Summary of the Childhood Cancer Targeted Therapeutics Workshop Sponsored by the American Cancer Society and the National Cancer Institute

List of workshop participants in alphabetical order is at end of document

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Summary for Childhood Cancer Targeted Therapeutics Workshop

Abstract:

The American Cancer Society (ACS) and the National Cancer Institute (NCI) jointly sponsored a workshop in May 2005 entitled "Childhood Cancer Targeted Therapeutics Workshop". The workshop focused on ways in which the public and private sectors can expedite application of state-of-the-art technology to the task of identifying and validating childhood cancer therapeutic targets. Participants in the Workshop included pediatric and medical oncology preclinical and clinical researchers, representatives from pharmaceutical companies and from FDA, childhood cancer advocates, and leaders of foundations supporting health research.

Workshop participants agreed that the identification and validation of therapeutic targets for childhood cancers is critical to future progress in identifying more effective treatments for children with cancer. This task is especially important today for two reasons: 1) current treatment approaches have reached a plateau in improving outcome for children with cancer, and 2) the introduction of targeted agents in the childhood cancer setting will benefit children only if they are utilized with a sound knowledge of relevant therapeutic targets for specific pediatric cancers.

Workshop participants identified research strategies that have a high probably of identifying valid therapeutic targets if they are systematically applied in the childhood cancer setting. These approaches include high-throughput gene resequencing, gene expression profiling and array-based methods for characterizing genomic abnormalities in cancer cells, and high-throughput RNA interference (RNAi) functional screens.

Public-private partnerships could support the research required for target identification and validation using one of several models, with each of the models having in common the need for governance structures involving all relevant constituencies and the need for rapid dissemination of research results. The childhood cancer targets discovered through the efforts of such partnerships may be pediatric-specific, with no counterpart among adult cancers. For such targets, translation to the clinic will be challenging with a requirement for substantial resources from public and private sources. Alternatively, the targets discovered may be ones for which there are ongoing clinical programs for adult indications, in which case translation to pediatric clinical application could be rapid.

Conclusion: The identification of validated therapeutic targets is critical to future progress in identifying more effective therapies for children with cancer. Public-private partnerships can expedite these discoveries and can help to ensure that they are translated to clinical application in a timely manner.

Introduction:

The American Cancer Society (ACS) and the National Cancer Institute (NCI) jointly sponsored a workshop in May 2005 entitled "Childhood Cancer Targeted Therapeutics Workshop". The workshop focused on ways in which the public and private sectors can expedite application of state-of-the-art technology to the task of identifying and validating childhood cancer therapeutic targets. Participants in the Workshop included pediatric and medical oncology laboratory and clinical researchers, representatives from pharmaceutical companies and from FDA, childhood cancer advocates, and leaders of foundations supporting health research.[1]

Why is the task of childhood cancer target identification and validation so important? As Ruth Hoffman of the Candlelighters Childhood Cancer Foundation emphasized at the workshop, childhood cancer is the leading cause of disease-related mortality among children and too many survivors of childhood cancer are left with serious late effects that can be life-threatening. The *status quo* is not acceptable. Unfortunately, as noted by Dr. Malcolm Smith of the National Cancer Institute, pediatric oncologists have reached an impasse in their ability to cure more children with cancer. From 1975 to 1998 the death rate from childhood cancer declined at an annual rate of 2.7% per year, continuing a consistent decline in childhood cancer mortality that began in the 1960s. However, from 1998 through 2002 childhood cancer mortality remained essentially unchanged.[1] Continuing improvement in outcome during these years was not achieved despite application of very aggressive treatments that are near the limits of tolerability. Because of the high level of toxicity associated with many current treatments, future success in once again achieving declining rates of mortality must involve new therapeutic approaches.

Another reason that target identification and validation is important is that the number of new treatments for pediatric oncologists to pursue has increased substantially in the past decade. For example, over 25 new agents have been studied in pediatric clinical trials in the past 5 years, but only a small fraction of these agents will be systematically studied against specific childhood cancers. For each type of cancer, clinical researchers will need to pick two or three agents on which to focus. As noted by Dr. Smith, it is enticing to think that one of these new agents, alone or in combination, is very effective against a childhood cancer for which current therapy is woefully inadequate (e.g., MYCN amplified neuroblastoma or juvenile myelomonocytic leukemia or atypical teratoid rhabdoid tumor). It is sobering to realize that this effective treatment may never be tested against the appropriate childhood cancer because other new treatments of lesser true benefit are prioritized higher for clinical evaluation. Without guidance from the laboratory about the most important therapeutic targets to focus on for different childhood cancers, researchers will essentially be proceeding blindly. Progress in discovering more effective treatments for children with cancer will likely depend upon clinical researchers obtaining better guidance from the laboratory about the therapeutic targets on which they should be focusing.

Childhood cancer researchers and patient advocates are concerned that the same incentives for target identification and validation that apply to many adult cancers do not apply in the pediatric setting. Pharmaceutical companies and adult cancer centers have extensive resource-intensive programs for target identification and validation for adult cancers, but similar programs are lacking in the pediatric setting.

[1] See list of Workshop participants at end of document.

Action needs to be taken to ensure that state-of-the-art technologies for target identification and validation are expeditiously applied in the childhood cancer setting. A primary basis for the workshop was the concept that this research activity is something that no single entity can accomplish by itself. Therefore, the public and private sectors need to affirm childhood cancer target identification and validation as a high priority and then need to pursue ways to work together to address this challenge.

The Targeted Therapeutics Workshop focused on several distinctive areas. The first panel focused on optimal technologies and scientific approaches for identifying and validating childhood cancer targets. Another panel focused on intellectual property and data-sharing issues and the extent to which these are barriers to efforts for target identification and validation. Other panels addressed issues related to the organizational resources that could be used for target research (e.g., research institutes, cancer centers, and Cooperative Groups) and addressed the potential contributions of pharmaceutical companies to this endeavor. Public-private partnerships were a final topic of discussion, with perspectives presented from the Foundation for the National Institutes of Health (Foundation for NIH) and from foundations supporting health research. The summary of the workshop presentations that follows highlights the key issues discussed and the primary conclusions that were reached.

Summary of Molecular Methods for Target Identification and Validation

Presentations by Drs. Golub, Heimbrook, Adams, Weitman, Staudt, and Helman outlined the preclinical technologies that now exist for identifying and validating cancer therapeutic targets. In the description that follows, attribution to specific speakers is not given, except when providing specific examples from their work.

The first question addressed was whether additional therapeutic targets beyond those currently available are needed for childhood cancers. The answer was clearly affirmative, as relatively little is known about the molecular basis of childhood cancers. Specific molecular abnormalities are known to be associated with some childhood cancers (e.g., EWS translocations for Ewing sarcoma, FKHR translocations for alveolar rhabdomyosarcoma, and MYCN amplification for some cases of neuroblastoma). Despite this knowledge, the fundamental dysfunctions of the cancer cells that result in dysregulated growth and survival are largely unknown. Understanding these cancer dependencies is essential, as these dependences represent the “Achilles heels” of the cancer cells and their identification may lead to validated therapeutic targets that provide the basis for rational childhood cancer therapeutics development in the era of molecularly targeted agents.

While it is frustrating that so little is known about the growth and survival dependencies of childhood cancers, there is cause for optimism because methods are now available that allow the systematic characterization of cancer cells. These methods include gene resequencing to identify mutations associated with specific cancers, methods for copy number assessment to identify regions of the genome that are amplified or lost in cancer cells, gene expression profiling to identify cancer cells’ RNA repertoire, methods for identifying functional dependencies [e.g., RNA interference (RNAi) and small molecule library screens], and proteomic methods for identifying the activation status of proteins and signaling pathways in cancer cells. Each of these discovery opportunities is discussed in more detail below.

The most reliable method to date for identifying validated cancer targets is the observation of genomic alterations that result in activation of a specific gene product. These genomic alterations include gene amplification, translocations resulting in activation, and activating mutations. Imatinib remains the archetype for targeted therapeutics because of its remarkable effectiveness against chronic myeloid leukemia (CML).[2] Imatinib's target, the tyrosine kinase Abl, was validated based on Abl's constitutive activation resulting from the fusion of the BCR and ABL genes. Likewise, tretinoin, an agent that has transformed the treatment of acute promyelocytic leukemia (APL), has as its target the retinoic acid receptor RARα.[3] The characteristic PML-RARα translocation of APL modifies RARα function, and identifies this receptor as a valid target for APL therapeutics development.

