PEDIATRIC PRECLINICAL TESTING PROGRAM CONCEPT PROPOSAL (11/2002)

NARRATIVE JUSTIFICATION FOR RFP FOR CONTRACT OR MASTER AGREEMENT: EC AND BSA CONCEPT REVIEW

1. **Background:**

Approximately 400 agents are currently under evaluation for cancer indications in adults. Although the proportion of children with cancer that enroll on clinical trials is higher than adults, the absolute number of children with cancer is relatively small compared to adults, placing a limitation on the number of pediatric clinical trials that investigators can conduct. Because of the increasing imbalance between the large number of agents potentially available for clinical testing and the more limited number of agents that can be systematically evaluated in pediatric clinical trials, it is essential to develop predictive preclinical models of pediatric cancers to help clinical investigators prioritize new anticancer agents and combinations of agents for testing in children. The proposed contract will provide support to the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD) by systematically testing agents in childhood cancer preclinical models. As described in the "Preliminary Data" section, preclinical antitumor activity for agents tested in several pediatric tumor models has correlated with subsequent clinical activity for the same agents. A systematic evaluation of a panel of pediatric preclinical models is needed to validate this strategy for prioritizing new agents for study in children with cancer.

The NCI has a long-standing program for *in vitro* and *in vivo* testing of agents using adult cancer models, but pediatric preclinical testing has not received such support. Neither pharmaceutical companies nor NCI have included pediatric models as standard components of their preclinical testing programs. The Division of Cancer Biology, through the Mouse Models of Human Cancer Consortium and through other grant programs, funds several laboratories to study genetically engineered murine models of childhood cancers. These models are primarily studied for the biological insights that they may provide, but opportunities may exist for preclinical testing. CTEP will work with Program Staff in the Division of Cancer Biology to either include genetically engineered models in the Preclinical Testing Program's core set of models or to include them on an *ad hoc* basis for specific targeted agents. Thus, the proposed contract will complement existing NCI preclinical activities.

NCI supports a broad clinical program for children with cancer, including:

- Children's Oncology Group (COG) for the conduct of phase 2 and phase 3 trials,
- COG Phase 1/Pilot Consortium for the conduct of phase 1 and pilot studies,
- Pediatric Brain Tumor Consortium (PBTC) for the conduct of studies evaluating novel therapeutic strategies in children with brain tumors, and
- The New Approaches to Neuroblastoma Consortium.

The pediatric preclinical testing contract will complement these clinical programs, by providing systematic preclinical efficacy and pharmacokinetic data to correlate with clinical findings for tested agents.

The proposed pediatric preclinical testing contract is responsive to the Best Pharmaceuticals for Children Act, which was enacted by Congress in January, 2002. Section 15(c) of the Act (Pre-clinical Models to Evaluate Promising Pediatric Cancer Therapies) states that the NCI Director "shall expand, intensify, and coordinate the activities of the Institute with respect to research on the development of preclinical models to evaluate which therapies are likely to be effective for treating pediatric cancer".

2. **Preliminary Data:**

Although there has not been a systematic approach to pediatric preclinical drug testing, preclinical antitumor activity for agents tested in several pediatric tumor models has correlated with clinical activity for the same agents. Rhabdomyosarcoma is the best studied tumor. Retrospective studies have demonstrated a strong correlation between the activity of agents against rhabdomyosarcoma xenografts and clinical activity of the same agents (1). Melphalan was first identified as an active agent against rhabdomyosarcoma in xenograft models, and subsequent clinical experience with melphalan in children with newly diagnosed rhabdomyosarcoma mirrored the activity observed in the xenograft models (2). The prospective identification of topoisomerase 1 inhibitors as active agents against rhabdomyosarcoma xenograft models (3) and the subsequent demonstration of antitumor activity for these agents in children with rhabdomyosarcoma further supports the predictive ability of these xenograft models (4). Activity of topoisomerase 1 inhibitors observed in xenograft models of neuroblastoma, similar to rhabdomyosarcoma, has correlated with the clinical activity of these agents in children with neuroblastoma (3;5). The observation that neuroblastoma cell lines established at different points of therapy acquire a sustained drug-resistant phenotype that mirrors the clinical resistance pattern of patients supports the clinical relevance of the drug sensitivity pattern of these neuroblastoma cell lines (6).

