Fusion Oncoproteins in Childhood Cancers
Recommendation of the Blue Ribbon Panel Pediatric Working Group

Recurrent translocations are a hallmark of childhood cancer and are often pathognomonic of specific cancer types (e.g., EWS-FLI1 in Ewing Sarcoma or PAX-FOXO in alveolar rhabdomyosarcoma). These translocations generate fusion oncoproteins that target developmental programs critical for transformation of the unique cell of origin for each cancer. Fusion oncoproteins are well-defined cancer drivers that are often found in cancers with few other genetic lesions. The goals of this proposal are to enhance our understanding of the molecular and biochemical mechanisms of transformation driven by fusion oncoproteins, to develop faithful models of these pediatric cancers, to identify their key dependencies, and to use this information to develop novel therapeutic approaches that target these mechanisms.

Recommendation:

1) Develop model systems of each cancer to be studied. This should include mouse models (patient-derived xenograft (PDX) and genetically engineered mouse models (GEM), cell line models, and potentially iPS models of each cancer subtype for mechanistic interrogation of fusion protein biology. Fusions proteins to be interrogated include EWS-FLI1, EWS-ERG, PAX-FOXO, SS18-SSX, MLL-fusions, NUP98-NSD1, ETV6-RUNX1, E2A-PBX, FUS-ERG, and others as defined by working groups. Because many fusion oncoproteins have a distinct biology, collaborative efforts should start with a studies of 10 to 15 oncoproteins. Brain tumors (astrocytomas, medulloblastomas) are cancers of particular interest as several fusion oncoproteins are missing. Newly developed models will provide preclinical models for the assessment of candidate therapeutics

2) Perform detailed cell biological, gene expression and chromatin based/epigenomic studies of these models to define how each fusion protein influences gene expression to perturb normal cellular programs to block lineage differentiation and development. Regulation, particularly epigenomic regulation, likely will take a more predominant role in childhood cancer studies over time.

3) Perform detailed proteomic analyses to identify protein complexes bound to fusion oncoproteins. Perform structural studies to define the three dimensional structure of the domains within the fusion proteins and associated protein complex members; a structural understanding will elucidate the low mutational burden seen in pediatric cancers. Leverage this structural data to nominate domains that are potentially targetable by small molecules that either directly interfere with protein function or that can be designed to induce targeted degradation of the fusion oncoprotein.

4) Complement the proteomic studies with high resolution CRISPR “domain scanning” of fusion oncogenes and associated complex members in cell lines/samples that harbor

pediatric cancer translocations (EWS-FLI1, EWS-ERG, PAX-FOXO, SS18-SSX, MLL-fusions, NUP98-NSD1, ETV6-RUNX1, E2A-PBX, FUS-ERG, others) to identify the key functional domains for targeting.

5) Determine the **dependencies** of specific translocation associated tumors through functional genomic screening (CRISPR and shRNA) of cell lines derived from these cancers. This should include detailed assessment of dependencies on proteins present in complexes with the fusion protein, as well as novel synthetic lethal dependencies in the presence of the fusion protein.

6) Develop **therapeutic approaches** that target fusion protein stability, function and/or interaction with critical protein complex members. Focus on small molecule approaches to target enzymes identified in fusion protein complexes, to disrupt critical complex interactions or to promote degradation of fusion proteins or associated complex members. Determine if competitive inhibitors, irreversible inhibitors or degradation is the best approach to inhibit fusion protein function. Novel synthetic lethal dependencies identified in functional genomic screens should also identify other novel therapeutic targets that could potentially be targeted either through drug repurposing or de novo small-molecule screens for new inhibitory drugs.

Where are we now?

