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Pediatric Preclinical Testing Consortium (PPTC) Pre-Application Webinar (with Post-Teleconference additions)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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Competing Preclinical Testing Activity as a Cooperative Agreement

- RFA-CA-14-018
  - Pediatric Preclinical Testing Consortium: Research Programs
  - http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-14-018.html
- RFA-CA-14-019
  - Pediatric Preclinical Testing Consortium: Coordinating Center
  - http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-14-019.html

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Role of the PPTP/PPTC

- Role of the PPTP/PPTC
  - To develop evidence to support the presence or absence of a **therapeutic window** for specific agents against selected childhood cancers
  - To increase the effectiveness of NCI's clinical trials programs for children with cancer
- Initiated testing in 2005
- More than 80 agents tested from more than 50 different companies.
- A resource to the pediatric research community.

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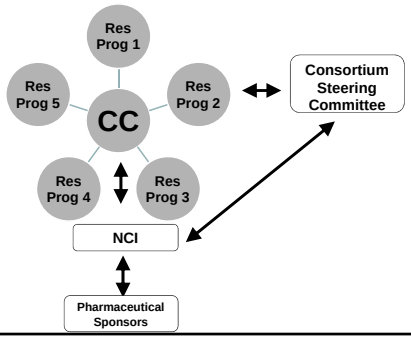
Pediatric Preclinical Testing Consortium



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Eligibility

- Higher education institutions
- Nonprofits other than institutions of higher education
- For-profit organizations
- Governments
- Foreign institutions (for Research Programs but not for Coordinating Center)

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Letter of Intent

- Not required.
- Allows IC staff to estimate the potential review workload and plan the review.
- Send to Malcolm.Smith@nih.gov
- October 13, 2014

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Research Programs

- Type A: Research Program for leukemia *in vivo* testing that will be responsible for drug ALL (required) and AML (optional);
- Type B: Research Program for tumors of central nervous system *in vivo* testing that will be responsible for drug testing on CNS tumors, including medulloblastoma, high-grade glioma (including diffuse intrinsic pontine glioma), and ependymoma;
- Type C: Research Program for other solid tumors *in vivo* testing that will be responsible for drug testing on one or more of the following tumors: Wilms tumor, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, neuroblastoma, and others (e.g., rhabdoid tumor, hepatoblastoma, etc.); and
- Type D: Research Program for *in vitro* testing using cell lines representing common pediatric cancers

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Research Strategy (in Vivo Testing)

A. Capabilities of the team for preclinical testing
B. Preclinical models proposed
   - Molecular characterization (also use "Other Attachments" for details)
   - Direct transplantation without prior in vitro passage preferred for xenograft models
C. Approach to testing
   - Strategy and methodology (also use "Other Attachments" for details)
   - Ability to quantitatively assess tumor regression and time to event
   - Capacity for 6 to 10 agents per year per disease panel

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Research Strategy (in Vitro Testing)

A. Capabilities of the team for preclinical testing
B. Preclinical models proposed
   - Molecular characterization (also use "Other Attachments" for details)
C. Approach to testing
   - Strategy and methodology (also use "Other Attachments" for details)
   - Approach to assessing in vitro testing parameters such as IC_{50}, Y_{min} (minimum T/C%), and ratio of final cell number to starting cell number.
   - Throughput

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Research Strategy: Agents (Combinations of Agents) Proposed for Evaluation (in Vivo)

- List three agents (or combinations of agents) for in vivo testing against their proposed tumor panel(s):
  - Provide a succinct rationale for why these agents warrant prioritization for testing.
  - Base on the biology of the models in the proposed panel(s) and on the mechanism of action of the agents.
- Briefly describe the experimental approach for testing these agents.
- Note: PD & PK studies may be proposed as part of the agent evaluations.

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Research Strategy: Agents (Combinations of Agents) Proposed for Evaluation (in Vitro)

- Propose a screening experiment for a set of agents or combinations of agents
  - Provide a succinct rationale for why these agents warrant prioritization for testing.
  - Base on the biology of the models in the proposed panel(s) and on the mechanism of action of the agents.
- Describe the potential for the experiments to generate hypotheses that the PPTC in vivo Research Programs can further evaluate.
- Describe he potential contribution of the screen results to childhood cancer drug development

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Research Program: Other Attachments (Section IV.2)

- Relevant standard operating procedures for maintaining and testing preclinical models (use file name "SOPs").
- Information on the clinical/demographic characteristics of the models proposed for testing (use file name "Models Demographic Characteristics").
- Information on the molecular characterization of the models proposed for testing, including relevant genomic alterations (SNVs/mutations, copy number gains and losses, etc.) for each of the models (use file name "Models Molecular Characteristics").
- Upload these materials as pdf files using file names indicated in the list (these file names will become bookmarks in the application).