Gene amplification can result in over-expression of a specific protein and connote a dependency of the cancer cell on this protein. For example, breast cancer cells with ErbB2 amplification are susceptible to growth inhibition and apoptosis induction through reduction of ErbB2 activity,[4] which is the basis for the effectiveness of the monoclonal antibody trastuzumab in treating women with breast cancer that has ErbB2 amplification.[5] Trastuzumab's success has stimulated the search for small molecule inhibitors of ErbB2 to use for treating this subtype of breast cancer, which like trastuzumab are able to induce objective responses in women with ErbB2 over-expressing breast cancer.[6] Array-based comparative genomic hybridization methods allow detection of regions of gene amplifcation and gene loss with a high level of resolution.[7] An alternative array-based approach uses single nucleotide polymorphism (SNP) analysis to infer regions of loss-of-heterozygosiity and to estimate chromosome copy number.[8-10]

Activating mutations are another way in which cancer cells can gain survival and growth signals. Multiple examples support the position that gene products with activating mutations are valid targets for cancer therapeutics development. For example, such mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase domain occur in a subset of patients with non-small cell lung cancer (NSCLC), and patients with tumors that have these mutations are much more likely to respond to EGFR inhibitors such as gefitinib and erlotinib than are patients whose tumors lack these mutations.[11,12] These mutant receptors activate anti-apoptotic signaling pathways upon which NSCLCs become dependent for survival.[13] Similarly, gastrointestinal stromal tumors (GIST) has gain-of-function mutations in the tyrosine kinase receptor c-KIT. Imatinib (an inhibitor of c-KIT as well as of Abl) is effective in blocking signaling from these mutant c-KIT receptors and has high levels of clinical activity against GIST.[14] Another example is the subset of AML cases with activating mutations of FLT3 for which small molecule FLT3 inhibitors have shown anti-leukemia activity.[15,16] A final example is the subset of melanoma cases that have activating mutations of B-RAF.[17] Suppression of mutant B-Raf in melanoma cells abrogates their transformed phenotype, supporting B-Raf as a therapeutic target for this melanoma subset.[18,19]

In Spring 2005, mutations in JAK2 were reported in a high proportion of patients with polycythemia vera.[20-23] This discovery has completely reordered therapeutics development for this condition, highlighting the significance of identifying validated targets as an essential component for rational therapeutics development for serious medical conditions. By analogy, the discovery of activating mutations for one or more childhood cancer could dramatically alter the clinical research program for these cancers. Dr. Stephen Sallan of the Dana-Farber Cancer Institute described for workshop participants the recent discovery of activating NOTCH1 mutations in more

than 50% of T-cell ALL cases, which illustrates this point.[24] A NOTCH1 signal inhibitor had been studied previously in adults as a possible treatment for Alzheimer's disease and this agent was rapidly incorporated into a clinical trial for children and adults with T-cell ALL (see http://clinicaltrials.gov/show/NCT00100152). The discovery opens new avenues of preclinical and clinical research directed towards the goal of identifying more effective treatments for children and adults with T-cell ALL.

High-throughput resequencing of genes is becoming increasingly efficient as a means for screening for activating mutations. This approach is being applied by several groups to systematically study specific gene classes (e.g., kinases and phosphatases) in particular cancer types. These resequencing efforts have led to the discovery of mutations of B-RAF in melanoma,[17] the phosphoinositide-3-kinase, catalytic, alpha (PIK3CA) in colorectal cancer,[25] and *EGFR* in NSCLC.[12] A systematic approach to gene resequencing was also the basis for one of the reports of JAK2 mutations in polycythemia vera.[23] Future efforts could be expanded to include a wider variety of genes whose function implicates them as potential targets for cancer-related mutations, including kinases, phosphatases, G-protein coupled receptors, transcription factors, non-tyrosine-kinase receptors, proteases, and others. Other genes to consider for resequencing are those lying within regions known to be lost or amplified in specific childhood cancers, as these genomic changes often indicate the presence of a gene whose activity may be modified in cancer cells by point mutation.

Gene expression profiling can contribute to target identification and validation by identifying cancer subgroups that utilize distinct oncogenic pathways and by defining the gene expression patterns of these subgroups.[26,27] Comparison of gene expression profiles between different groups of specimens can identify preferential activity of sets of genes that have shared biological function, chromosomal location, or regulation.[28] Gene expression profiling may be particularly useful to target identification and validation research efforts through establishing suitably homogeneous subgroups of cancers that can be further evaluated with other methods, including gene resequencing, *in situ* detection of protein modification and protein sub-cellular localization, and functional assays.

Because carcinogenesis is a multistep process, abnormalities within a number of pathways may be required for cancer development and maintenance. These include pathways for evading apoptosis, for self-sufficiency in growth signals as well as insensitivity to anti-growth signals, for tissue invasion and metastasis, for limitless replicative potential, and for sustained angiogenesis. A key step in target validation is determining the functional significance of specific potential targets within these pathways, which requires reliable methods for evaluating whether the candidate target is necessary for cancer cell growth, survival, and local and distant dissemination.

A number of laboratory methods have been applied to the task of determining whether a particular target is necessary for cancer cell growth and survival, including: dominant negative mutations, antisense methods, antibodies, small molecule inhibitors, and RNA interference (RNAi). RNAi is an especially promising tool for helping researchers to select the 'right' targets: i.e., those that are of greatest importance to the cancer cell for growth/proliferation and/or survival.[29,30] RNAi is mediated by double-stranded RNA (dsRNA) that has sequence homology to the targeted mRNA. dsRNAs can be processed by cellular RNAses into small

interfering RNAs (siRNAs) that are approximately 21-23 nucleotides long, and these are then incorporated into the RNA-induced silencing complex (RISC) that recognizes and degrades homologous mRNA. For the purposes of target validation, interfering RNAs can be introduced into cells either through chemically synthesized short RNA duplexes (siRNA) or as plasmids or viral vectors that produce short hairpin RNAs (shRNA) with sequences complementary to the targeted gene.[31,32]

RNAi methods can be applied to a specific candidate gene of interest to determine the effect of "knocking down" expression of that gene on a particular biological endpoint.[31] As an example, RNAi methods were used to demonstrate the requirement of the EWS-FLI1 fusion protein for Ewing sarcoma cell growth and survival.[33] When used in this manner, RNAi has proven to be an invaluable tool for validation of suspected targets in cancer cells and for validation of cell-based assays for inhibitor identification.

Of potential greater utility for target identification and validation are RNAi methods that allow specific pathway and genome-wide screening of gene function. These RNAi methods can screen the functional role of 1000s of genes and can identify previously unsuspected targets for therapeutic exploitation.[29,30,34,35] The primary large-scale RNAi screening methods that have been described use shRNA libraries that include multiple shRNA constructs per gene and that are bar-coded to allow array-based methods for detection of the relevant abundance of each shRNA within populations of transfected cells.[34,35] High throughput siRNA methods have also been developed for target identification.[36]

Dr. Staudt described the development and application of methods for identifying shRNAs that block the proliferation or survival of cancer cells. Retroviral constructs were developed that allow the inducible expression of shRNAs and the selection of stably transformed cell lines. shRNAs were prepared that targeted 1856 human genes with 3 shRNA constructs per gene, with all containing a 60-mer identifying bar code sequence. Target genes included all protein kinases, all PI3-kinases, all deubiquitinating enzymes, NF-κB pathway regulators, apoptosis regulators, oncogenes, and tumor suppressors. The shRNA library is used for screening purposes by infecting a relevant cancer cell line, inducing shRNA expression in one population of cells and not another, applying a selective pressure, PCR amplifying the bar codes, and then using a barcode microarray assay that allows quantitation of shRNA abundance. As an example, if the selection pressure is growth for one week, then those shRNAs that block cell proliferation or survival are identified by their deletion from the shRNA-induced cell population.

Limitations to RNAi methods need to be recognized in order to assess the ways in which they can best contribute to target identification. First, RNAi methods have limited utility for evaluating the therapeutic index of knocking down expression of specific genes. This limitation may be addressed in the future by methods that allow disseminated inducible target knockdown *in vivo*. Another caveat is that target elimination produced by RNAi may not be equivalent to target inhibition produced by small molecule inhibitors. A third issue is that off-target activity can occur with some siRNAs and shRNAs. Mistaken attribution resulting from off-target activity can be minimized by using multiple functional RNAi probes for each gene evaluated. Finally, while small RNAi libraries can be used at reasonable cost, broad pathway screens can be expensive, labor-intensive, and context-selective. These screens require a major commitment and have extensive bio-informatics requirements.

