by the NCI in translational research is therefore more important than ever.

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At the same time, the needs of the translational research community have evolved since the inception of the SPORE Program. A number of NCI-sponsored programs (e.g., NCI Clinical Trials Network [NCTN], NCI Experimental Therapeutics [NExT]) were established during this period and the Frederick National Laboratory for Cancer Research is able to support aspects of translational research. Although infrastructure to support translational research is now more prevalent within Cancer Centers and interdisciplinary research has become more commonplace, many challenges remain. The cost of translational research remains high, and the shrinking size of most NCI grants has forced investigators to think incrementally and conservatively, rather than boldly and ambitiously. Moreover, the structure of the SPORE Program, with specific requirements for numbers and types of projects, and the requirement to include a population science-focused project component, has in some cases constrained innovation and hindered problem-solving. Although opportunities for translational research have exploded during the past 2 decades, the rigid structure of the SPORE Program has not allowed for flexibility in size and scope of such research initiatives. The complexity of cancer and the precision medicine initiative almost demand multi-institutional collaborations. Achieving precision medicine goals also requires that we effectively engage pharma in more innovative ways since getting access to these drugs is still rate limiting. New mechanisms need to have incentives to encourage this.

In addition, there have been no mechanisms for the extramural research community to participate with the NCI leadership in the identification or articulation of the most pressing problems and the most important opportunities facing the translational research community and the cancer patients they serve, thereby making it more difficult for the NCI to ensure that its portfolio of investments (grants and contract awards) is well-matched to the most important problems facing the translational research community and patients affected by cancer.

Need for Assessment

Driving the discovery engine and translating basic discoveries to diminish the burden of cancer is paramount to the mission of the National Cancer Institute (NCI). In this regard, the Board of Scientific Advisers (BSA)/National Cancer Advisory Board (NCAB) SPORE Evaluation Working Group has been established and charged to reassess the ways in which the NCI should support translational science in the future and whether the SPORE Program is the most suitable mechanism for fulfilling those needs in the context of the NCI research portfolio. The NCI (and the National Institutes of Health [NIH]) can remain flexible only by reviewing, renewing, revising, or turning over its existing programs. The goals of the Working Group are different from the analysis of data on the SPORE Program assembled for the Clinical Trials Advisory Committee by the IDA Science and Technical Policy Institute (STPI) in 2014.

Charge to the Working Group

Former NCI Director Harold Varmus charged the Working Group at its initial meeting on December 3, 2014, to recommend how the NCI should best support translational science in the future, with particular emphasis on whether the SPORE Program addresses NCI's overall goal of supporting impactful translational research. This charge was restated by the current Acting Director, Douglas Lowy.

Functioning of the Working Group

The BSA/NCAB SPORE Evaluation Working Group (hereafter Working Group) was established in 2014 and held three in-person meetings: 3 December 2014 and 26 March 2015 (Bethesda, Maryland); and 17-18 August 2015 (San Francisco, California); and, two virtual meetings held 29 January 2016 and 8 June 2016. The Working Group is comprised of members of the Board of Scientific Advisors (BSA), National Cancer Advisory Board (NCAB), and Clinical Trials and Translational Research Advisory Committee (CTAC), as well as *ad hoc* members. The roster includes Cancer Center Directors and investigators, SPORE principal investigators (PIs), and a patient advocate involved with SPORES, the NCTN and several NCI-sponsored working groups.

The Working Group's discussions focused on perspectives across the NCI, its Cancer Centers, and the advocacy community, and on formulating a series of recommendations in response to its charge. The group also received briefings on the historical and current perspectives of the program, its relation to the overall NCI budget, its relationship to the Cancer Centers program, and a perspective from the advocacy community. The Working Group requested and received additional information regarding; 1) the overall NCI translational research portfolio; 2) organ-specific funding across the NCI; 3) the distribution of translational research funds across funding mechanisms; 4) breakdown of SPORE awards with respect to therapeutic, biomarker, or correlative interventions; and 5) a number of therapeutic trials in which the drug was developed by a SPORE grantee. A list of invited speakers at the Working Group's meetings is provided in the Appendix.

As the Working Group discussions evolved, it was clear that the Group felt that two changes would greatly enhance the productivity of translational research at NCI. The short-term change involves only the SPORE program, and aims to increase its ability to leverage resources and increase flexibility in today's environment. The longer-term change involves a re-alignment of all translational research conducted in the publicly-funded system.