An essential aspect of interpreting the activity observed in murine preclinical models is a comparison of the human pharmacokinetic data for the tested agent to that obtained in the mouse models. Mice may tolerate much higher systemic exposures of some drugs compared to humans (e.g., DMP0840, 15-20X higher; carzelesin, 80X higher; and sulofenur, 8X higher) and may tolerate lower systemic exposures of other drugs (e.g., etoposide) (P. Houghton, unpublished observations). Comparison of the pharmacokinetic behavior of 9-aminocamptothecin and irinotecan in mice and humans indicated that the systemic exposures associated with anti-tumor activity in mice were achievable in man for irinotecan (7) but not for 9-aminocamptothecin (8), an observation that correlated with the relative clinical activity of each agent. The pediatric preclinical testing of new agents will optimally occur around the time that agents are entering adult phase 1 evaluation, and this timing should make it possible to incorporate human pharmacokinetic data into the interpretation of the pediatric preclinical test results.

Moving to develop a more systematic approach to the prioritization of new agents for pediatric evaluation, CTEP sponsored a meeting on June 26-27, 2001 in Rockville, Maryland of investigators who have studied preclinical models potentially applicable to childhood cancer. Data presented at the meeting documented the existence of a number of preclinical models (xenograft, transgenic, and *in vitro*) potentially applicable to drug testing for a number of childhood cancers, including: rhabdomyosarcoma, osteosarcoma, Ewing sarcoma / peripheral primitive neuroectodermal tumor (PNET), neuroblastoma, various types of brain cancers, juvenile myelomonocytic leukemia (JMML), and acute lymphoblastic leukemia (ALL). The participating investigators supported the concept of establishing a systematic preclinical testing program, and a summary of the meeting was accepted for publication in *Clinical Cancer Research* (9).

Key to the success of a Pediatric Preclinical Testing Program is its ability to obtain new agents from pharmaceutical companies at an appropriate time in their development for pediatric preclinical testing. Optimally, agents will be available for preclinical pediatric testing near the time that a decision is made by the pharmaceutical sponsor to pursue phase 1 development in adults. To address the issue of timely access to agents for pediatric preclinical testing, CTEP sponsored a meeting on May 29, 2002 with two primary objectives: 1) to examine industry and academic issues regarding early access by pediatric investigators to anti-cancer agents in the clinical development pipeline for preclinical testing in pediatric tumor models, and 2) to establish the essential components of a model Materials Transfer Agreement (MTA) design that would facilitate timely preclinical investigation of new agents and that would maintain/enhance the pharmaceutical sponsor's drug development plan. Representatives of NCI, academia, the FDA, and pharmaceutical companies participated in the meeting. The meeting identified substantial common ground between the academic representatives and the pharmaceutical sponsors. This included a general consensus that NCI could draft a model MTA, with input from the involved parties, that would satisfy academic and pharmaceutical interests and that would facilitate timely access to new agents for pediatric preclinical testing.

3. **Objectives/Scope:**

The primary objective of this RFP is to identify a panel of predictive pediatric preclinical models to inform pediatric oncologists' prioritization of new agents for evaluation in children with cancer. NCI will utilize a contract mechanism to systematically test 10-15 agents or combinations of agents per year against a panel of preclinical models of the childhood cancers that occur most commonly in children. For agents tested, pharmacokinetic studies will be performed to determine the serum drug levels and systemic exposures associated with antitumor activity. Results obtained from the preclinical testing program will be correlated with the clinical activity and with the pharmacokinetic profile of the tested agents to assess the predictive capabilities of the program. The intended outcome of the project is to improve survival for children with cancer by identifying for clinical testing the most effective agents from among the universe of oncologic agents potentially available for evaluation in children with cancer.

4. **Methods:**

The design for the preclinical testing program is presented in the attached figure. The program will utilize a panel of preclinical models for approximately 6 childhood cancers, with each cancer type represented by 6-10 different xenografts. For agents with general cytotoxic activity for which a molecular target is not defined, the program would initially test the agent at its MTD against the entire xenograft panel. For tumor types in which responses were observed, the program would develop a full dose response curve, and also study the agent in orthotopic or genetically engineered mouse models of these tumor types when they are available. This sequential design minimizes the resources required to study drugs by avoiding complete dose response studies for agents with little or no activity in tumor models.

The design for the program anticipates that many of the agents available for testing will have known molecular targets and that relevant genetically engineered mouse models will exist for some of these targeted agents. For those agents with defined molecular targets, testing will begin at doses below the MTD if there are convincing data documenting significant target modulation at lower doses; however, even for agents with known molecular targets, an advantage may exist for performing the initial testing at the MTD. Antitumor activity associated with modulation of the agent's known target would likely be detected by testing at the highest dose level tolerated and activity associated with previously unrecognized targets may be identified. Regardless of the dose used for the initial testing, if activity were observed then the program would perform full dose response testing to relate antitumor response to target inhibition. If the target of an agent was one for which there was a murine genetic model with suitable characteristics for preclinical testing, evaluation against this model would occur in the first tier of testing. If activity was observed in the first tier of testing for specific tumor types, the agent would also be studied in available orthotopic models for these tumors.