Small molecule screens are also applicable to target validation. An advantage of small molecule screens is that they are likely to be most representative of likely pharmacological outcome for a particular target. The use of small molecules also facilitates *in vivo* validation and toxicology, allowing an early assessment of the potential therapeutic window associated with the target. From a pharmaceutical company perspective, small molecule approaches also have the advantage of allowing cross-disease exploration of high-risk targets with minimal risk, as illustrated by the exploration of both cancer and non-cancer uses of γ-secretase inhibitors and COX-2 inhibitors. Small molecules can also be easily distributed for evaluation by multiple investigators. Achieving adequate small molecule reagents for target validation is time and resource intensive. Appropriate reagents are rarely achieved from high throughput screens, but require additional dedicated chemistry effort for optimization. Researchers employing small molecules for target validation must also be cognizant of potential confounding off-target activities, meaning that observed efficacy or toxicity effects may be representative of the molecule, rather than the target. As an example of the potential utility of well-characterized small molecule inhibitors, Dr. Heimbrook described the nutlins, a class of potent and selective small-molecule inhibitors of the p53-MDM2 interaction developed by Roche researchers that activate the p53 pathway only in cells with wild-type but not mutant p53.[37,38] These small molecule inhibitors could serve as probes to evaluate the potential utility of MDM2 as a therapeutic target for different childhood cancers.

Proteomic methods can also contribute to target identification and validation, particularly through documenting the activation status of cellular signaling pathways. Tissue microarrays, reverse phase protein microarrays, and forward phase protein microarrays are among the arraying methods that have distinctive and complementary contributions to make in the analysis of target expression and cell signal profiles. Tissue microarray technology allows rapid visualization of molecular targets in hundreds of tissue specimens simultaneously, either at the DNA, RNA or protein level.[39] Tissue microarrays allow localization of proteins within the cell, which may be particularly important for those proteins whose activation state can be deduced from their cellular localization (e.g., NF-kappaB nuclear localization upon activation). Reverse phase protein microarrays, which involve immobilizing the protein repertoire of multiple specimens on a single slide with subsequent interrogation by highly specific antibodies, are well-suited for evaluating the phosphorylated status of signal proteins.[40] Dr. Helman described the use of phosphoproteomic profiling of rhabdomyosarcoma tumor specimens to identify associations between outcome and specific phosphorylation and expression patterns of proteins involved in the mTOR signaling pathway.[41]

A late step in the target validation process is evaluation of candidate agents directed at the target using *in vivo* efficacy models. For adult cancers, subcutaneously implanted human tumor xenografts have had limited success in predicting clinical activity for specific tumor types. Possible contributing factors include the absence of immune effects, the artificial environment, and differences in drug exposures tolerated by mice compared to humans. Alternative models exist, including carcinogen-induced models, orthotopically implanted xenograft lines, syngeneic models, and genetically engineered models (e.g., transgenics and knock-outs). However, no systematic evaluation of the predictive utility of these alternative models has been published. At this time, the primary utility of *in vivo* data for pharmaceutical companies is for internal decision-making and prioritization, to document non-interference in combination studies, and to spur interest of clinical sites in the company's agent.

In the pediatric oncology setting, pediatric preclinical models have had some success in predicting clinical activity.[42] Most notable is the prediction from preclinical studies of the activity of topoisomerase-I inhibitors for neuroblastoma and rhabdomyosarcoma,[43,44] the identification of optimal schedules of topoisomerase-I inhibitors for clinical evaluation,[43] and the identification of active combinations including topoisomerase-I inhibitors.[45,46] Building upon these observations, NCI has initiated a Pediatric Preclinical Testing Program (PPTP) to systematically evaluate whether childhood cancer preclinical *in vivo* models can prospectively identify novel agents with clinical activity against specific cancers of children and adolescents.[47] Pharmacokinetic studies will be performed to determine the systemic drug exposures associated with antitumor activity, which will allow comparison between the drug exposures required for activity in childhood cancer preclinical models and those achievable in humans. The PPTP tumor panel will be molecularly characterized to ensure that the lines used for *in vivo* testing replicate the human cancers of the same type and to facilitate identification of associations between antitumor activity and biological characteristics of tumors (e.g., gene expression, genomic abnormalities, etc.).[48]

The general conclusions from the discussions of methods for target identification and validation were that the requisite methods are available for expeditiously identifying and validating childhood cancer targets. The rate-limiting step in making progress is not technological, but rather is a lack of resources committed to applying relevant methods in the childhood cancer setting. The likelihood of identifying therapeutic targets for childhood cancers would be high if appropriate methods (e.g., high-throughput gene resequencing, gene expression profiling, and RNAi screens) were systematically applied in the childhood cancer setting. While much of the research would likely be done in academic laboratories, opportunities for collaborations with pharmaceutical companies and research institutes exist that could accelerate the discovery timeline while reducing overall project costs.

FDA Role:

Dr. Ramzi Dagher, a member of FDA's Division of Oncology Drug Products, outlined the basic complementary programs under which FDA either encourages or requires industry to conduct pediatric clinical studies for new and previously approved drugs that have already been studied for adult use.

The *Best Pharmaceuticals for Children Act (BPCA)* of 2002, which extended the Food and Drug Modernization Act of 1997, includes provisions for a voluntary program (pediatric exclusivity) whereby a drug sponsor can earn a 6-month extension on marketing exclusivity for an agent if they successfully pursue an acceptable plan of pediatric studies for the agent. The extension is based on the sponsor having current marketing exclusivity for the drug. FDA issues Written Requests for pediatric studies to manufacturers when it determines that information related to the use of the drug in the pediatric population may produce health benefits. Alternatively, sponsors can request FDA to issue Written Requests for their agents based on a proposed evaluation plan. The Written Request describes in detail the studies needed and the time frame for their completion, and it serves as the basis for evaluating whether submitted study reports qualify the sponsor for pediatric exclusivity. Sponsors are free to accept or decline pediatric studies in response to a Written Request. BPCA's pediatric exclusivity provisions are applicable to drugs for orphan diseases.

The Pediatric Research Equity Act (PREA) of 2003 allows FDA to mandate a sponsor to study a drug in children if the adult indication and disease are also applicable in pediatric populations. Unlike BPCA, PREA does not apply to orphan drugs, which limits to some extent its applicability in the childhood cancer setting. PREA also mandated the creation of a new FDA Pediatric Drugs Advisory Committee.

Both the pediatric exclusivity incentive and the PREA mandatory provisions have limitations in ensuring that appropriate studies are done for agents with potential utility in the childhood cancer setting. For example, an agent may be effective for adult cancers but have no obvious applications in pediatric oncology, and conversely an agent may be relevant to childhood cancers but not have a sufficient adult market to make the pediatric exclusivity incentive attractive.

The FDA's traditional focus for pediatric exclusivity Written Requests has been on clinical trials data from phase 1 forward. Of particular relevance to the Workshop is that there is precedent for FDA including non-clinical data as a component of Written Requests. For example, FDA has included requirements for non-clinical studies to address carcinogenicity potential in some Written Requests for non-oncologic drugs. Similarly, requirements for non-clinical data may be able to be included in Written Requests for pediatric oncology drugs. These non-clinical data could allow for a more sophisticated approach to defining relevant patient populations for clinical studies and could help to focus development on specific tumors.

Intellectual Property and Data Sharing:

A major topic discussed at the workshop was the extent to which intellectual property issues are a barrier to collaborations between pharmaceutical companies, research institutes, and childhood cancer researchers for the purpose of identifying and validating childhood cancer therapeutic targets. This topic was addressed at the workshop from the pharmaceutical perspective and also from the government-sponsored academic research perspective.

Former Abbott Laboratories Global Director, Research Operations and attorney Michael Hurley noted that the IP issue is a "hurdle, but not an insurmountable barrier" to forging public-private partnerships for conquering childhood cancers. He discussed barriers as well as motivators for collaboration and early data sharing, and then ended by discussing steps that could be taken to overcome barriers and facilitate timely data sharing.

Intellectual property resulting from a sponsor's research represents a competitive advantage: it is the return on investment for the time, effort, and resources that the sponsor committed to research. A primary disincentive to early sharing of research results is the loss of this advantage.

Part of what may be lost by early data sharing is an exclusive period of opportunity to successfully pursue new leads based on the initial discovery. Newly created intellectual property is a platform upon which the inventor can stand and look beyond the current horizon to view potential new areas for discovery. Early data sharing may reduce the opportunity of the sponsor to build upon its initial discoveries and to make additional discoveries before its competitors. In essence, industry and researchers who hold patents realize that a patent is not an end in itself—it's part of a process. A discovery resulting in an initial patent often leads to the realization that there are additional follow-on areas that could be pursued, given additional time and

research, resulting in more patents. This concept of "perfection of a chain of patents" makes sponsors very hesitant at an early stage to share information about their new intellectual property and is one of the reasons why scientific publication often occurs so long after discovery.

Another potential barrier to early data sharing is concern about the effectiveness of a contract to preserve this exclusive period of opportunity to pursue new leads. If a partner violates intellectual property rights, the patent holder may win redress through legal action, but the "cat may be out of the bag" in terms of third parties becoming aware of this new horizon of opportunity.