II. RELATIONSHIP OF THE NCI SPORE AND CANCER CENTERS PROGRAM

The Current P50 SPORE Program

The SPORE Program awards center grants specifically designed to support multi-project, interdisciplinary, translational research involving investigators conducting basic, applied, and population science research with the goal of developing diverse new approaches to the prevention, detection, diagnosis, and treatment of human cancers. Each award has primarily focused on a specific cancer or organ site, such as breast or lung, or a group of highly related cancers, such as gastrointestinal cancers and sarcomas. All grants include at least four translational research projects that must include a human endpoint such as a clinical trial, human observational study, or experiment using human specimens for discovery or development of biomarkers. SPORE grants also support Developmental Research awards for funding pilot projects as well as Career Development awards that support junior faculty and established investigators in expanding their careers into translational research. Other key features of SPORE awards include support of specialized core services (e.g., bio-specimen acquisition and storage, pathology, and biostatistics) and the flexibility to terminate projects that either are not

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progressing well or have been completed ahead of schedule and replace them with new projects. Currently, there are 52 fully funded SPORE awardees, all located within academic institutions and NCI Cancer Centers in 21 states at 30 institutions plus 1 consortium.¹

In response to the recommendation of the NCI Clinical Trials and Translational Research Advisory Committee SPORE Evaluation Group in January 2014, criteria for SPORE applications were changed to encourage a focus on themes as well as specific organ sites. Other programmatically appropriate groups of cancers may include those centered on a common biological mechanism critical for promoting tumorigenesis and/or cancer progression in organ sites that belong to different organ systems. For example, a SPORE grant may focus on cancers caused by the same infectious agent, or sustained and promoted by dysregulation of a common signaling pathway or specific oncogenic driver (i.e., the RAS Project). The requirement for an early detection, prevention, or population project was eliminated for all organ sites, and made optional. However, applicants may request an additional \$200,000 funding if such a project is included. Finally, SPORE-supported investigators are explicitly expected to participate in collaborations with other SPORE and non-SPORE research groups to facilitate the progress of translational research. At the same time, there is no specific mechanism to fund these collaborations.

Enhancing Synergies and Relationships between SPOREs and Other NCI Translational Research Initiatives

The awarding of a SPORE grant to a Cancer Center has become a measure or hallmark of success for its tumor-focused research efforts. As such, every Cancer Center works to foster groups of investigators to successfully compete for SPORE grants and other multi-investigator, programmatic grant initiatives, and frequently provides essential matching funds, infrastructure, access to shared resources, and administrative support to ensure that these critical research efforts are successful.

In addition, the wealth and diversity of patients, science, and scientific opportunities across the Cancer Centers Program, and the multi-ethnic diverse populations they serve, help to promote collaborations among many Centers and research groups to participate in translational research. Given the synergies that have developed between these two programs, it is not surprising that all currently funded SPORE grants are held by institutions that also have successful Cancer Centers.

Leveraging Cancer Centers' Resources

Over the last decade, Cancer Centers have built significant research infrastructures and shared resources for the conduct of translational, clinical, and population research which can serve as the backbone of NCI's translational research initiative. Cancer Centers invest heavily in the development of these resources with multiple revenue streams at their disposal, including state and institutional support, philanthropy, other grant mechanisms, and clinical revenues, as well as NCI support. As these funding sources frequently serve as critical and essential matching support for the overall success of many NCI initiatives, care should be taken to leverage this matching investment in the design and optimization of new NCI advanced translational research

¹ List of P50 awardees (by organ location and state) are available on the NCI website at <http://trp.cancer.gov>.

initiatives. Within the Cancer Centers, shared resources and special capacities for the conduct of translational research frequently include:

- Human Tissue Banking
- Biostatistics and Clinical Trial Design
- Informatics: Bioinformatics, Data Warehouses, Data Analysis, and Integrated Platform/Enterprise-Wide Data Management for Informatics in Cancer Centers (NCI Cancer Centers Informatics Initiative and Working Group)
- Clinical and Clinical Trials Research Infrastructure (Clinical Protocol and Data Management/Data and Safety Monitoring, Protocol Review and Monitoring System, Early Phase Clinical Research Support Center)
- Tissue Analysis and/or Correlative Science Cores (often Clinical Laboratory Improvement Amendments [CLIA]-certified): Histopathology, Pathology Review, Molecular Diagnostics, Genomics, Next Generation Sequencing
- Other Research Cores: Pharmacology, Population Science Cores (patient recruitment, cohort development, community/behavioral interventions)