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Coordinating Center: Research Strategy

A. Scientific and administrative capabilities
   A. Research management
   B. Data collection, storage and analysis
   C. Bioinformatic analysis
B. Consortium administrative coordination
C. Data management and statistical support
D. Consortium scientific coordination

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Coordinating Center: Other Attachments (Section IV.2)

- Details of the analytical methods proposed to analyze in vitro and in vivo data to be generated by the PPTC Research Programs.
- Upload these materials as a single pdf file using file name "Analytical Methods" (this file name will become a bookmark in the application).
- NOTE: These will have to be "negotiated" with selected Research Programs after PPTC is established.

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Review Criteria

- Note the "specific to this FOA" criteria and that these are addressed in the application.

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Research Program Responsibilities (see RFA for complete listing)

- Membership on the PPTC Steering Committee: Scientific leadership.
- Participation in interpretation of testing results, in preparing study reports, in proposing additional testing based on results from initial testing, and in co-authoring manuscripts.
- Performance of toxicity testing of agents as needed to identify the appropriate dose of the test agent for efficacy evaluations.
- Performance of the testing of agents prioritized by the PPTC Steering Committee with submission of results to the PPTC-Coordinating Center (anticipate 6 to 10 agents per year for *in vivo* testing for each disease panel).
- Electronic submission of testing results to the PPTC-Coordinating Center for analysis and archiving.

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Research Program Responsibilities (see RFA for complete listing)

- Performance of dose-response testing as appropriate for agents with activity in initial fixed dose testing that are prioritized by the Steering Committee for further evaluation.
- Collection of timed blood & tissue specimens for PK/PD studies.
- Performance of pharmacodynamic testing for selected agents prioritized by the Steering Committee for such evaluations.
- Performance of regular identity testing of cell lines and xenografts.
- Ensuring that molecular characterization data for PPTC preclinical models are available to the investigator community.

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NCI Staff Program Responsibilities (see RFA for complete listing)

- Negotiating Material Transfer Agreements (MTAs) with pharmaceutical companies (MTAs will be based on the PPTC Model MTA template)
- Serving as a scientific resource with respect to other ongoing NCI activities that may be relevant to the Consortium research efforts.
- Assisting awardees by reviewing research plans prior to submission to pharmaceutical companies and reviewing PPTC manuscripts prior to submission for publication.
- Advising awardees regarding mechanisms for ensuring appropriate quality control of preclinical testing.

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NCI Staff Program Responsibilities (see RFA for complete listing)

- Participating in the Activities of the Consortium Steering Committee and its Scientific Meetings.
- Reviewing compliance with Federally mandated regulatory requirements.
- Monitoring Consortium progress.
- Integrating the efforts of the PPTC with other NCI-supported programs for children with cancer (e.g., COG, the COG Phase 1 Consortium, and the Pediatric Brain Tumor Consortium).

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Coordinating Center Responsibilities: Administrative Coordination (see RFA for complete listing)

- Management of the PPTC Steering Committee.
- Organization of an annual meeting of PPTC Research Program awardees.
- Provision of other support as needed for successful Consortium operations (e.g., communications, subcommittee meetings, telephone conference calls, e-mail communications).
- Development and maintenance of a site for the confidential sharing of documents (e.g., SharePoint) and for collaborative development of research plans, reports, and manuscripts.
- Development and maintenance of an interactive web page to publicize the Consortium and to announce the availability of Consortium-supported resources and receive input from investigators.
- Establishment and implementation of a Conflict of Interest Policy for the Consortium.

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Coordinating Center Responsibilities: Data Management & Statistical Support (see RFA for complete listing)

- Development and implementation of standard procedures for data collection of testing results from the Research Programs.
- Development and implementation of standard procedures for the statistical analysis of data collected from the Research Programs.
- Development and implementation of procedures for bioinformatic analysis of testing results to relate treatment effects to molecular characteristics of the preclinical models studied.