- Current state
    - Recent studies suggest that most fusion proteins work via deregulation of protein complexes that control gene expression or chromatin state, which provides a path toward mechanistic understanding. However our mechanistic understanding of the protein complexes required to drive cancer associated gene expression remains rudimentary.
    - It is generally recognized that fusion oncoproteins represent critical drivers of many childhood cancers and that they transform developmentally restricted cells of origin. To date, however, there has been no systematic attempt to determine the dependencies generated by these unique oncogene/cell of origin combinations. Recent developments in CRISPR-Cas9 associated screening will allow detailed assessment of genes required for specific fusion oncoprotein-associated tumors and to also define specific functional domains within each protein that are of critical importance.
    - Recent drug development efforts suggest small molecule approaches that target gene regulatory mechanisms may have therapeutic efficacy in patients, however, these approaches have been developed to target only a small number of the potential therapeutic opportunities within each cancer. Indeed, very little therapeutic development has specifically focused on fusion protein driven pediatric cancers in spite of the fact that the fusion proteins are common cancer drivers and often found in cancers with few other genetic lesions. Detailed

functional studies will likely point to new opportunities for small molecule development.

- The recent development of small molecules approaches that can induce targeted degradation of oncoproteins suggests that more detailed understanding of the domain structure of fusion oncoproteins may open novel avenues for therapeutic development.

- Barriers
  - The number of models of fusion oncoprotein-driven pediatric cancers is limited. For some diseases there is a marked paucity of models for studying the basic molecular mechanisms of the disease as well as therapeutic approaches.
  - There is a lack of systematic characterization of genomic and epigenomic characteristics of fusion-driven pediatric cancer models. Co-localization of this data within a single database would be highly valuable but has not been attempted.
  - While CRISPR/Cas9 screening is widely used, the identification of key dependencies broadly across fusion-driven childhood cancers will require a collaborative, systematic approach to cell line collection/generation, data generation and storage and analyses.
  - The ability to progress from structure-function data, to biological insight, to small molecule inhibitor to therapeutic testing requires a highly dynamic and collaborative network of investigators with unique expertise. Such groups with overlapping/complimentary interests specific pediatric cancers are rarely found within one lab/institution. Collaboration is critical. Collaboration would be spurred by targeted efforts to develop therapies for specific childhood cancers.

Where do we need to be in 1-5 years?

- Key priorities
  1) Develop a comprehensive collection of genomically characterized cell line, mouse, and iPSC models of fusion-driven pediatric cancers.

  2) Advance our understanding of the mechanisms of action of each of the common fusion oncoproteins in childhood cancers.

  3) Determine the key vulnerabilities in these fusion-driven pediatric cancers through functional genomic screening, and generate a map of the key functional domains for each fusion oncoprotein. Establish a pipeline for performing systematic CRISPR/Cas9 and shRNA screening.

4) Determine the key protein members of each fusion oncoprotein protein complex and their key functional domains.

5) Develop a pipeline for small-molecule screening and the validation of lead small molecules in cell line and mouse models of fusion-driven cancers.

6) Develop a network of collaborating investigators with expertise in proteomics/structural biology, genomics/epigenomics, chemistry, experimental therapeutics, and disease-specific biology.

- Rationale for investing
    - Despite significant progress made in the treatment of children with cancer, in the U.S. cancer remains the leading cause of death from disease in children, with significant short and long term toxicity of treatment continuing to impact the majority of children with cancer.

    - Fusion oncoproteins are well-defined cancer drivers that are found in *de novo* and relapsed refractory childhood cancers. They are often found in cancers that are otherwise genetically "silent". Therefore they represent highly credentialed targets for potential therapeutic development.

    - Understanding in these pediatric cancers will also inform adult cancers with similar fusion oncoproteins (e.g., TMPRSS2-ERG in prostate cancer)

    - Development of systematic approaches to target these oncoproteins will serve as a paradigm for targeting diseases driven by other "undruggable" proteins.

What will it take to get there?