The Working Group recommends that a “SPORE Successor” Program and Cancer Centers harmonize infrastructure use. Such harmonization would allow the “SPORE Successor” Program to focus on funding science more than infrastructure and avoid costly duplication of NCI investment in essential resources. However, new funding mechanisms and constructs within the new “SPORE Successor” Program should allow for investigators to request support for full-time equivalent (FTEs) or user fees to access these existing Center-based cores and infrastructures, rather than build independent and separately functioning resources. Cores within the “SPORE Successor” Program should conduct impactful research to support the projects and not overlap with existing cores. Utilizing the resources and infrastructure of large programs such as Cancer Centers for newly designed translational research initiatives also provides for greater compliance, accountability, and synergy for the conduct of patient-centered translational research. To encourage Cancer Centers to invest in infrastructure, significant weight should be given to the infrastructure environment during the peer review of Cancer Centers.

III. SPORES AND DISEASE MANAGEMENT

Leveraging and Creating Synergies with Other Translational Research Programs

To develop a new vision and strategic focus for advanced translational research at the NCI, it is important to continue to *sustain*, *integrate*, and further *leverage* translational research capacities between new NCI translational research initiatives (such as enhanced and more flexible SPORE-like applications, U54 programs, and other impactful programs that support the most important translational science), Cancer Centers, and other NCI Programs (National Clinical Trials Network [NCTN], NCI Experimental Therapeutics Program [NExT], Experimental Therapeutics Clinical Trials Network [ETCTN], NCI Community Oncology Research Program [NCORP], Early Detection Research Network [EDRN], and others). Increased emphasis on information management and analysis, as well as knowledge communication to users (clinicians, scientists and patients) is needed.

Similar to the Cancer Centers Program, other existing NCI programs and initiatives should be used and leveraged with the new “SPORE Successor” Program to maximize resources and ensure that scientific teams can efficiently, expeditiously, and effectively move their discoveries into clinical trials and interventions, within Cancer Centers, and disseminated within cancer communities. These include the NCTN, ETCTN, NExT, NCORP, EDNR, SEER, and other intramural and extramural clinical trials programs and resources.

In addition to these relationships with NCI programs, the most successful teams of scientists engaged in research at the translational/clinical interface often develop critical collaborations and partnerships with the data science, pharmaceutical and biotechnology industries, philanthropic organizations focused on disease-specific and/or clinical research, and other innovative research groups. These interfaces and innovative partnerships should be encouraged and further leveraged, and new guidelines and recommendations should be carefully considered as the “SPORE Successor” Program is further developed.

Key challenges for the NCI to consider in promoting collaboration among its translational research programs include: addressing barriers that discourage interfacing among programs, particularly between the SPORE Program and Cancer Centers; identifying ways to improve interfaces; and harmonizing goals, targets, and trials between the need to translate SPORE science to trials with the NCI Cooperative Groups, NExT, and other programs.

Recommendation: Increase integration, leveraging, and interfacing of NCI- and NIH-funded translational programs with each other and with the data science, biopharmaceutical and biotechnology industries, philanthropic organizations and other funding agencies, as well as within the NCI’s programs, to accelerate translation of scientific advances to the bedside.

Core Principles for Improved Cancer Prevention, Treatment, and Disease Management

The Working Group identified seven core principles relevant to SPOREs and the management of disease:

1. Encourage Flexible SPORE Programs That Address Fundamental Problems in Translational Cancer Medicine. As the knowledge of cancer biology, cancer medicine, and pathogenesis has exploded, conducting state-of-the-art translational research that addresses central mechanistic questions has become more challenging. The “SPORE Successor” Program should be encouraged to develop highly collaborative projects that address central questions in translational research, which may be best developed as a single focused project, or a single focused project with many parallel lines of investigation, as well as a series of linked interacting projects. The Working Group supported an emphasis on assembling the best teams of scientists, which will frequently include participants from multiple institutions. With the elimination of the requirement for a minimum of four projects, the “SPORE Successor” Program would provide increased flexibility with programs ranging from one or more small focused projects to one or more large scale team based projects. As new projects emerge that follow this paradigm, metrics for assessing the success of individual Cancer Centers (such as those outlined in the requirements for the NCI Cancer Center Support Grants, specifically related to metrics in the NCI Data Tables) should be modified to acknowledge the scientific contributions of individual center

members to multi-institutional projects, including those where the overall PI resides at another university. Allowing two or more Centers to “count” research funding that is truly collaborative or accrual to clinical trials at another Center would enhance rather than inhibit such collaboration. To further enhance the translational cancer research performed in SPORE projects and increase efficiency, existing administrative structures and core facilities within Cancer Centers should be leveraged. SPOREs should concentrate on executing innovative translational projects rather than on building infrastructure or fostering “silos” within individual institutions.