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Coordinating Center Responsibilities: Scientific Coordination (see RFA for complete listing)

- Contribute along with PPTC Research Program PD(s)/PI(s) to the scientific leadership of the PPTC and oversee the PPTC Steering Committee.
- Coordinate drug shipments of agents supplied by pharmaceutical companies or other entities to Research Programs.
- Produce and maintain a Manual of Operations and procedures manuals incorporating information and materials provided by the Research Programs.
- Develop and implement a Quality Control/Quality Assurance (QC/QA) program for the PPTC.

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Coordinating Center Responsibilities: Scientific Coordination (see RFA for complete listing)

- Manage and coordinate the acquisition and shipping of tumor specimens and biological fluids as specified by approved research plans to the appropriate laboratories for testing.
- Manage the Pharmacokinetic-Pharmacodynamic (PK-PD) Research Fund ($50,000 per year)
- Develop and implement metrics for evaluating the performance of PPTC Research Programs.
- Coordinate preparation of Study Reports for Pharmaceutical Collaborators describing testing results for agents evaluated by the PPTC.
- Coordinate preparation of manuscripts describing PPTC results.

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Questions:

- What is the number of tumor types per group that is expected?
  - Applicants may propose 1 or more tumor types. For example, for solid tumor applications (Type C) multiple solid tumors (e.g., neuroblastoma, Wilms tumor, rhabdomyosarcoma, and Ewing sarcoma) may be proposed or a single tumor type (e.g., only Ewing sarcoma) may be proposed.

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Questions:

- Is an application with purely transgenic models (i.e., no xenografts) responsive?
  - Yes.
  - Need to document clinical relevance of models for specific childhood cancers.
  - Need to document ability to meet required throughput.

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Questions:

- Will low-grade glioma models be considered responsive?
  - Yes
  - Note: The PPTC will want to include a brain tumor panel(s) such that a range of histologies are encompassed.

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Questions

- Can Research Program applications include multiple institutions or should they be from a single institution?
  - Applications should be from single institutions.
  - NCI leadership wanted to encourage the most open competition possible, and this aim could be thwarted by “preformed” consortia applying.

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Questions:

- Most of our models are well characterized (mutation, gene expression and DNA copy number), but there are several newly developed models that need to be fully analyzed. Can funds be requested for this purpose?
  - No.

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Questions:

- Regarding the Models Molecular Characterization “Other Attachments”, many of the files with the requested data (SNVs, CNAs etc.) can be very large. Is there a limit to the size of the files to be linked to the application? How should this be addressed?
  - Provide data documenting scope of characterization and clinical relevance of models. Examples are listed below.
  - Relevant mutations known to be present in disease as well as cancer-associated mutations
  - Relevant copy number alterations known to be present in disease as well as cancer-associated mutations
  - Gene expression data documenting concordance with clinical specimens.

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Questions:

- Will the Research Program teams have input into which agents are tested?
  - Yes.
  - The Research Programs, through the Steering Committee will drive the testing program and will select agents.

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Questions:

- Must all agents to be tested come from CTEP?
  - No.
  - The PPTC Steering Committee can prioritize agents from pharma or from academia without consideration of whether they are in the CTEP portfolio.
  - NCI will establish MTAs for agents that are selected by the Steering Committee for PPTC evaluation.

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Questions

- Must applicants acknowledge their institutions acceptance of the model MTA template?
  - Since testing of agents from pharmaceutical companies will employ the terms incorporated in the MTA template, acceptance of the template is required.

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Questions:

- May individual sites test agent(s) discovered by their own research and/or related to their own individual research?
  - Yes.
  - The PPTC Steering Committee can prioritize agents from academia. Depending on the research plan approved by the Steering Committee, these agents may be tested at a single PPTC Research Program or at multiple Research Programs.
  - Institutions must be willing to provide agents under the PPTC model MTA.
  - NOTE: The PPTP requires that agents be close to clinical testing (or in the clinic). The PPTC will need to develop its own prioritization criteria.

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Questions:

- Does permission from the relevant pharmaceutical companies need to be obtained for the three testing projects proposed in applications for in vivo testing?
  - No

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Questions

- Should we be concerned about proposing combinations of novel agents from different companies? If we do so are we likely to be scored poorly in terms of feasibility due to IP issues having to be sorted out between companies?
  - Assume that NCI will be able to work out IP issues for all agents or combinations of agents proposed.