1) Establish collaborative groups of scientists focused on development of model systems, cell biological studies and epigenomic studies to define mechanisms of action of each of the fusion oncoproteins. The groups could coalesce around specific fusion oncoproteins and/or specific technologies (i.e. epigenomics), starting with 10 to 15 oncoproteins.
2) Establish collaborative efforts, such as centers, for proteomic and biochemical studies. Establish a limited number of centers with expertise in the most sophisticated proteomic approaches to identify protein complexes associated with each fusion oncoproteins, and forge collaboration with groups focused on cell biology/epigenomic studies.

3) Develop collaborative efforts, such as centers of expertise, for structural biological studies to be performed on functional domains in fusion oncoproteins and critical protein complex subunits.

4) Identify groups expert in chemistry and chemical biological approaches to perform small molecule screens, initiate structure-guided small molecule development, and medicinal chemistry to design/refine small molecule probes that can be used for target validation and ultimately initial in vivo pre-clinical studies.

5) Develop collaborative efforts, such as centers of expertise, for assessment of new small molecules *in vitro* and *in vivo* with an early focus on combination therapeutic approaches.

What would success look like?

This proposal would provide insight into childhood cancer development and potentially uncover new therapeutic opportunities. Fusion oncoproteins are well-defined pediatric cancer drivers where focused experimentation could rapidly drive the field forward. The work described here should lead to a better understanding of the biology and mechanisms of action of these proteins that are a common hallmark of childhood cancer. Bringing together groups with expertise across the cell biological, epigenomic, proteomic and drug development spectrum should lead to the development of novel small molecule probe compounds and potentially drugs. This would galvanize continuing drug development in biotechnology and pharmaceutical companies by lowering the barriers to successful drug development for pediatric cancers. Given that most of the fusion oncoproteins subsume normal developmental and gene regulatory pathways it is likely that the drug development performed here will have utility in a number of other cancers that span the pediatric – adult cancer divide.

IMMUNOGENOMICS-IMMUNOTARGETS FOR CHILDHOOD CANCERS

RECOMMENDATION OF THE BLUE RIBBON PANEL PEDIATRIC WORKING GROUP

Recommendation

Define the cell surface landscape of high-risk pediatric cancers and how it differs from normal childhood tissues in order to develop highly specific immunotherapies. Central to the definition of "optimal immunotherapeutic target" is selective uniform expression on tumor cells and a requirement of the molecule for cellular viability. In parallel, enhance our understanding of the fundamental biology responsible for the immunosuppressive microenvironment that exists within pediatric solid tumors. Discovery of pediatric cancer immunotherapeutic targets combined with an improved understanding of the immunosuppressive tumor microenvironment will lead to new, more effective immune based therapeutic regimens for currently incurable pediatric cancers.

Where we are now?

We have witnessed an unparalleled period of discovery of pediatric cancer tumor cell intrinsic oncogenic drivers, with advanced sequencing technologies delivering robust information on pediatric cancer initiation and progression. In parallel, immunotherapeutic approaches to childhood cancer has been clearly credentialed, with sustained complete responses in children with refractory leukemia using an anti-CD19 chimeric antigen receptor engineered T cell approach, and with improvement in survival for children with high-risk neuroblastoma using an anti-GD2 chimeric monoclonal antibody strategy. However, for most patients with high-risk or refractory childhood cancers there is no effective immunotherapeutic option. This reflects both a lack of credentialed immunotherapy targets as well as a poor understanding of the immunosuppressive tumor microenvironment (TME), which contributes to the limited effectiveness of immunotherapies for childhood cancers.

There are several major barriers to fully realizing the potential of immunotherapeutic approaches to childhood cancers. First, childhood cancers typically have relatively low mutation burdens, and thus are much less likely to express neoantigens and/or be susceptible to immune checkpoint blockade therapies. This is also true of the majority of malignancies that afflict adolescents and young adults, typically driven by oncogenic fusion events with few (if any) additional driver mutations. Second, most immunotherapeutic strategies in the pipeline are being developed for adult malignancies and the expression pattern for the target has not been fully considered in childhood cancers, especially in regard to expression relative to normal

developing tissues in children from birth through adolescence. Third, while it is clear that suppressive effects mediated by the tumor microenvironment play a major role in immune evasion both in adult and pediatric cancers, essential core elements of the tumor microenvironment are not well understood, and the degree to which pediatric versus adult solid tumors are similar or distinct in this regard are not yet known.