There are a number of approaches to overcoming these hurdles: use of a neutral entity trusted by all parties, "blinded" sharing arrangements, "strictly limited" uses, creation of structural and procedural safeguards, long term assurance and use of motivators.

There are a number of motivators that can induce industry, as well as non-profit and academic institutions, to collaborate with each other. An obvious motivator is when the collaboration is likely to result in a technological advantage for one or both parties over their respective competitors. Another major motivator is the ability to generate additional return on investment, whether in the form of increased income (e.g., increased sales, additional grant money, or greater charitable donations) or in the form of reduced expenses (e.g., lower tax burden). Large pharmaceutical companies may be able and willing to wait for a future benefit—such as a future tax deduction or gaining an additional indication for their drug some years in the future. Smaller companies, such as biotechnology firms, are more likely interested in a present benefit. They are less enticed by the opportunity for a charitable deduction for *pro bono* work since they often have more expenses than income. They may be better incentivized to collaborate by using mechanisms that can channel income to them in the present.

Although not as strong as a technological advantage or increased income, charity and public image are also motivators for collaboration and data sharing The monetary value of what a company provides to an eleemosonary project can be quantified and claimed as a corporate tax deduction. For example, a company can provide an established charitable entity with "blinded" access to a unique library of compounds for use in testing against certain childhood cancer cell lines. The commercial value of such access can be calculated and may represent a sizeable corporate charitable deduction. Public image enhancement, to be motivating, must be elaborated in terms of a company's or institution's core business; i.e. participation will enhance the academic reputation of a university's science department, or will create an image of service superior to competitors among a company's target customers, or will raise the awareness among new donors of the good work and fiscal stewardship practiced by a charitable foundation.

Karen Maurey, acting chief of NCI's Technology Transfer Branch, provided an overview of NIH's perspective on intellectual property and data sharing. Current policy is based upon the Bayh-Dole Act of 1980 which set forth policies for recipients of NIH funding. NIH-funded institutions are generally allowed to take title (ownership) of any resulting inventions under the stipulations that they: file for a patent (except for biological materials); cannot assign ownership (except to patent management organizations); provide "march-in rights" to the federal government; and maintain the government's non-exclusive license on the invention.

In recognition that data sharing is essential for expedited translation of research results into knowledge, products and procedures to improve human health, NIH published in 2003 a statement extending NIH policy on sharing research resources and reaffirming NIH support for the concept of data sharing (http://grants.nih.gov/grants/policy/data_sharing/). For investigator-initiated applications with direct costs more than $500,000, there must be timely release and sharing of final research data from NIH-supported studies for use by other researchers no later than acceptance for publication of main findings. Of note, data sharing may be limited by the need to protect patentable and other proprietary data, including data subject to third party restrictions.

The Bayh-Dole statute has been refined and interpreted numerous times over the years. Many of the changes focused on ensuring timely research resource sharing and data sharing. In 1999, NIH published a policy statement "Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts" (http://ott.od.nih.gov/RTguide_final.html). The document provides guidelines for exclusive licensing of research tools and also provides guidelines for grantbacks and option rights when acquiring materials from a for-profit entity for use in NIH-funded research. For the latter, for-profit collaborators may be granted non-exclusive, royalty-free rights to use improvements and new uses, and they may also be granted an option for an exclusive or non-exclusive commercialization license.

Dr. Sherry Ansher of NCI's Cancer Therapy Evaluation Program (CTEP) discussed the data access and intellectual property provisions used for CTEP-sponsored clinical trials and preclinical studies. CTEP has established collaborations with many different pharmaceutical companies and has developed standard language for addressing these issues in Clinical Trial Agreements and in Material Transfer Agreements. Of particular relevance to the workshop are the model Material Transfer Agreements that were developed to support the Pediatric Preclinical Testing Program. CTEP convinced NIH of the need for flexibility in the agreement terms for the pediatric testing program. These terms include the following:

- Academic researchers must use agent as provided without making any modifications to agent or attempting to analyze compound provided—agent is provided blinded for testing at all sites;
- The Research project is clearly defined to protect all interests;
- The Academic institution indemnifies industry for its use of agent and data, and industry indemnifies academic institution for its use of data resulting from the project;
- Reports are provided to NCI/industry at least quarterly;
- The industry collaborator has a 45 day time period for review of all manuscripts (10 days for abstract review), and the Academic Institution may not submit the manuscript without written approval from CTEP; and
- Industry participants are granted right to use all data and results for any purpose. Industry receives a non-exclusive royalty free license to any invention for all purposes, including commercial and an option to negotiate an exclusive royalty bearing license. In contrast to normal IP option, company has one year to notify institution of interest in obtaining an exclusive license. This extended time period is provided because of the early access provided by the collaborator to the agent and is to allow additional time for the collaborator to decide if the invention will be useful.

Testing of agents by the PPTP began in April, 2005, so there is not yet a substantial track record to evaluate the effectiveness of the PPTP's model MTA approach. However, the early response to the model MTA from potential industry collaborators appears positive, and both large and small pharmaceutical companies have agreed to provide agents for use by the PPTP.

Organizational Issues for Optimal Research Sites:

Another focus of the TARGET Workshop was the resources and infrastructures that can be brought to bear on the task of childhood cancer target identification and validation. These include research institutes, academic cancer centers, and pharmaceutical sponsors.

Dr. Ellen Feigal, Senior Vice President of Research and Deputy Scientific Director for *Translational Genomics Research Institute (TGen)*, a non-profit research institute, provided an overview of TGen as a possible model for how to organize the different components for the childhood cancer initiative, in terms of scientific expertise, core technologies, and the types of partnerships to have in place to move forward drug and diagnostic development projects.

TGen, founded 2002 in Phoenix, Ariz., is positioned to straddle the translational gaps between basic research at academic centers, patient care and needs at the clinic, and product development activities within industry. The Institute offers core competencies and expertise in DNA sequencing, gene profiling, familial genetics, and bioinformatics/computational biology. TGen leverages those competencies through collaborations with three Arizona universities as well as through partnerships with local clinics and hospitals, such as the Phoenix Children's Hospital. Finally, TGen works extensively with companies in both the biotech and pharmaceutical industries to help translate research discoveries into products.

TGen strives to bridge some of the translational gaps by building translational "accelerators". This has involved the Institute in establishing spin-off companies with some of their partners: Center for Translational Drug Development; Molecular Profiling Institute; and Nanobiomics, Inc. These new entities are contributing to TGen's major therapeutic focus areas in cancer, neurological diseases, diabetes, and pathogen genomics. Dr. Feigal cited TGen's organization of an Alzheimer's research consortium. The project involves 9 different sites across the state and about 100 researchers. This complex collaboration requires considerable organizational effort, including creating legal agreements among the different sites so that all can share data and information. TGen also coordinated sharing of technology resources among the members and provides bioinformatics and data-collection services to the consortium.

Dr. Sharon Murphy described the *Children's Cancer Research Institute (CCRI),* a recently established institute located in San Antonio, Texas that she leads. CCRI is funded by an endowment from the state's share in the tobacco industry settlement. The Institute focuses on discovery and basic, epidemiologic, and translational research.

Dr. Murphy identified a series of barriers that limit work on childhood cancer target research in academia. First, the "universe" of specialized pediatric cancer centers is small and often hard-pressed to compete for space and resources within large academic health institutions. Academic-based researchers are also hampered by

traditional institutional approaches to peer review and grant administration, with their bias towards "big science". Academia policies on tenure and professional advancement are predicated on the "gold standard" of the individual, investigator-initiated grant application. The collaborative team science necessary for many childhood cancer initiatives in which a researcher plays a small part in a large, multi-disciplinary project makes it difficult for young investigators to make the necessary career progressions to get promoted and stay in academics. In addition, pediatric oncology initiatives must pay close attention to "conflict of interest" issues, since research related to children is especially sensitive.

Academic centers involved in childhood cancer research also have a number of positive attributes, including intellectual capital and expertise in specific childhood cancers, tissue/specimen banks, a culture of collaboration, and strong research advocacy. If these strengths are to translate into discoveries, then pediatric cancer researchers need access to high throughput screening tools (libraries, robotics, informatics, etc.) and preclinical models for target validation. As an example, CCRI is investing heavily in small animal imaging technology.

Dr. Stephen Chanock (*NCI intramural Center for Cancer Research*) presented another research model focusing on the potential benefit of collaborations involving extramural researchers and NCI intramural researchers. One example of this model is the Breast and Prostate Cancer Cohort Consortium (BPC3), which was funded for 4 years beginning in June 2003 to study the role of genetic variation in steroid hormone pathways, the insulin-like growth factor (IGF) pathway, and associated receptor proteins in the etiology of breast and prostate cancer (http://epi.grants.cancer.gov/BPC3/). The BPC3 is conducted through the Consortium of Cohorts, and includes both NCI intramural and extramural laboratories for gene resequencing, for single nucleotide polymorphism (SNP) and haplotype identification, and for phyogenetic tree definition.