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Questions:

- When proposing “Combinations of Agents”, can one of the treatment arms be an established agent or a combination of established agents to show efficacy and tolerability of a novel agent when combined with established chemotherapy?
  - Yes.
  - Clearly describe the rationale and clinical importance for the proposed combination.

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Questions:

- Are 'combinations' that incorporate ionizing radiation with novel agents responsive?
  - Yes.
  - The PPTP has not performed radiation therapy combinations, but this capability is welcomed for tumor panels for which radiation therapy is a relevant treatment modality.

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Questions:

- Apart from the preclinical testing of 6-10 agents in the corresponding relevant models of human disease, it is unclear whether concomitant hypothesis driven research/specific aims would be supported by this mechanism?
  - The PPTC mechanism is for testing of agents under consideration for clinical evaluation for children with cancer.
  - Agents prioritized by the Steering Committee will presumably have a hypothesis supporting their evaluation.
  - Potential clinical applicability is an expectation for agents studied by the PPTC.

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Questions:

- From the FOA, it appears that the Coordinating Center will be in charge of data management and statistical analysis. Is there going to be a centralized mouse model database for all the animals involved in PPTC?
  - The intent is to have data collected centrally for preparation of manuscripts/reports.
  - Each Research Program will need to develop mechanism for submitting (exporting) results to the Coordinating Center.
  - The Coordinating Center will need a database for accepting and storing the testing results.

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Questions:

- Should Research Programs allocate funds for travel to the annual PPTC meeting?
  - Travel support to the annual meeting will be the responsibility of the Coordinating Center.
  - The PPTP practice was for the annual meeting to co-locate with a meeting like AACR.
  - The Coordinating Center should budget for approximately 12 trips per year to cover the annual meeting and limited travel to other meetings to present PPTC results.

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Questions:

- How will PK/PD studies be prioritized and supported?
  - The PPTC Steering Committee will determine the need for PK/PD studies for agents tested.
  - PK/PD studies may be supported through funds provided to the Coordinating Center for this purpose, with the Coordinating Center distributing the funds to Research Programs as per Steering Committee instructions.
  - PK/PD studies may also be conducted/supported by the pharmaceutical collaborator.

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Questions:

- For the 3 agents proposed for evaluation, should we propose to study the mechanism of cell death and/or therapy resistance?
  - PK/PD studies that provide potentially clinically relevant information are contributory.

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Questions

- Will the PPTC consider zebrafish models, or are you limiting it to mouse?
  - At this time, the PPTC is focusing on mouse models.

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Questions:

- Some would recommend that DNA fingerprinting be periodically re-performed (Q3months) to ensure the integrity of the cells/xenografts established. This can be costly if talking about a robust pre-clinical testing platform, but is a necessary step to ensure integrity of research; would funds be available to investigators to continue this type of molecular surveillance during the testing of the agents?
  - Performance of regular identity testing of cell lines and xenografts is one of the responsibilities of the Research Programs and should be included in applications.
  - The Steering Committee will need to determine the frequency with which such testing is performed, but annual testing can be assumed for applications.

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Questions

- If we have both a transgenic model and a PDX, can both be combined together in one vivo application?
  - Yes.

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Questions

- Is it OK to focus on just one solid tumor, but use multiple in vivo models for that tumor rather than multiple different solid tumors?
  - Yes.
  - Applicants may propose to study a single tumor type, or multiple tumor types.
  - Note: Separate applications are not needed for studying multiple tumor types within a category (e.g, multiple solid tumor types), but are required for applicants wishing to study across multiple categories (e.g., solid tumors and brain tumors, solid tumors and in vitro testing, solid tumors and leukemia, etc.).

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Questions

- For Part A (leukemia panel) does this require that any site interested in AML, must also submit an ALL panel to be considered? Is there the possibility for more than 1 ALL site?
  - An AML panel will be considered responsive.
  - The wording of the RFA was to indicate that an ALL panel will be selected, and not to exclude someone from submitting an AML panel that did not include ALL models.
  - More than one leukemia Research Program may be selected.

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Questions:

- Contact Malcolm Smith, MD, PhD for additional information or questions: Malcolm.Smith@nih.gov