Recommendation: The “SPORE Successor” Program should be flexible and strongly encourage impactful research projects that bring investigators from multiple institutions and disciplines together. The Program should prioritize collaborative projects addressing both the most important questions within organ sites as well as “cross cancer” initiatives that focus on targeting commonly mutated genes (pathways) or public health challenges, including cancer disparities. Eliminating the requirement for a minimum number of projects within each “SPORE Successor” Program will facilitate the development of both small focused projects and large scale team based projects.

2. Preserve Interactions Between Clinical, Laboratory, Population Science, and other Disciplinary Investigators. A novel aspect of the SPORE structure is that all research projects embedded within SPORE grants have co-leaders: one who conducts research in the clinical setting and the other who is primarily laboratory-based. This structure anticipated the advent of “team science” efforts that harness the complementary expertise of different researchers in an increasingly technical and specialized scientific environment. It has benefitted both types of investigators by demonstrating that collaborative translational research projects have the potential to advance cancer medicine because the “sum is much greater than the individual parts.” This structure also has revealed the inherent challenges of working in clinical, laboratory, populations and other scientific environments and has fostered joint efforts to resolve the problems. Given these advantages, the Working Group felt that this model adds substantial value and should be retained and enhanced when needed to focus collaborations between basic, population science, and clinical investigators.

Recommendation: Each individual research project should continue to include a clinical investigator and other disciplinary based principal investigator.

3. Preserve the intent of clinical impact. Current SPORE guidelines mandate that each project include achieving a clearly defined clinical endpoint by the end of the funding period. The Working Group felt that this requirement precludes proposing some impactful projects that will not reach a clinical endpoint within 5 years. The Working Group therefore recommends allowing SPORE programs to include one or more projects without an obvious clinical endpoint, provided that they address a compelling translational question integral to the overall goals of the overall program.

Recommendation: At least one – but not all – projects within the “SPORE Successor” Program must incorporate a defined clinical endpoint.

4. Use of “SPORE Successor” Program Resources to Fund Innovative Infrastructure and Technologies. The Working Group endorsed the use of “SPORE Successor” Program resources to fund critical infrastructure and innovative methodologies that will enable investigators to execute “high content,” mechanism-driven clinical trials. Although organ systems and therapeutic approaches (e.g., immunotherapy vs. targeted agents) will differ in their needs, a central principle should be to support efforts such as collecting and serially archiving high-quality tumor specimens with appropriate consent for future molecular analysis and harnessing new technologies to analyze them. Infrastructure should not duplicate existing resources and cores, but should leverage expertise and infrastructure within Cancer Centers and other institutional facilities. At the same time, SPORE investigators and projects should be encouraged to pioneer the use of emerging technologies that are not available at their institutions to answer translational questions and to disseminate these methodologies broadly after they are established and validated.

Recommendation: The TREX Program should be open to establishing translational research cores that fill broad institutional infrastructure gaps, such as tissue acquisition, informatics, patient-reported outcomes, observational data, registries, and emerging technologies. Importantly, these efforts should utilize existing cores within Cancer Centers and other institutional facilities wherever feasible. A core to support collection of tumor specimens is optional. SPORE tissue cores are expected to deploy novel expertise or methodologies to support impactful research, and not overlap with existing institutional cores.

5. Promote “Backward” Translation by Improving/Enhancing Preclinical Capabilities. A current and entirely appropriate focus of the translational research performed within many SPORE projects is to conduct correlative laboratory studies of primary tumor specimens from patients enrolled in clinical trials to identify biomarkers and mechanisms of response and resistance. An important opportunity that has received less attention is to use primary tumor specimens collected from these patients to establish new and renewable resources to enhance preclinical research. The Working Group encouraged support for systematic efforts to generate patient derived xenografts (PDX) and organoids through existing improved laboratory models, as well as blood, buccal smears, and blood for circulating tumor cells (CTCs) and cell-free circulating tumor DNA (ctDNA). The Working Group supports a “SPORE Successor” Program that will enhance testing drugs and drug combinations in the preclinical setting and ultimately inform impactful new clinical trials.

Recommendation: Informative laboratory models of important aspects of cancer should be encouraged and supported (i.e., collection of primary tumor specimens to generate patient derived xenografts (PDX) and organoids, paired germline samples, engineered tissues, etc.).