A second example provided by Dr. Chanock is the Cancer Genetic Markers of Susceptibility (C-GEMS) project, a collaborative effort to help identify inherited susceptibility genes for breast and prostate cancer. C-GEMS involves NCI's Division of Cancer Etiology and Genetics (DCEG) and the NCI Core Genotyping Facility (CGF), with collaboration from the Cancer Genome Anatomy Project. Through this initiative dense whole genome SNP scans (300,000 SNPs/subject) will be performed using samples from persons with breast cancer and prostate cancer. C-GEMS leverages the expertise of intramural NCI laboratories (DCEG/CGF) and provides for rapid public access to data through the NCI's cancer Biomedical Informatics Grid (caBIG).

Dr. Chanock noted several lessons learned to date through these collaborations. One is the utility of early public release of data, as documented by the heavy usage of these datasets by other academic researchers and by commercial entities. A second lesson is the advantage of centralizing dense, resource intensive technologies, both in terms of resource utilization efficiency and in terms of quality control. These two projects also illustrate the potential utility of extramural/intramural collaboration, with core resources in the intramural program (e.g., the Core Genotyping Facility) providing support and rapid feedback for extramural researchers. A final lesson is that "big science" can be organized to incorporate central roles for younger investigators that include primary roles in publication authoring as well as other opportunities that support career growth.

Dr. Julian Adams (*Infinity Pharmaceuticals*) discussed ways of incentivizing/inducing pharmaceutical and biotechnology companies to share technologies for childhood cancer target identification and validation. Most of the requisite technologies are already widely available and are not different between adult and childhood cancers. Elucidating the biology of the target is largely an academic pursuit, whereas robust target validation has been the purview of industry and has followed target discovery by academic researchers. A key role for clinical academic centers in the target validation process is providing access to tissue repositories to allow prevalence of target expression to be assessed and to allow correlation of clinical characteristics with target expression. Screening for small molecules that address specific targets is probably best done at this time by pharmaceutical companies, which have large libraries of well-characterized chemicals. The rate-limiting step in developing drug candidates for specific targets is not screening of small molecules, but rather is in subsequent steps of chemistry and optimization.

In terms of future steps, Dr. Adams noted that many laboratory efforts that mimic screening automation efforts of industry are beginning at academic institutions and that these could potentially be recruited to work on childhood cancer projects. The NCI Cooperative Research and Development Agreement (CRADA) process (http://ttb.nci.nih.gov/cradaopp.html) is an excellent mechanism for drug development partnerships, but can require considerable time to establish. Biotechnology companies generally do not have marketing hurdles for pursuing credentialed targets, as illustrated by Genzyme's development of a treatment for Gaucher's disease. The main barrier for biotechnology companies in pursuing such targets is knowledge and degree of validation. Pharmaceutical companies are less likely to be interested in validated targets that are relevant to only small numbers of patients. Childhood cancer researchers also need to follow the progress of drug development programs for adult cancers, as these may translate to childhood cancers (e.g., as illustrated by the hedgehog pathway antagonists).

Dr. Peter Adamson, Chair of the *Children's Oncology Group (COG)* Phase 1 Consortium, spoke on behalf of Dr. Gregory Reaman (COG Chair) in describing COG resources for target identification/validation efforts. COG has extensive tumor banks with well-annotated specimens and clearly defined procedures by which researchers can request and receive tissue specimens. Approximately 250 COG member institutions submit specimens each year to COG tissue repositories, which currently contain over 181,000 specimens from more than 48,000 patients. As an example, leukemia cells are banked from 90% of the 3220 children enrolled in recent COG clinical trials for children with acute lymphoblastic leukemia. In addition, COG supports major translational research efforts using clinical specimens for the identification and validation of biological prognostic factors. COG researchers successfully competed for NCI Director's Challenge awards for childhood acute leukemias and solid tumors (sarcomas & Wilms tumor). In 2005, COG researchers received Strategic Partnering to Evaluate Cancer Signatures (SPECS) awards that focus on the translation of promising molecular profiles toward clinical application and that include both leukemia and solid tumor cohorts.

Organizational Issues for Public-Private Partnerships:

A third area on which Workshop participants focused was the need for the public and private sectors to jointly support research directed towards childhood cancer target identification and validation. Neither the public sector nor the private sector working independently will be able to support all of the research needed for this task.

However, a coordinated effort involving the public sector, through the NCI and potentially other NIH institutes, in collaboration with pharmaceutical companies and with private not-for-profit supporters of childhood cancer research may be successful.

Dr. Susan Weiner, founder of the *Children's Cause for Cancer Advocacy* and co-editor of the IOM's April 2005 report on "Making Better Drugs for Children with Cancer", presented the IOM report's recommendations. Of greatest relevance to the Workshop discussions was the first recommendation: "A new public–private partnership, involving government, industry, academic and other research institutions, advocacy groups, philanthropies, and others, should be formed to lead pediatric cancer drug discovery and development." Many of the elements required for this task already exist. For example, NCI supports a clinical trials infrastructure for testing new agents in children from the phase 1 level all the way through to phase 3 trials. Similarly, NCI supports a pediatric preclinical testing program to allow new agents to be systematically tested against relevant childhood cancer models. However, not all components required for a pediatric drug discovery and development program currently exist, and furthermore there is not yet the coordinating and managing partnership to facilitate and lead such efforts. Neither industry nor government (NCI, etc.) can be expected to play this coordinating role alone, but rather there needs to be broader involvement from all relevant sectors/partners—industry, government, academia, research institutes, and the advocacy community. An entity including representation from each of these groups may be able to establish a virtual pediatric cancer discovery and development network that builds upon existing components while adding additional critical components as needed.

Janis Mullaney, senior advisor for public-private partnerships at the Foundation for NIH, described her organization's role as a neutral third-party administrator and fund-raiser in a number of collaborations between NIH institutes and outside organizations (http://www.fnih.org/). The Foundation for NIH is the sole entity authorized to raise private funds to support all aspects of NIH's mission and leverages public funds to raise private support—earning a $28 return on each dollar appropriated annually. Over the past three years, the Foundation has played a role in several major research initiatives, including leveraging a $200 million contribution from the Bill & Melinda Gates Foundation to pursue "Grand Challenges in Global Health." Other research challenges spearheaded by the Foundation include implementation of FDA's "Best Pharmaceuticals for Children Act", overcoming barriers to early phase clinical trials, and osteoarthritis and Alzheimer's disease initiatives.

The *Alzheimer's Disease Neuroimaging Initiative* (ADNI) was presented in detail by Dr. Susan Molchan [program director for Alzheimer's disease clinical trials at the National Institute of Aging (NIA)], as an example of a public-private partnership supported through the Foundation for NIH. The overall goal of this initiative is to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer's disease. Within the federal government, the NIA is joined in the partnership by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and by the FDA. The Foundation for NIH is managing corporate and other private participation, and has received commitments totaling more than $20 million in contributions from multiple pharmaceutical and imaging companies as well as from the Institute for the

Study of Aging and the Alzheimer's Association. About two-thirds of the funding is expected to come from the Federal Government while private partners are expected to make up the other third. Ancillary studies will be funded by additional NIH grants.

A key goal of the ADNI is rapid public access to all raw and processed data. There is a central repository for all quality assured MRI and PET imaging studies as well as a linked clinical database. Governance for the ADNI consists of an Executive Committee composed of project investigators and NIH; an industry Scientific Advisory Board; and a Steering Committee that includes investigators, industry, NIH, FDA, and the Foundation for NIH. Industry involvement in the ADNI is based on several principles, including: clearly defined specific goals, the pooling of resources (within the context of NIH's overall leadership of the project), and the solicitation of direction and ideas from industry participants. The extensive communication with industry partners that occurred during the ADNI planning stages was critical in obtaining support from industry, and ongoing communication with industry partners is essential for maintaining this support.

Dr. Susan Fitzpatrick, vice-president of the James *S. McDonnell Foundation (JSMF)*, traced the history and philosophy of private philanthropic funding of biomedical research, particularly noting the 1974 report of the "Commission on Private Philanthropy and Public Needs" (the Filer Commission). The report noted the ability of private philanthropy "to assist, and even goad, democratic government…toward better performance of civic duties and closer attention to social requirements" and its ability "to stand aside from and criticize state action, or inaction, in the interest of the inarticulate man in the street". Private funding initiatives can fill gaps between government and industry spending. Private philanthropy can also allow for the flourishing of alternative models and approaches that challenge the common wisdom and *status quo*.