We have a unique opportunity to identify optimal immunotherapeutic targets for childhood cancer, define the essential elements responsible for tumor cell intrinsic and extrinsic mechanisms of immune evasion, develop novel regimens (e.g., vaccines) to target both the tumor and the immunosuppressive microenvironment, and develop a new generation of basket-design clinical trials that define eligibility by the presence of the newly defined immunotherapeutic target biomarker.

Where do we need to be?

- While a tremendous amount of discovery-based genomic profiling work has been completed, we first need to integrate DNA and RNA sequencing approaches with cellular membrane proteomic profiling to define the proteins that are uniquely and abundantly expressed on pediatric cancers, and show little or no expression in normal childhood tissues. Recent examples in the identification of Var2, MCAM and GPC2 as novel pediatric cancer specific immunotherapeutic targets can serve as exemplars for future efforts.

- Next, there needs to be integrated public-private partnership to develop the right immunotherapeutic tools (drugs) to exploit these targets. Both protein-based (antibody; antibody drug conjugates) and cellular-based (engineered T or NK cells) therapies will be created. Embryonal antigens could serve as potential vaccine targets. A combination of epigenetic agents should be considered.

- Third, murine models that recapitulate the immunosuppressive tumor microenvironment characteristic of embryonal solid tumors need to be developed and we need to create a robust preclinical testing program that leverages immune competent models and the infrastructure to both test new strategies for anti-tumor efficacy, but also toxicity in the right systems.

What will it take to get there?

- Intensified discovery efforts to define the optimal immunotherapeutic targets in childhood cancers via cell surface proteomic profiling (transmembrane and MHC-restricted) of high-risk pediatric cancers, with an emphasis on samples with complete

DNA and RNA sequencing and diagnostic-relapse pairs and or primary-metastatic site pairs. A parallel profiling of normal tissues from birth through adolescence is required. CRISPR screens directed towards candidate immunotherapeutic targets would define cancer-specific vulnerabilities.

- Investment in yeast and phage display technologies to develop the highly specific scFv binders for novel pediatric cancer immunotherapy targets.

- Dedicated efforts to define the cancer cell intrinsic and extrinsic mechanisms of immune evasion during tumorigenesis and therapy.

- Investment in the development of immune competent pediatric cancer models, and a distributed mouse hospital dedicated to novel immunotherapy preclinical testing, including pharmacokinetics and toxicology in appropriate models. Key to this effort will be preclinical testing of combination approaches integrating immunotherapy into standard of care and/or small molecular therapeutic regimens.

- Investment in extant clinical trials networks to allow for rapid testing and dissemination of novel cell-based immunotherapies.

What does success look like?

Credentialing of new immunotherapeutic strategies focused on pediatric cancer specific targets that show broad activity across histotypes in a biomarker-restricted fashion. This would result in improved cure rates for multiple high-risk pediatric cancers where progress has been limited with dose intensive chemoradiotherapy.

New Therapeutic Targets to Overcome Cancer Drug Resistance
(Joint Recommendation from Pediatric Cancers and Tumor Evolution)

What is the recommendation (1-3 sentences)?

Launch multi-disciplinary studies to identify new drug targets elaborated by cancer drug resistant states. Such studies will include approaches to overcome drug resistance in exemplary pediatric and adult tumor types and therapeutic contexts.

Where are we are now (2-3 paragraphs)?