6. Develop Intellectual Capital Across the Translational Research Spectrum. Data are conflicting regarding the future biomedical workforce, with NIH data indicating that too many Ph.D. postdoctoral investigators are being trained for the number of jobs available in academia and industry. At the same time, the recent Physician-Scientist Workforce Working Group report

of the National Institute of Medicine (IOM)² documented severe challenges to the physician/scientist pipeline with the supply of well-trained researchers falling far short of the need in cancer and other diseases. Translational research is particularly dependent on physician/investigators who can bridge between the laboratory and clinic. Because clinical trials take substantial time to design and complete, the training of translational scientists frequently is extended, and it may take considerable time for any individual to become fully independent. The Career Development award component of existing SPOREs recognizes and partially addresses this problem, although awards are typically small (~\$50,000) and of short duration (1–2 years). In addition, the Developmental Research award component of SPORE grants provides a mechanism to attract established researchers into translational cancer research, which facilitates new approaches and cross-disciplinary studies. Given the need to maintain and renew the translational research community, the “SPORE Successor” Program should continue to emphasize the development of new translational investigators. Additionally, the “SPORE Successor” Program should encourage the development of a multidisciplinary translational workforce that accumulates and trains investigators from many different but specialized backgrounds.

Recommendation: The Career Development component should be continued in the “SPORE Successor” Program to support the development of new translational investigators.

7. Inform and Improve Cancer Prevention, Behavioral or Population Intervention, and Treatment Through Involvement of Research Advocates³ in Translational Research. This principle distinguishes the SPORE Program from other NCI initiatives. Any “SPORE Successor” Program should adhere to the goal of involving Research Advocates to interact with the research team and provide a lay perspective to the research process.

Recommendation: Effective involvement of research advocates with a collective patient perspective should continue to be an integral component of the “SPORE Successor” Program.

Translational Research and Data Science

A central goal of a SPORE Successor Program will be to identify ‘omic, image and clinical features that are associated with patient outcome and that can be measured to guide individual cancer management. The Working Group identified data standards, data security, data exchange, data use consent, and data interpretation as key elements of data science that will be needed in a “SPORE Successor” Program.

² Physician-Scientist Workforce Working Group report for the National Institute of Medicine - http://acd.od.nih.gov/reports/PSW_Report_ACD_06042014.pdf

- ³ A **RESEARCH ADVOCATE** brings a non-scientific viewpoint the research process and communicates a collective patient perspective.
- A **COLLECTIVE PATIENT PERSPECTIVE** is created when a person has knowledge of multiple disease experiences and conveys this collective perspective rather than his or her own exclusive experience

1. Data security. Development of cancer management strategies that are optimal for individual patients will require acquisition, management and integrative interpretation of large amounts of confidential background information about individual patients, laboratory measurements of their tumors and normal tissues, past and current treatments and responses to treatment. It is reasonable to expect that the amount of information generated on an individual patient may exceed 1 Terabyte. The laboratory information – especially genome sequence – is sufficiently rich that it is likely that individual patients can be reidentified by comparing laboratory data with patient-linked data available in the public domain. Thus, high data security is essential.

Recommendation: Development of and adoption of community consensus standards for clinical and biological metadata, including data security, should be key components of the “SPORE Successor” Program.

2. Data standards and data exchange. The high level of heterogeneity that exists between human cancers suggests that implementation of precision medicine will ultimately require integrative analysis of data from tens of thousands cancer patients collected worldwide in order to identify clinically important features that can define patient subpopulations that can be managed according to procedures that are optimal for that subpopulation. This will require adoption of community defined standards such as those being developed by the Global Alliance for Genomics and Health (Global Alliance), the NIH Big Data to Knowledge (BD2K) program, NCI, National Institute of Standards and Technology (NIST), U.S. Food and Drug Administration (FDA) and similar bodies. The “SPORE Successor” Program could serve as a catalyst for data standardization by using standards that are common among all “SPORE Successor” and allied translational research programs.

Recommendation: A “SPORE Successor” Program should encourage and value properly managed exchange of data between “SPORE Successor” Programs and with the larger cancer community and should encourage adoption of community data standards as they emerge.

3. Patient consent. Integration of information from multiple data generation programs – public and private – is essential to implementation of precision medicine. However, the data exchange needed to accomplish this goal may require uses of data that are not envisioned at the time of data collection. In addition, information generated during the course of research may reveal germline and somatic events that predispose to cancer risk and/or that suggest new therapeutic approaches. This will require that patients be adequately informed about the risks and rewards of participating in “SPORE Successor” Program research.