Several types of private funders were described by Dr. Fitzpatrick. First are the privately endowed foundations that fund particular areas of science selected via an analysis of the opportunities best suited to limited private investment. This might be considered the "social venture capital" model where private funds are invested not for material gain but on behalf of some "common good".

A second type of private funders are the privately endowed foundations that focus on particular disease(s). Often, these foundations are established by families with a connection to a particular disease who believe the mainstream research effort was insufficient or not appropriately focused on treatments. Examples include the Goldhirsh Foundation and the Sontag Foundation, both of which have an interest in supporting brain cancer research as a result of having a family member affected by brain cancer. Maintaining control and decision-making authority, as well as the ability to act flexibly, are important to their vision and mission. To some extent these foundations view themselves as "serial partners" with NIH in providing the seed funds needed to help an investigator with a novel idea obtain the preliminary data needed to garner NIH support.

A third type of private funders are the voluntary health organizations that represent a large number of the private funders supporting biomedical research. They usually fill several roles, including education, advocacy, and representing large constituencies of individuals with a particular disease together with dedicated friends and families. In general, these funding organizations raise and disperse funds on an annual basis. Some of these organizations (e.g., the Juvenile Diabetes Foundation

and the ACS) have a long history of encouraging research directly via grants, and indirectly via advocacy, education, and increasing awareness. Many successful scientists with significant NIH funding have, at some time or another, also been grantees of the leading voluntary health organizations. In recent years, new voluntary health organizations have developed based on their perception that a specific disease is "falling through the cracks" and not being funded with the urgency that is warranted. Examples include the Children's Neurobiological Disease Foundation and Cure Autism Now.

Dr. Fitpatrick noted the potential gains as well as the losses that can occur when private funders of research enter partnerships with public research funders. There can be gains in efficiency, shared knowledge and experience, shared resources, and "moral-suasion". There can also be potential negative consequences from such partnerships, including reduced diversity of seed capital, reduced independence from dogma, and a reduction in the plurality of approaches being studied. Public-private partnerships should be entered into with these trade-offs in mind so that gains are maximized to the extent possible while losses are kept to a minimum.

Dr. Nancy Sung, senior program officer with the Burroughs Wellcome Fund, described the role of philanthropic funders in partnerships for drug discovery. She first noted that within the overall universe of spending for health research (2002 overall spending total was more than $90 billion) over 50% comes from industry, 25% comes from NIH, and 1.7% ($1.6 billion) comes from private foundations and voluntary health organizations. In light of the need to ensure that the latter research dollars are efficiently utilized, a coalition of 15 foundations and voluntary health organizations is now formalizing the Health Research Alliance to improve communication, foster collaboration, and enhance overall effectiveness of grantmakers supporting biomedical and health research.

Voluntary health organizations are increasingly attracted to private-public partnership models for fostering research. This is in response to the changing landscape for drug development, with the growth of specialized biotech companies growing out of academic labs and the trend towards outsourcing of research and development by the traditional pharmaceutical industry. This disaggregation of the components of drug development programs make the "theoretical concept of a 'virtually' organized, publicly funded, privately conducted research entity more of a practical possibility".[49]

Public-private partnerships involved in drug development represent innovative combinations of different skills and resources from institutions in the public and private sectors to address persistent health problems. The need for these partnerships is generally dictated by whether a market exists for the health problem, and thus they tend to fall into two categories. One category of public-private partnerships are addressing neglected/tropical diseases and are exemplified by the Medicines for Malaria Venture (1999), the Global TB Alliance (2000), and the International AIDS Vaccine Initiative (1996). A second category of these partnerships are addressing "orphan" diseases and are exemplified by the Cystic Fibrosis Foundation Therapeutics, Inc (2000) and the Juvenile Diabetes Research Foundation (JDRF) Industry Discovery and Development Partnerships (2004). Because of the timeline required for drug development and the recent start dates for these programs, it is too early to say how effective these public-private partnerships are at identifying effective new treatments.

The Medicines for Malaria Venture (MMV, www.mmv.org) exemplifies current drug development efforts by public-private partnerships. This project draws support from foundations (Gates, Rockefeller, and Wellcome Trust), government agencies (USAID, WHO, and World Bank), and industry (ExxonMobil, BHP Billiton, and the International Federation of Pharmaceutical Manufacturers & Associations). The goal of the MMV is to create one new drug every five years. MMV has adopted modern business management techniques in pursuit of malaria treatments. It uses a portfolio approach of simultaneously developing several agents rather than investing in a single project. MMV conducts "virtual" drug discovery with all research activity outsourced but closely managed by staff and an external advisory committee of academic and industry experts. Continued funding of projects depends on success meeting benchmarks on time and several agents have been dropped for failing to do so.

There are several general characteristics of public-private partnerships that are involved in drug development. Most of these, like the MMV, start by screening existing compounds for new indications and require adequate funding at the outset to demonstrate early success that can then be parlayed into attracting new partners and funding. In contrast to typical foundation and government procedures, these entities structure their partnerships in line with industry management practices, including commitment to meeting timelines and milestones, rigorous review of progress, clearly stated responsibilities of each partner, and frequent communication among virtual team members. The public-private partnerships also utilize a portfolio approach to spread risk over several projects, and "virtual" processes so that the partnering relationship can organically grow as it progresses.

A cautionary note on public-private partnerships comes from the Roll Back Malaria (RBM) Global Partnership that was launched in 1998 by the World Health Organization, UNICEF, UNDP and the World Bank with the goal of halving the burden of malaria by 2010. Seven years after the partnership was launched a *Lancet* editorial described the partnership as "…an expansive list of missed opportunities and dismal failures…Moving from advocacy to action—turned out to be a challenge too big to face…".[50] The editorial noted that the RMB's organizational structure inhibited decision making and limited accountability and that the RMB was institutionally isolated within WHO and therefore limited in its ability to draw upon the WHO's strengths in addressing communicable diseases. While this assessment of the RMB was challenged,[51] it nonetheless draws attention to the observation that good intentions may not be sufficient to overcome deficits in organizational structure and leadership methods.

Michael Hurley described features of public-private partnerships for drug development. He identified four key resources needed to develop targeted therapeutics for childhood cancers: research facilities, scientists from multiple disciplines, information technology, and funding. The potential backers for this endeavor are the seven "partners" in attendance at the meeting: patient advocates, oncologists, academia, industry, NCI, FDA, and charities. He suggested that a venture capital model could be used by these partners to create and nurture a Center of Excellence or a set of Virtual Teams.

A Center of Excellence model utilizes a centralized research and development organization that encompasses most, if not all, of the necessary expertise and technologies within its walls. The arguments in support of this approach are that it achieves a critical mass of scientific disciplines, develops on-site synergism, and is

able to achieve national and international visibility. On the negative side, the approach can handle only a limited number of projects, might suffer from “group think”, and places a lot of eggs in one basket.

An alternative approach is the use of Virtual Teams for specific projects. The budget for each Virtual Team would be about one-fifth the amount for a Center of Excellence. The Virtual Team approach has the potential for being more agile in responding to new opportunities and for allowing more lines of research to be pursued. The key to the success of this approach is a partners’ steering committee and a small centralized project management group.

Summary:

A primary conclusion from the Workshop was that the requisite methods are available for expeditiously identifying and validating childhood cancer targets. The rate-limiting step in making progress is not technological, but rather is a lack of resources committed to applying relevant methods in the childhood cancer setting. The likelihood of identifying therapeutic targets for childhood cancers would be high if appropriate methods (e.g., high-throughput gene resequencing, gene expression profiling, and RNAi screens) were systematically applied in the childhood cancer setting. While much of the research would likely be done in academic laboratories, opportunities for collaborations with pharmaceutical companies and research institutes exist that could accelerate the discovery timeline while reducing overall project costs.

Public-private partnerships could support the research required for target identification and validation using one of several models, with each of the models having in common the need for governance structures involving all relevant constituencies and the need for rapid dissemination of research results. The discovery of childhood cancer targets resulting from such partnerships could be translated quickly into the clinical setting when there are ongoing clinical programs addressing the same targets for adult indications. This scenario represents “low hanging fruit” with a very favorable cost to benefit ratio, and it supports aggressively applying existing technologies to the task of identifying and validating childhood cancer therapeutic targets.

For therapeutic targets that appear to be pediatric-specific, translation to the clinic will be challenging with a requirement for much more substantial resources from public and private sources. Potential collaborators include industry, government, academia, research institutes, and the advocacy and philanthropic communities. An entity including representation from some or all of these groups may be able to establish a virtual pediatric cancer discovery and development network that could build upon existing components while adding additional critical components as needed to develop pediatric-specific anticancer agents. However, initial steps directed towards childhood cancer target identification and validation need not wait until such an entity is established.