- Summary of the current state of the science/practice
  Most cancer patients die because their tumors exhibit intrinsic resistance or develop acquired resistance to available therapies. However, our knowledge of the spectrum and mechanistic underpinnings of drug-resistant cell states remains incomplete. It has become well-recognized that resistance can be highly multifactorial and heterogeneous, with multiple independent resistance mechanisms operant in the same patient, tumor focus, or even the same tumor cell. Furthermore, some drug resistance programs may be non-cell autonomous and may overlap significantly with programs that drive metastasis and overall tumor survival/maintenance.

- Identify barriers to progress and/or emerging opportunities
  Barriers to progress in understanding cancer cell resistance exist on genetic, molecular, cellular, and physiological levels. Understanding why, when, and how resistance develops is complicated by gaps in understanding regarding, but not limited to, tumor cellular heterogeneity; cell plasticity among potential cancer stem cell/tumor initiating cell populations; rewired and/or reprogrammed signaling pathways; compensatory signaling mechanisms; positive/negative signaling feedback loops; contributions of genetic polymorphisms (SNPs, CNVs); and the contribution of non-cancer cell components within the tumor microenvironment. Moreover, this multifactorial and heterogeneous nature of resistance means that multiple mechanisms can be operant in the same patient and even the same cell. That said, a growing body of evidence suggests that many individual resistance mechanisms may converge onto certain drug-resistant cell states, the understanding of which may provide new opportunities for combination therapies capable of circumventing this challenge.

Where do we need to be (in 1-5 years)?

4. Apply systematic experimental studies in appropriate model systems to define spectra of resistance mechanisms and dependencies linked to drug-resistant states.

New genome editing (e.g. CRISPR) and unbiased small molecule screening to systematically discover their vulnerabilities and make it possible to identify genes and pathways that are essential to tumor cells that harbor specific genetic or molecular alterations. Specifically, it is paramount that there is a focus on pediatric cancers with a low probability of cure (metastatic solid tumors, select CNS tumors, AML, certain high risk subsets of ALL, and all refractory and recurrent cancers). These approaches may be leveraged to discover individual resistance

mechanisms, common resistant cell states onto which they may converge, and genes/pathways that become essential after evolution to drug resistance. The interrogation of translocation-based tumors and identification of ways to expand the view of signal transduction pathways, particularly those involved in metastatic disease, is important. This effort should yield many new insights into tumor pathways and molecular contexts underpinning drug resistance that could be exploited using existing or future therapeutic regimens.

Priority should be given to efforts that approximate the clinical environment linked to drug resistance as closely as possible. Examples include diverse models (e.g., organoids, patient-derived xenografts, co-cultures in physiologic/"hypoxic" conditions, genetically engineered mouse (GEM) models, etc.), and assessment of drug-resistant states in addition to "steady-state" 2-D cell culture. Patient-derived models will be of particular interest but mouse models capable of interrogating aspects of tumor evolution as they relate to drug resistance are also important, particularly as they allow investigators to address these processes in the context of an intact immune system. New technologies that assess drug resistance mechanisms in primary tumor material directly will be a plus. In addition, model systems that assess non-cell autonomous effectors of cancer drug resistance (e.g., derived from the microenvironment or immune cells) would also be of interest.

5. Comprehensive characterization of drug-resistant clinical specimens, including 3-dimensional and 4-dimensional cancer cell atlases linked to drug-resistant states.

Emerging single-cell technologies are making it possible to produce high-resolution characterization of all major cell types (malignant, microenvironment, and immune) in tumor tissues. Both this recommendation and the accompanying recommendation on metastasis could include single-cell and/or multiplexed in situ cellular analysis of biopsies obtained from individual cancer patients throughout the course of disease and treatment, including the advent of drug resistance. Single-cell analysis will ideally be combined with new *in situ* technologies that read out cell/tissue topology to ascertain the cellular adjacencies that may influence particular functional states. Moreover, the atlases generated by this approach should be linked to model systems that allow experimental testing of the hypotheses generated. Such information could bring forth major new insights into tumor biology and heterogeneity, as well as cell states that identify new therapeutic targets and predict treatment response in metastasis and drug resistance.