Recommendation: A “SPORE Successor” Program should encourage development of a program-wide consent process that would inform patients about the risks and rewards of participating in “SPORE Successor” Program, the possibility that some data may be made available to private sector collaborator and that would enable use of individual patient information in research that is not envisioned at the time of consent.

4. Data interpretation. “SPORE Successor” Program research will require functional interpretation of molecular and architectural abnormalities associated with cancer prognosis, progression and response to treatment. Association studies will need to be complemented by functional studies in experimental laboratory systems in order to establish causality. Large scale functional studies are now being carried out under the auspices of the NIH BD2K and Library of Integrated Network-Based Cellular Signatures (LINCS) programs, the NCI Cancer Target Discovery and Development (CTD²) initiative and throughout the R01 community. These data, if made easily accessible to “SPORE Successor” Program researchers, should contribute substantially to the interpretation of their data.

Recommendation: “SPORE Successor” Programs should contribute to the development of a functional data commons that will organize functional data being generated throughout the NCI research community in ways that will allow it to be readily accessed by research and clinical investigators in order to facilitate identification of causal relationships and that will contribute to the development of clinical decision support tools.

Enhancing and Expanding Resources for an Enhanced Translation Cancer Research Program

Translational progress can be slowed by many different factors – for example, lack of access to drugs, imperfect understanding of specific disease mechanisms, ethical considerations associated with novel treatments, technical inability to acquire needed serial tumor samples, and inability to manage and interpret big data. A mechanism is needed to identify the most important problems in translational cancer research that directly impact on patient care and on the overall burden of cancer in our nation. The question “what are the most pressing research or operational problems that need to be addressed to improve cancer management?” should be viewed on the level of a “Provocative Question” and not as a portfolio review of activities.

Recommendation: Ensure that the first priority for funding is to support the activities (research, process development, technology, etc.), that will mitigate the most important problems limiting translational research, and ensure that such activities are adequately resourced for success.

Retaining Autonomy and Flexibility of the Principal Investigator (PI)

Given these opportunities and synergies, as new funding opportunities are developed within the overall “SPORE Successor” Program, applicants should have the freedom to develop the most qualified team of accomplished investigators to tackle the most important problems in translational cancer research. Leaders of such teams should retain autonomy and flexibility as an independent principal investigator(s) to drive their research program to achieve its goals, while seeking to leverage existing capabilities and infrastructures within the Cancer Centers and other NCI programs at the translational/clinical/community interface (NCTN, ETCTN, NExT, NCORP, EDRN, and other intramural and extramural programs) and other NIH programs (BD2K, NCBI, etc.). There should be a way to interface SPORE leaders/translational research group leaders in the leadership/decision making of Cancer Centers—particularly those translational projects or groups that choose to leverage or interface with Cancer Centers—

assuring that these SPORE PIs have the full support of the Cancer Center and the Center's direction and strategy coordinates with the goals of the SPORE.

Recommendation: While the WG suggests enhanced coordination of the "SPORE Successor Program" with NCI-designated Cancer Centers, the WG recommends that "SPORE Successor" Program PIs retain full autonomy so as to fulfill the Program's stated goals.

IV. REBRANDING AND THE VISION FOR AN NCI ADVANCED TRANSLATIONAL CANCER RESEARCH PROGRAM

Opportunities in translational science have changed and expanded since the SPORE Program's inception. The Working Group recommends establishing a new vision for translational research that is empowered to effectively translate the scientific opportunities that exist today. A critical element to the success of this Working Group effort is to evolve the way that translational research is organized at the NCI. The goal is to more rapidly translate basic scientific concepts that can directly affect patient outcomes.

Characteristics of a Future NCI Translational Cancer Program

A near-term goal is to envision a "SPORE Successor" Program, such as a Translational Research Excellence (TREN) Program, that would organizationally span the major NCI-sponsored translational research programs and funding mechanisms and that would engage relevant NIH, philanthropic, industrial, and translational programs. The essential components would emphasize focus on generating impact for patients and would:

- Provide greater flexibility in the program focus, structure, and organization to facilitate the conduct of translational research that focuses on impactful solutions to scientific and operational problems with clear clinical relevance.
- Develop methods to expand clinical investigator/basic science investigator collaborations across Cancer Centers and with other institutions to include expanded opportunities to link therapeutic opportunities to the NCI early clinical trials program or NCTN, as appropriate.
- Provide opportunities to conduct high-risk, high-reward science, including opportunities to perform a deep scientific study of patients or biospecimens from smaller carefully designed clinical trials.
- Enable greater integration with Cancer Centers. For example, not only leveraging Cancer Center infrastructure around biospecimen acquisition and conduct of clinical trials, but also providing a mechanism to facilitate expansion of Cancer Center infrastructure through conduct of impactful translational research science.
- Support operational activities (e.g. arranging drug access processes, support for investigational new drug (IND) filing, developing of community institutional review board (IRB) processes, developing spinoff business models, development of community Clinical Laboratory Improvement Amendments (CLIA) laboratories, etc.) needed to enable advanced cancer management.
- Develop incentives to encourage interactions, collaboration and data sharing within the NCTN and other collaborative networks.

- Support the development of standards, information management and analysis procedures and infrastructure needed for national clinical trials.
- Specifically reward collaborations with computer, pharmaceutical and biotechnology industries that provide access to advanced technologies and drugs needed to enable advanced translational activities and/or to commercialize inventions or procedures.
- Provide training and/or support for aspects of translational research that may not be readily available in a typical academic setting (e.g. access to high throughput screening, CLIA assay for “new analytics”, advanced imaging, Good Manufacturing Practice (GMP) Facilities, small business development, access to FDA approved drugs at cost, IND development, and IP management principles).
- Engage Big Data initiatives now being developed across the NIH (e.g. BD2K) and in the private sector that encourage and enable management and interpretation of “big data” on cancer being generated worldwide.
- Develop strategies that increase funding flexibility for translational research across programs and funding mechanisms, of which a reinvigorated P50 SPORE mechanism would be an important part.
- Support development of policies and procedures that mitigate risks associated with sample and information exchange.
- Develop an approach to messaging the new TREX Program to SPORE directors, advocates, Cancer Center directors, basic scientists, clinicians, etc. to encourage collaborations.

Recommendation: Re-brand the SPORE Program as the TREX Program, providing investigators with increased flexibility on how best to structure their research programs (ranging from small, focused projects to large-scale, team-based projects).

Recommendation: Maintain or increase the current level of support for patient-centered translational research.

Recommendation: Develop incentives that will encourage collaborations with other academic institutions and industry.

National Standing Translational Research Strategy Subcommittee

The NCI translational research leadership would receive advice from a strategic planning group, NCI Translational Research Strategy Subcommittee (NTRS), which could be a subcommittee of the BSA (with representatives from NCAB, CTAC as well as *ad hoc* members) that would be charged with surveying scientific horizons broadly to: 1) help identify the most provocative/impactful translational research questions; 2) examine and identify the most important opportunities for application of new technologies to translational research; 3) identification of translational knowledge gaps that might be addressed by the R01 research community, and 4) new Funding Opportunity Announcements concepts for NCI program staff and BSA consideration. The NTRS also would provide broad advice to the BSA and NCI leadership on enhancing and broadening the overall translational research portfolio.

Recommendation: Create a standing NCI Translational Research Strategy Subcommittee (NTRS). The subcommittee should be comprised of extramural investigators, as well as

representatives from pharmaceutical, biotechnology, computational and advocacy organization(s). The charge of the NTRS will be to identify the most important opportunities to benefit patients, so as to serve as an integrated guide for NCI's translational investments. The NTRS should be aligned with the NCI's Board of Scientific Advisors.

V. OVERALL RECOMMENDATIONS

The Working Group provides the following recommendations to the NCI in the area of translational research:

- Ensure that the first priority for funding is to support the highest quality science (whether basic, translational, population, or clinical), addressing the most important problems, and ensure that such projects are adequately resourced for success.
- Maintain or increase the current level of NCI funding support for patient-centered translational research at all stages.
- Develop incentives that will encourage collaborations with other academic institutions and industry.
- Increase integration, leveraging, and interfacing of NCI currently funded translational programs (such as the NCI SPORE, NCI Cancer Centers, NCTN, NCORP, intramural programs, the Center for Cancer Research, SEER, and Frederick National Laboratories), with the biopharmaceutical industry, advocacy groups and other funding agencies to accelerate translation of scientific advances to the bedside.
- Continue the current policy of funding incentives to incorporate population scientists into SPORE/TREX programs. Develop incentives to focus on cancer disparities.
- Create a standing NCI Translational Research Strategy Subcommittee (NTRS). The subcommittee should be comprised of extramural investigators across the entire spectrum of translational research, as well as representatives from pharmaceutical, biotechnology, computational and advocacy organization(s). The charge of the NTRS will be to identify the most important opportunities to benefit patients, so as to serve as an integrated guide for NCI's translational investments. The NTRS should be aligned with the NCI's Board of Scientific Advisors.
- Re-brand the SPORE Program as the Translational Research Excellence (TREX) Program, providing investigators with increased flexibility on how best to structure their research programs (ranging from small, focused projects to large-scale, team-based projects).