Reference List

1. Ries, L. A. G., Eisner, M. P., Kosary, C. L., Hankey, B. F., Miller, B. A., Clegg, L., Mariotto, A., Feuer, E. J., and Edwards, B. K. SEER Cancer Statistics Review, 1975-2002. 2005. National Cancer Institute. Bethesda, MD.
Ref Type: Internet Communication

2. Druker, B. J. Imatinib as a paradigm of targeted therapies. Adv.Cancer Res., *91*: 1-30, 2004.

3. Parmar, S. and Tallman, M. S. Acute promyelocytic leukaemia:a review. Expert.Opin.Pharmacother., *4*: 1379-1392, 2003.

4. Yang, G., Cai, K. Q., Thompson-Lanza, J. A., Bast, R. C., Jr., and Liu, J. Inhibition of breast and ovarian tumor growth through multiple signaling pathways by using retrovirus-mediated small interfering RNA against Her-2/neu gene expression. J Biol.Chem., *279*: 4339-4345, 2004.

5. Vogel, C. L., Cobleigh, M. A., Tripathy, D., Gutheil, J. C., Harris, L. N., Fehrenbacher, L., Slamon, D. J., Murphy, M., Novotny, W. F., Burchmore, M., Shak, S., Stewart, S. J., and Press, M. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol, *20*: 719-726, 2002.

6. Gomez, H. L., Chavez, M. A., Doval, D. C., Chow, L. W., Wood, B. A., Berger, M. S., and Sledge, G. W. A phase II, randomized trial using the small molecule tyrosine kinase inhibitor lapatinib as a first-line treatment in patients with FISH positive advanced or metastatic breast cancer. J Clin Oncol 23(16), Abstr #3046. 2005.
Ref Type: Abstract

7. Barrett, M. T., Scheffer, A., Ben Dor, A., Sampas, N., Lipson, D., Kincaid, R., Tsang, P., Curry, B., Baird, K., Meltzer, P. S., Yakhini, Z., Bruhn, L., and Laderman, S. Comparative genomic hybridization using oligonucleotide microarrays and total genomic DNA. Proc.Natl.Acad.Sci.U.S.A, *101*: 17765-17770, 2004.

8. Bignell, G. R., Huang, J., Greshock, J., Watt, S., Butler, A., West, S., Grigorova, M., Jones, K. W., Wei, W., Stratton, M. R., Futreal, P. A., Weber, B., Shapero, M. H., and Wooster, R. High-resolution analysis of DNA copy number using oligonucleotide microarrays. Genome Res, *14*: 287-295, 2004.

9. Wang, Z. C., Lin, M., Wei, L. J., Li, C., Miron, A., Lodeiro, G., Harris, L., Ramaswamy, S., Tanenbaum, D. M., Meyerson, M., Iglehart, J. D., and Richardson, A. Loss of heterozygosity and its correlation with expression profiles in subclasses of invasive breast cancers. Cancer Res, *64*: 64-71, 2004.

10. Wong, K. K., Tsang, Y. T., Shen, J., Cheng, R. S., Chang, Y. M., Man, T. K., and Lau, C. C. Allelic imbalance analysis by high-density single-nucleotide polymorphic allele (SNP) array with whole genome amplified DNA. Nucleic Acids Res, *32*: e69, 2004.

11. Lynch, T. J., Bell, D. W., Sordella, R., Gurubhagavatula, S., Okimoto, R. A., Brannigan, B. W., Harris, P. L., Haserlat, S. M., Supko, J. G., Haluska, F. G., Louis, D. N., Christiani, D. C., Settleman, J., and Haber, D. A. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N.Engl.J Med, *350*: 2129-2139, 2004.

12. Paez, J. G., Janne, P. A., Lee, J. C., Tracy, S., Greulich, H., Gabriel, S., Herman, P., Kaye, F. J., Lindeman, N., Boggon, T. J., Naoki, K., Sasaki, H., Fujii, Y., Eck, M. J., Sellers, W. R., Johnson, B. E., and Meyerson, M. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science, *304*: 1497-1500, 2004.

13. Sordella, R., Bell, D. W., Haber, D. A., and Settleman, J. Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. Science, *305*: 1163-1167, 2004.

14. Heinrich, M. C., Corless, C. L., Demetri, G. D., Blanke, C. D., von Mehren, M., Joensuu, H., McGreevey, L. S., Chen, C. J., Van den Abbeele, A. D., Druker, B. J., Kiese, B., Eisenberg, B., Roberts, P. J., Singer, S., Fletcher, C. D., Silberman, S., Dimitrijevic, S., and Fletcher, J. A. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol, *21*: 4342-4349, 2003.

15. Stone, R. M., DeAngelo, D. J., Klimek, V., Galinsky, I., Estey, E., Nimer, S. D., Grandin, W., Lebwohl, D., Wang, Y., Cohen, P., Fox, E. A., Neuberg, D., Clark, J., Gilliland, D. G., and Griffin, J. D. Patients with acute myeloid leukemia and an activating mutation in FLT3 respond to a small-molecule FLT3 tyrosine kinase inhibitor, PKC412. Blood, *105*: 54-60, 2005.

16. Levis, M. and Small, D. Small molecule FLT3 tyrosine kinase inhibitors. Curr.Pharm.Des, *10*: 1183-1193, 2004.

17. Davies, H., Bignell, G. R., Cox, C., Stephens, P., Edkins, S., Clegg, S., Teague, J., Woffendin, H., Garnett, M. J., Bottomley, W., Davis, N., Dicks, E., Ewing, R., Floyd, Y., Gray, K., Hall, S., Hawes, R., Hughes, J., Kosmidou, V., Menzies, A., Mould, C., Parker, A., Stevens, C., Watt, S., Hooper, S., Wilson, R., Jayatilake, H., Gusterson, B. A., Cooper, C., Shipley, J., Hargrave, D., Pritchard-Jones, K., Maitland, N., Chenevix-Trench, G., Riggins, G. J., Bigner, D. D., Palmieri, G., Cossu, A., Flanagan, A., Nicholson, A., Ho, J. W., Leung, S. Y., Yuen, S. T., Weber, B. L., Seigler, H. F., Darrow, T. L., Paterson, H., Marais, R., Marshall, C. J., Wooster, R., Stratton, M. R., and Futreal, P. A. Mutations of the BRAF gene in human cancer. Nature, *417*: 949-954, 2002.

18. Sumimoto, H., Miyagishi, M., Miyoshi, H., Yamagata, S., Shimizu, A., Taira, K., and Kawakami, Y. Inhibition of growth and invasive ability of melanoma by inactivation of mutated BRAF with lentivirus-mediated RNA interference. Oncogene, *23*: 6031-6039, 2004.

19. Hingorani, S. R., Jacobetz, M. A., Robertson, G. P., Herlyn, M., and Tuveson, D. A. Suppression of BRAF(V599E) in human melanoma abrogates transformation. Cancer Res, *63*: 5198-5202, 2003.

20. Baxter, E. J., Scott, L. M., Campbell, P. J., East, C., Fourouclas, N., Swanton, S., Vassiliou, G. S., Bench, A. J., Boyd, E. M., Curtin, N., Scott, M. A., Erber, W. N., and Green, A. R. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet, *365*: 1054-1061, 2005.

21. James, C., Ugo, V., Le Couedic, J. P., Staerk, J., Delhommeau, F., Lacout, C., Garcon, L., Raslova, H., Berger, R., Bennaceur-Griscelli, A., Villeval, J. L., Constantinescu, S. N., Casadevall, N., and Vainchenker, W. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature, *434*: 1144-1148, 2005.

22. Kralovics, R., Passamonti, F., Buser, A. S., Teo, S. S., Tiedt, R., Passweg, J. R., Tichelli, A., Cazzola, M., and Skoda, R. C. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N.Engl.J Med., *352*: 1779-1790, 2005.

23. Levine, R. L., Wadleigh, M., Cools, J., Ebert, B. L., Wernig, G., Huntly, B. J., Boggon, T. J., Wlodarska, I., Clark, J. J., Moore, S., Adelsperger, J., Koo, S., Lee, J. C., Gabriel, S., Mercher, T., D'Andrea, A., Frohling, S., Dohner, K., Marynen, P., Vandenberghe, P., Mesa, R. A., Tefferi, A., Griffin, J. D., Eck, M. J., Sellers, W. R., Meyerson, M., Golub, T. R., Lee, S. J., and Gilliland, D. G. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell, *7*: 387-397, 2005.

24. Weng, A. P., Ferrando, A. A., Lee, W., Morris, J. P., Silverman, L. B., Sanchez-Irizarry, C., Blacklow, S. C., Look, A. T., and Aster, J. C. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science, *306*: 269-271, 2004.