The role of *in vitro* testing is not specified in the figure. For those tumor types with well characterized cell lines, *in vitro* testing could occur in parallel with *in vivo* testing. For those agents showing activity in one or more xenograft or transgenic models, *in vitro* testing could be especially useful in identifying combinations including the active agent that warrant further preclinical testing.

The Pediatric Preclinical Testing Program will be led by a Prime Contractor who will be selected for their experience and excellence in preclinical testing. The Prime Contractor's responsibilities will include:

- Providing administrative support and fiscal management for the Preclinical Testing Program.
- Overseeing a competitive selection process within the first 3 months of the contract for the laboratories that will serve as subcontractors to perform the testing for individual tumor types. Initially, the preclinical

testing program will focus on systematically testing panels of rhabdomyosarcoma, neuroblastoma, Ewings family of tumors, acute lymphoblastic leukemia, selected brain tumors, and osteosarcoma.

- Implementing a flexible mechanism for including additional laboratories as needed for testing specific agents with known molecular targets.
- Preparing timely cost estimates and detailed descriptions of the technical approach to be used in implementing Work Assignments for the testing of specific agents (see below).
- Providing biostatistical support for the design and analysis of the testing program's experiments.
- Providing for the conduct of pharmacokinetic studies and for the analysis of data from these studies. As described in the previous section, serum drug levels and systemic exposures in preclinical models are essential in attempting to make correlations with clinical activity.
- Providing for the conduct of correlative science studies as appropriate in the evaluation of agents targeting specific signal transduction pathways. Correlative studies may establish whether molecularly targeted agents have achieved target inhibition under test conditions and will assist in understanding a targeted agent's activity or lack of activity (i.e., illustrating an association between pathway modulation and antitumor activity). They may serve as a basis for establishing doses of targeted agents for use in combination studies (i.e., selecting doses that modulate target, even though these doses may not have antitumor activity as single agents).

NCI will establish a Pediatric Preclinical Decision Group that will include experts in childhood cancer drug development to assist in selection of agents for preclinical testing. This group will include clinical investigators leading nationwide pediatric drug development efforts in the extramural and intramural NCI-supported clinical trials community for children with cancer.

The NCI will issue Work Assignments to the Prime Contractor for testing the selected agents. The NCI Project Officer, based on input from the Decision Group, will initiate the Work Assignments. The Work Assignments will indicate the period of performance, the specific work to be performed, and the deliverables. The Prime Contractor will submit to the Project Officer a detailed description of the technical approach to be used in carrying out the Work Assignment and an estimate of the required effort and cost. The Prime Contractor's assessment will include the estimated effort and cost from each of the subcontractors for the agent to be tested under the Work Assignment. The performance of the contract in implementing and completing each Work Assignment will be monitored by NCI staff from CTEP, the Developmental Therapeutics Program (DTP), and the Mouse Models of Human Cancer Consortium (Division of Cancer Biology).

The correlative science activities of the contract will be facilitated by the availability of tissue and cell microarrays of the cell lines and xenografts that will be components of Preclinical Testing Program. These arrays will be developed using a separate source of DCTD funds in a collaborative effort between the COG Phase 1 Consortium, CTEP, and the NCI intramural program. The arrays will serve as a resource to qualified investigators to identify the expression and activation status of potential therapeutic targets in the Preclinical Testing Program's cell lines and xenografts. Gene expression profiles of the Preclinical Testing Program's tumor models will also be obtained.

The evaluation of the Pediatric Preclinical Testing Program will focus on several factors, including: the number of agents tested; adherence to time lines for implementation and completion of testing for agents; timely performance of pharmacokinetic studies and analysis of data from these studies for agents for which this assignment is made; timely performance of correlative science studies and analysis of data from these studies for agents for which this assignment is made; and timely dissemination of results in peer-reviewed journals and in presentations at national meetings. NCI will assess the overall value of the Pediatric Preclinical Testing Program to childhood cancer drug development by retrospective and prospective comparisons of the preclinical activity observed for specific tested agents with the clinical activity observed for these same agents to determine if a correlation exists between the preclinical and clinical results.

5. **Contract Justification:**

There are a large number of new agents potentially evaluable by NCI-supported clinical trials programs for children with cancer. If NCI is to assure that optimal use is made of its pediatric clinical trials resources so that more effective therapies can be identified for children with cancer, then it is critical to develop procedures for assessing the potential utility of these agents in the preclinical setting and to use this information to make informed decisions about which agents warrant development in children. Investigator-initiated mechanisms of grants and cooperative agreements serve essential needs of industry and academia; however, the investigator-initiated mechanisms do not have deliverables as their anticipated outcome, and it is difficult to control timelines and quality control through these mechanisms. A contract mechanism is the most rapid, efficient, and cost-saving method to address the critical issue of timely completion of preclinical testing with the requisite quality control measures required for a robust preclinical testing program.