6. Develop a collection of drug-resistant cancer models designed to fill key gaps and emphasize areas of unmet medical need.

For many cancer types, we still lack appropriate experimental model systems that would allow us to study the salient tumorigenic programs linked to drug resistance and to discover new therapeutic targets. Recent years have witnessed advances that could enable a dramatic expansion in various types of models, including cell culture systems (e.g., organoids and tissue slice cultures where cells are in their unperturbed environment), patient-derived xenografts, genetically engineered mouse models, and the possibility of generating tumor-bearing mice with "humanized" immune systems. Thus, the above recommendations may include new cancer model generation that is most representative of clinical areas of unmet medical need.

Rationale for investing (Why is this priority ripe for accelerating?)—see above

Opportunity brought about by recent development in science, technology, practice: The advent of new tools to perturb cancer cells (e.g., through systematic gain- and loss-of-function studies), to culture such cells ex vivo or in PDX settings, and to conduct serial sampling of tumor cells throughout the course of treatment offer unprecedented opportunities

Does it address an unmet need or important gap in knowledge or practice?

The development of drug resistance underlies cancer recurrence and accounts for significant cancer-associated mortality. Notably, despite significant progress made in the treatment of children with cancer, in the U.S. cancer remains the leading cause of death from disease in children, with intrinsic and acquired resistance being central to mortality. With no current means to predict who will develop resistance, or when resistance will arise, there is a substantive gap in knowledge and a clinically unmet need.

What would be needed for success? *For example*:

- New or expanded resources: support for serial collection of tumor tissue and blood during treatment and upon frank drug resistance; deployment of technologies and analytical capabilities for high-resolution characterization of these tumor cells prior to treatment, during treatment, and upon resistance; implementation of experimental approaches to perturb appropriate models ex vivo, in vitro, or in vivo;
- Barriers/roadblocks eliminated or reduced: support scaling of existing experimental efforts, augment existing infrastructures for biopsies and blood collection; support for data generation efforts; establishment of new computational teams focused on deconvolving the biology linked to resistance
- New or enhanced technologies: scalable functional studies (gain-of-function studies, loss of function studies, genome editing efforts); single-cell analysis, high-content tissue topographic analysis, etc.

Strategy: What will it take to get there?

- Concrete actions to take in the next 1-5 years

  We recommend that the cancer moonshot effort pursue a multi-disciplinary effort that consists of both systematic experimental studies and comprehensive characterization of clinical specimens obtained prior to treatment and upon relapse to exemplary cancer therapeutics in selected tumor contexts (targeted therapy, immunotherapy, and/or chemo-radiotherapy). Collaborative efforts dedicated to the study of childhood cancers, which could include establishment of centers of excellence, in addition to separate studies of adult cancers should include: 1) adult and pediatric dependency screening; 2) pediatric and adult cancer model generation; 3) preclinical therapeutic testing. In addition, there should be a dedicated effort to develop and test circulating free DNA (cfDNA) methods in pediatric and adult cancers. This effort will incorporate technologies such as single-cell sequencing as well as tissue-based characterization, which may allow specific investigations into the roles of microenvironmental cells and specific patterns of heterogeneity in the overall tumor drug-resistant state. In parallel, both systematic and in-depth functional studies of drug resistance will be conducted using appropriate tumor model systems so that correlative features

observed in clinical specimens could be characterized mechanistically (and conversely, resistance mechanisms identified in vitro could be queried using the clinical data).