25. Samuels, Y., Wang, Z., Bardelli, A., Silliman, N., Ptak, J., Szabo, S., Yan, H., Gazdar, A., Powell, S. M., Riggins, G. J., Willson, J. K., Markowitz, S., Kinzler, K. W., Vogelstein, B., and Velculescu, V. E. High frequency of mutations of the PIK3CA gene in human cancers. Science, *304*: 554, 2004.

26. Yeoh, E. J., Ross, M. E., Shurtleff, S. A., Williams, W. K., Patel, D., Mahfouz, R., Behm, F. G., Raimondi, S. C., Relling, M. V., Patel, A., Cheng, C., Campana, D., Wilkins, D., Zhou, X., Li, J., Liu, H., Pui, C. H., Evans, W. E., Naeve, C., Wong, L., and Downing, J. R. Classification, subtype discovery, and prediction of outcome in pediatric acute lymphoblastic leukemia by gene expression profiling. Cancer Cell, *1*: 133-143, 2002.

27. Ferrando, A. A., Neuberg, D. S., Staunton, J., Loh, M. L., Huard, C., Raimondi, S. C., Behm, F. G., Pui, C. H., Downing, J. R., Gilliland, D. G., Lander, E. S., Golub, T. R., and Look, A. T. Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia. Cancer Cell, *1*: 75-87, 2002.

28. Subramanian, A., Tamayo, P., Mootha, V. K., Mukherjee, S., Ebert, B. L., Gillette, M. A., Paulovich, A., Pomeroy, S. L., Golub, T. R., Lander, E. S., and Mesirov, J. P. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. Proc Natl.Acad.Sci.U.S.A, *102*: 15545-15550, 2005.

29. Silva, J., Chang, K., Hannon, G. J., and Rivas, F. V. RNA-interference-based functional genomics in mammalian cells: reverse genetics coming of age. Oncogene, *23*: 8401-8409, 2004.

30. Willingham, A. T., Deveraux, Q. L., Hampton, G. M., and Aza-Blanc, P. RNAi and HTS: exploring cancer by systematic loss-of-function. Oncogene, *23*: 8392-8400, 2004.

31. Deveraux, Q. L., Aza-Blanc, P., Wagner, K. W., Bauerschlag, D., Cooke, M. P., and Hampton, G. M. Exposing oncogenic dependencies for cancer drug target discovery and validation using RNAi. Semin.Cancer Biol., *13*: 293-300, 2003.

32. Paddison, P. J., Caudy, A. A., Sachidanandam, R., and Hannon, G. J. Short hairpin activated gene silencing in mammalian cells. Methods Mol.Biol., *265*: 85-100, 2004.

33. Hu, S., Heidel, J. D., Barlett, D. W., Kohn, D. B., Davis, M. E., and Triche, T. J. Systemic targeted EWS-FLI1 siRNA abrogates growth of metastases in a murine Ewing's tumor model. Proc Am Assoc Cancer Res, *46*: Abstr #6104, 2005.

34. Paddison, P. J., Silva, J. M., Conklin, D. S., Schlabach, M., Li, M., Aruleba, S., Balija, V., O'Shaughnessy, A., Gnoj, L., Scobie, K., Chang, K., Westbrook, T., Cleary, M., Sachidanandam, R., McCombie, W. R., Elledge, S. J., and Hannon, G. J. A resource for large-scale RNA-interference-based screens in mammals. Nature, *428*: 427-431, 2004.

35. Berns, K., Hijmans, E. M., Mullenders, J., Brummelkamp, T. R., Velds, A., Heimerikx, M., Kerkhoven, R. M., Madiredjo, M., Nijkamp, W., Weigelt, B., Agami, R., Ge, W., Cavet, G., Linsley, P. S., Beijersbergen, R. L., and Bernards, R. A large-scale RNAi screen in human cells identifies new components of the p53 pathway. Nature, *428*: 431-437, 2004.

36. Azorsa, D., Evans, D., Kiefer, J. A., McCarty, T., Wang, H., Han, H., Tuzmen, S., Bittner, M., Kallioniemi, O., Trent, J., Von Hoff, D., and Mousses, S. Global RNAi phenotype analysis for identification of synthetic lethal drug targets in pancreatic cancer. Proc Am Assoc Cancer Res, *46*: Abstr #1704, 2005.

37. Carvajal, D., Tovar, C., Yang, H., Vu, B. T., Heimbrook, D. C., and Vassilev, L. T. Activation of p53 by MDM2 antagonists can protect proliferating cells from mitotic inhibitors. Cancer Res, *65*: 1918-1924, 2005.

38. Vassilev, L. T. Small-molecule antagonists of p53-MDM2 binding: research tools and potential therapeutics. Cell Cycle, *3*: 419-421, 2004.

39. Kallioniemi, O. P., Wagner, U., Kononen, J., and Sauter, G. Tissue microarray technology for high-throughput molecular profiling of cancer. Hum.Mol.Genet., *10*: 657-662, 2001.

40. Paweletz, C. P., Charboneau, L., Bichsel, V. E., Simone, N. L., Chen, T., Gillespie, J. W., Emmert-Buck, M. R., Roth, M. J., Petricoin III, E. F., and Liotta, L. A. Reverse phase protein microarrays which capture disease progression show activation of pro-survival pathways at the cancer invasion front. Oncogene, *20*: 1981-1989, 2001.

41. Espina, V. A., Yeung, C., Eichler, G., Krishnan, K., Midura, B., Tsokos, M., Qualman, S. J., Meyer, W. H., Petricoin III, E. F., Helman, L. J., and Liotta, L. A. Phosphoproteomic profiling identifies 4EBP1 and phosphorylated eIF4E as prognostic indicators as well as new drug targets in therapy resistant childhood rhabdomyosarcoma. Proc Am Assoc Cancer Res 46(Abstr #4336). 2005.
Ref Type: Abstract

42. Peterson, J. K. and Houghton, P. J. Integrating pharmacology and in vivo cancer models in preclinical and clinical drug development. Eur.J Cancer, *40*: 837-844, 2004.

43. Furman, W. L., Stewart, C. F., Poquette, C. A., Pratt, C. B., Santana, V. M., Zamboni, W. C., Bowman, L. C., Ma, M. K., Hoffer, F. A., Meyer, W. H., Pappo, A. S., Walter, A. W., and Houghton, P. J. Direct translation of a protracted irinotecan schedule from a xenograft model to a phase I trial in children. J.Clin Oncol, *17*: 1815-1824, 1999.

44. Pappo, A. S., Lyden, E., Breneman, J., Wiener, E., Teot, L., Meza, J., Crist, W., and Vietti, T. Up-front window trial of topotecan in previously untreated children and adolescents with metastatic rhabdomyosarcoma: an intergroup rhabdomyosarcoma study. J Clin Oncol, *19*: 213-219, 2001.

45. Thompson, J., George, E. O., Poquette, C. A., Cheshire, P. J., Richmond, L. B., de Graaf, S. S., Ma, M., Stewart, C. F., and Houghton, P. J. Synergy of topotecan in combination with vincristine for treatment of pediatric solid tumor xenografts. Clin Cancer Res, *5*: 3617-3631, 1999.

46. Pappo, A. S., Lyden, E., Breitfeld, P., Donaldson, S., Anderson, J., Qualman, S., Wiener, E., Crews, K. R., Houghton, P., and Meyer, W. H. Vincristine (V) and Irinotecan (CPT): A highly active combination in metastatic rhabdomyosarcoma. A Report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group (STSCOG). J Clin Oncol 23(16), Abstr #8509. 2005.
Ref Type: Abstract

47. Houghton, P. J., Gorlick, R., Friedman, H., Maris, J. M., Lock, R. B., Reynolds, C. P., Khan, J., Hewitt, S. M., Whiteford, C. C., and Smith, M. A. Pediatric Preclinical Testing Program (PPTP) - A molecularly characterized panel of childhood cancer models for new agent testing. Proc Am Assoc Cancer Res 46(Abstr #4731). 2005.
Ref Type: Abstract

48. Whiteford, C. C., Bilke, S., Greer, B. T., Cenacchi, N., Braunschweig, T. A., Wei, J. S., Smith, M., Houghton, P., Adamson, P., Reynolds, C. P., Lock, R. B., Gorlick, R., Sorensen, P., Hewitt, S. M., and Khan, J. Credentialing Preclinical Xenograft Models using Gene Expression Profiling and Tissue Arrays. Proc Am Assoc Cancer Res 46, Abstr #4462. 2005.
Ref Type: Abstract

49. Kettler, H. and White, K. Valuing Industry Contributions to Public-Private Partnerships for Health Product Development. 2003. Initiative on Public-Private Partnerships for Health.
Ref Type: Report

50. Reversing the failures of Roll Back Malaria. Lancet, *365*: 1439, 2005.

51. Lambo, E. More good than harm. Lancet, *365*: 1765, 2005.

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