Translational Research Excellence (TREX) Program specific recommendations (referred to within body of report as "SPORE Successor" Program):

June 8, 2016

- Effective involvement of research advocates with a collective patient perspective should continue to be an integral component of the “SPORE Successor” Program.
- Strongly encourage impactful research projects that bring investigators from multiple institutions together. The Program should prioritize collaborative projects addressing both the most important questions within organ sites as well as “cross cancer” initiatives that focus on targeting commonly mutated genes (pathways) or cancer public health challenges. Elimination of the requirement for a minimum number of projects within each TREX will facilitate the development of both small focused projects and large scale team based projects.
- Each individual research project should continue to include a clinical investigator and other disciplinary based principal investigator.
- Where appropriate, projects can include a population scientist investigator with an relevant research aim.
- At least one – but not all – translational research projects within the TREX program must incorporate a defined clinical endpoint.
- While the WG suggests enhanced coordination of the TREX Program with NCI-designated Cancer Centers, the WG recommends that the TREX Program PI retains full autonomy so as to fulfill the Program’s stated goals.
- Development of and adoption of community consensus standards for clinical and biological metadata, including data security, should be key components of the TREX Program.
- A TREX Program should encourage and value properly managed exchange of data between TREX Programs and with the larger cancer community and should encourage adoption of community data standards as they emerge.
- A TREX program should encourage development of a program-wide consent process that would inform patients about the: 1) risks and rewards of participating in a TREX program, and 2) possibility that some data may be made available to private sector collaborator that would enable use of individual patient information in research that is not envisioned at the time of consent.
- A TREX program should contribute to the development of a functional data commons that will organize functional data being generated throughout the NCI research community in ways that will allow it to be readily accessed by research and clinical investigators in order to facilitate identification of causal relationships and that will contribute to the development of clinical decision support tools.

- Informative laboratory models of important aspects of cancer should be encouraged and supported (i.e., collection of primary tumor specimens to generate patient derived xenografts (PDX) and organoids, paired germline samples, engineered tissues, etc.).
- The TREX Program should be open to establishing translational research cores that fill broad institutional infrastructure gaps, such as tissue acquisition, informatics, and emerging technologies. Importantly, these efforts should utilize existing cores within Cancer Centers and other institutional facilities wherever feasible. A core to support collection of tumor specimens is optional. TREX tissue cores are expected to deploy novel expertise or methodologies to support impactful research, and not overlap with existing institutional cores.
- The Career Development component should be continued in the TREX Program to support the development of new translational investigators.

VI. CONCLUSION

Twenty-three years ago, translational research was the exception rather than the rule. Today, translational research is a fundamental component of the bench to bedside continuum. The breadth of scientific and technological discovery in the past decade has opened many new pathways which have and will continue to improve patient outcomes.

The evolution of translational research needs has been recognized, with corresponding adjustments to the SPORE program. The most recent adjustment was in response to a review by the SPORE Evaluation Group in 2014. In addition, NCI has funded other translational mechanisms. The charge of the current Working Group, as defined by former NCI Director Harold Varmus and affirmed by interim NCI Director Douglas Lowy, was to step back and take a broad look at the requirements of the larger translational research community and develop recommendations which will help NCI-funded translational research move forward productively.

The Working Group recognized that translational research does not exist in a vacuum. Rather, it depends on a robust basic research discovery pipeline and integration with clinical or population science research, frequently conducted at Cancer Centers. Cancer Centers have scientific infrastructure which can be leveraged as part of an integrated translational research program. In addition, translational research demands differ by cancer site, reflecting a desire to develop a mechanism to identify critical questions facing different sites. The recommendations offered by the Working Group seek to address the broader scientific focus by development and implementation of a Translational Research Excellence (TREX) Program, as described in this document. The recommendations recognize that translational research requires collaboration, flexibility and input from multiple stakeholders, including research advocates.

The Working Group recognizes that these recommendations have many far-reaching implications. They are intended to provide a framework that will allow NCI to support translational research critical to patient outcomes, across all cancer sites. We recognize that they will require a vigorous discussion in the extramural community to move forward, and look forward to participating in that discussion.

APPENDIX: INVITED SPEAKERS

December 3, 2014

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