Similar to the "Metastasis" recommendation, these priorities may also require:

1. Scalable research biopsy and data generation programs. These initiatives will require fresh and/or serial biopsies of metastatic and drug-resistant specimens for deep tumor/microenvironmental characterizations and generation of ex new vivo models. Thus, the cancer moonshot should support collaborative efforts, such as the establishment and maintenance of centers of excellence, to procure these biopsies at scale and link them to state-of-the-art technologies for data generation and analysis (below Liquid biopsy protocols should be paired with tissue biopsy efforts to provide complementary cancer-derived materials (circulating tumor cells/DNA, exosomes, etc.). Materials obtained from these research biopsies should be seamlessly integrated with workflows capable of generating a wide range of data types.

2. Computational analysis capabilities. A critical need exists to develop algorithms that integrate and extract therapeutic meaning from data generated from metastatic biopsies using the latest technologies. Thus, we envision the establishment of collaborative efforts whose mission to design and implement such tools.

3. *Ex vivo* cultivation, perturbation, or target validation activities. Expansion of cancer models in vitro and in vivo would be aided by increased capacity for handling, distributing, and propagating cancer cell line and patient-derived xenograft models. Focused efforts to optimize approaches for generating and maintaining these models, building robust collections, and perhaps hosting research on these models done by individual investigators or moonshot teams should be considered.

What does success look like?

A cancer drug resistance landscape project, applied to representative tumor and therapeutic contexts (e.g., specific targeted therapy, immunotherapy, and chemo-radiotherapy regimens) in adult and pediatric cancers, should produce new information about the biology of drug-resistant states that directly informs the development and clinical testing of novel therapeutic combinations. The initiatives should make it possible to non-invasively detect and molecularly characterize recurrences at the earliest possible time point so that salvage therapy can be initiated at a point of minimal tumor burden, with minimal molecular diversity. By the end of five years, several of these might emerge that could be administered up-front in cancer patients and circumvent prevalent drug-resistant states (or even "push" cells into drug-sensitive states).

Appendix:
Survivorship, Global Disparities, Advocacy

SURVIVORSHIP. Currently, eight of every ten children and adolescents who are diagnosed with cancer will survive ≥ 5 years beyond their diagnosis. Childhood cancer survivors carry a tremendous cumulative burden of long-term morbidity, largely attributable to the therapeutic exposures used to treat the primary cancer. It is currently estimated that by 35 years from initial diagnosis, on average, a survivor will experience an average of three serious/life-threatening conditions. However, the significant inter-individual variability in the personal risk of developing these adverse outcomes suggests the role for individual variation in response to therapeutic exposures.

NCI-, foundation-, and institutionally-funded initiatives continue to provide critical information regarding outcomes among pediatric/adolescent cancer survivors. The Childhood Cancer Survivor Study (CCSS) represents a significant contributor to our understanding of the incidence and risk factors for adverse late-effects of the therapy. However, CCSS is limited by reliance upon self-report for the majority of outcomes and a biorepository that is not comprehensive relative to all members of the cohort or the type/quantity of material collected. The St. Jude Lifetime Cohort (SJLIFE) represents a population characterized by prospective comprehensive clinical assessment and collection of germline samples. However, SJLIFE is a single institution study of a more moderate sample size. The Children's Oncology Group has had a longstanding case-control study (COG-ALTE03N1) that represents a multi-institutional initiative (>100 institutions) with clinically-validated outcomes and biological specimens from childhood cancer survivors with adverse outcomes (cases) and without (controls). Funded by the NCI and foundation grants, the goal of this study is to understand the molecular pathogenesis of treatment-related adverse outcomes. However, The COG study is a prevalent case-control study with the attendant risk of potential survival bias. Intact, all 3 initiatives (CCSS, STLIFE, COG-ALTE03N1) are subject to survival bias – because of enrollment of patients several years after completion of treatment.

1. Enhance and expand efforts to undertake a comprehensive assessment of the pathogenesis of exposure-specific long-term morbidity.
2. Aggressively pursue development, testing, and dissemination of clinically relevant risk prediction models that identify patients at highest risk of treatment-related complications (risk prediction models based on demographic, clinical and molecular predictors of adverse outcomes) and use these risk prediction models to facilitate personalized treatment, and post-treatment screening for early detection, and targeted interventions.
3. Establish centers of excellence for these initiatives.
4. The recommendations for research would be exposure-specific and thus would result in support of research that directly influences long-term cancer morbidity and premature mortality across all cancer diagnoses.