References

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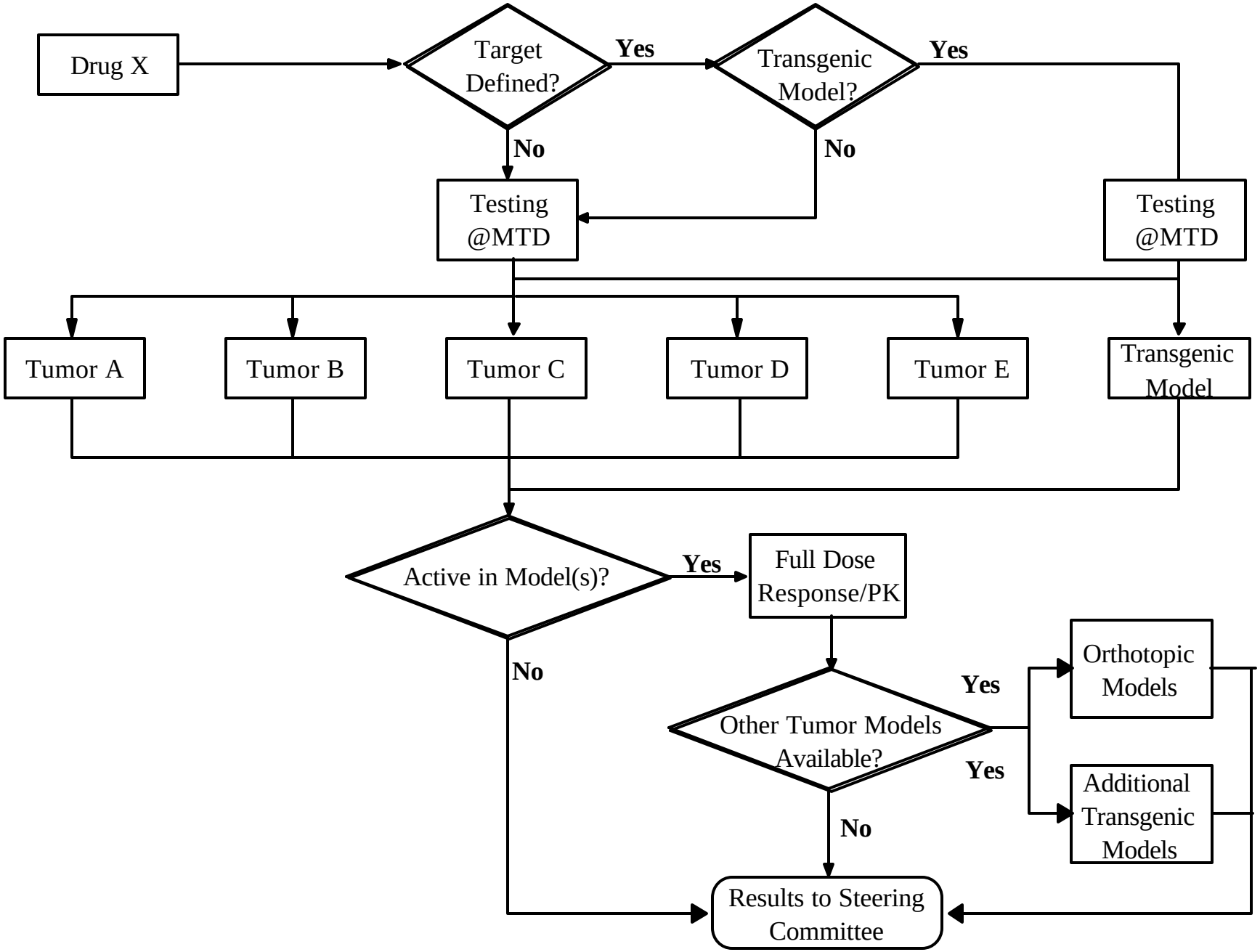
Drug X
Target Defined?
Yes
No
Transgenic Model?
Yes
No
Testing @MTD
Testing @MTD
Tumor A
Tumor B
Tumor C
Tumor D
Tumor E
Transgenic Model
Active in Model(s)?
Yes
No
Full Dose Response/PK
Other Tumor Models Available?
Yes
Yes
No
Orthotopic Models
Additional Transgenic Models
Results to Steering Committee