GLOBAL DISPARITIES IN CHILDHOOD CANCER CARE AND CONTROL. Advances in the treatment of childhood cancers have resulted in part from the development of national and international collaborative initiatives that have defined biological determinants and generated risk-adapted therapies that maximize cure while minimizing acute and long-term effects. Currently, greater than 80% of children with cancer treated with modern multidisciplinary treatments in developed countries survive ≥ 5 years; however, of the approximately 160,000 children and adolescents who are diagnosed with cancer every year worldwide, 80% live in low and middle-income countries (LMIC), where access to quality care is limited and chances of cure are low. The disease burden is not fully known due to the lack of population-based cancer registries in low-resource countries; regional and ethnic variations in the incidence of the different childhood cancers suggest unique interactions between genetic and environmental factors that could provide opportunities for etiological research. In sum, childhood cancer burden is shifted towards LMIC; global initiatives directed at pediatric cancer care and control are needed.

1. Develop a comprehensive assessment of the global childhood cancer burden that integrates epidemiology, health-services, and outcomes research. Through this initiative, an estimation of incidence and prevalence of childhood cancer, and a reliable evaluation of outcomes and barriers to access to care will be performed. Proper integration of epidemiological initiatives will also provide relevant cues to etiological research and facilitate collaborative research opportunities.
2. Develop a scaled approach to access to childhood cancer care and control worldwide, and a costing evaluation that includes cost effective analyses as well as modeling and simulation methods. Through this initiative, a detailed tiered system approach that integrates different dimensions in health systems and health services, and patient and family centered quality interventions, will provide innovative cost-effective models to enhance access to care.
3. Develop and support research and educational national regional networks to facilitate the implementation of the recommendations 1 and 2 and the development of capacity-building and research initiatives designed to address the local and regional disease burden worldwide. Through this initiative, sustainable national and regional models that aim to build capacity, facilitate access to care, and enhance quality will be developed. The integration of the research method and the development of solid research infrastructures will further the reach of this initiative and establish links for collaborative research with North American cancer centers.

CHILDHOOD CANCER RESEARCH ADVOCACY The childhood cancer patient advocate community is passionate and their missions range from funding research to providing support for patients and families. Opportunities exist to enhance, improve, and accelerate research initiatives for those willing to tap into that passion and energy and find productive ways to engage with them. A key goal is to leverage the power of the childhood cancer patient advocacy community to enhance childhood cancer research.

The DIPG community provides one vivid example of how effective parent communication has led to research success. Those in the DIPG patient community heard repeatedly that relapse tissue is critical to advancement of research, so they spearheaded an initiative to improve tissue acquisition. Such efforts have a higher likelihood of success when patient advocate groups are part of the research process from the beginning of a project. Genomic-based research provides another fertile opportunity for advocacy organizations to partner. A two-way flow of information will help educate patient and families about the opportunities to participate in studies as well as limitations of this type of research.

Bringing the voice of the patient and families to the table is vital for researchers and for the childhood cancer community. Given the large funding role of childhood cancer groups, strengthening communication channels will yield more transparent conversation about common goals and challenges. Allowing this conversation to happen on a broader in-depth scale may also lead to smarter funding decisions and increased efficiency and effectiveness. Creating collaborative opportunities to enhance research advocates knowledge and understanding of the landscape of childhood cancer research will ensure the patient voice exists in the research process.

1. Train Research Advocates from the patient advocacy community about the clinical research process and build their scientific knowledge of childhood cancer.
2. Incorporate trained patient Research Advocates in the peer review and scientific process when possible
3. Enhance coordination amongst childhood cancer groups with research community to ensure productive funding opportunities