

NCI Guidelines for Administrative Supplements in Support of Expanding the Childhood Cancer TARGET Initiative

Title: Childhood Cancer TARGET Initiative Expansion – Tissue Collections and Characterization

Announcement Number: [NOT-OD-09-056](#) NIH Announces the Availability of Recovery Act Funds for Administrative Supplements

Release Date: May 11, 2009

Receipt Date: June 12, 2009

Program Overview:

The [Therapeutically Applicable Research to Generate Effective Treatments \(TARGET\) Initiative](#) is committed to focusing the tools of modern genetics on the discovery of valid therapeutic targets in childhood cancers so that new, more effective treatments can be rapidly developed. The TARGET Initiative is based on the premise that genes that are consistently altered in specific childhood cancers are the key to discovery of new therapeutic targets for these cancers. The Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Initiative has to date focused on acute lymphoblastic leukemia (ALL) and neuroblastoma and has successfully identified new molecular targets for both high-risk ALL and neuroblastoma.

Purpose:

The Childhood Cancer TARGET Initiative is being expanded through this supplement mechanism to include additional pediatric cancers as well as to allow further progress to be made in understanding potentially addressable causes of treatment failure for ALL and neuroblastoma. The primary focus of the TARGET Initiative will remain identifying genomic alterations that offer rapid pathways to novel therapeutic interventions that may lead to more effective treatments. This specific administrative supplement solicitation requests submissions describing childhood cancer tissue collections that would be appropriate for inclusion in the Childhood Cancer TARGET Initiative. Supplement funds will support selected molecular characterization of the tissues and will support participation of researchers associated with the tissue collections in the TARGET Initiative. The next-generation sequencing that will be applied to the tissue collections will be supported through a separate research contract and will include large scale exome sequencing (e.g., the [6,000 genes and miRNA targets](#) selected by the TCGA network) or transcriptome sequencing.

The TARGET Initiative expansion will apply next-generation sequencing to 100 to 200 pathology-confirmed tumor specimens per childhood cancer type. Listed below are examples of the childhood cancers for which applications are encouraged, although applications proposing additional cancer types will also be considered.

- Pediatric brain tumors (medulloblastoma, ependymoma, brain stem glioma, etc.)
- Rhabdomyosarcoma
- Osteosarcoma
- Ewing sarcoma
- Hepatoblastoma
- Wilms tumor (patients with treatment failure and anaplastic histology)

For less common childhood cancers, tissue collections of less than 100 cases will be considered, if the collections are of high quality and the clinical need is great. Proposals for high-risk ALL and high-risk neuroblastoma cohorts are also encouraged to address central, therapeutically relevant questions related to genomic correlates of treatment failure. If multiple applications are received for a cancer type, NCI may request a joint effort by the proposing research teams for this cancer type.

The tissue collections proposed for study may already have some level of biological characterization performed, and the TARGET resources will support additional characterization as needed, to include pathology characterization, gene expression analysis, genomic characterization for copy number abnormalities (CNA) and loss-of-heterozygosity (LOH), microRNA profiling, and epigenomic characterization. If there is additional characterization work needed, applicants may propose a specific laboratory to perform this work, but other laboratories may be sought by NCI to perform the work. The laboratories proposed by applicants to perform the genomic characterization should have capabilities that are comparable to those describe in [RFA-CA-09-010 for Genome Characterization Centers](#) to perform high-throughput, high resolution technologies to comprehensively (i.e., genome-wide) detect genomic, epigenomic and transcriptome aberrations including: alterations in chromosome segment copy numbers, translocations, loss of heterozygosity, altered DNA methylation patterns and changes in gene expression (including microRNA expression), which may play a role in cancer.

Application Guidelines:

Applicants are encouraged to review NIH Announcement Number [NOT-OD-09-056](#) for guidance on how to prepare an administrative supplement request under the Recovery Act. Additional information regarding submission of supplement requests is provided in Appendix I of this announcement.

Funds Available:

Up to \$5,000,000 will be available to support administrative supplements under this announcement.

Eligibility:

This announcement is for administrative supplements to active NIH Research Grants and Research Program and Center Grants (Ps). The proposed supplement MUST be within the general scope of the peer-reviewed activities and aims approved within the parent grant, including projects on a no-cost extension; while supplemental funds may be awarded to grants during a no-cost extension, the period of support cannot extend beyond the award period for the additional time that was granted. There are no limits to the number of administrative supplement requests that may be submitted by an institution or Project Director/Principal Investigator. Applications from foreign institutions are not permitted.

Budgets and Project Periods:

- Funding for administrative supplements to existing grants will be available from Recovery Act funds in FY2009 and FY2010.
- Funds will be used to support involvement of the research team associated with the tissue specimens for each cancer type, including disease-specific expertise, pathology and statistical expertise with specific knowledge of the tissues proposed for study, and bioinformatics expertise.
- Budget proposals are limited to \$750,000 total costs for the two year funding period. Next-generation DNA sequencing will be supported through a separate funding mechanism. Because the nature and scope of the proposed research will vary, it is anticipated that the size of each award will vary. For tissue collections for which characterization work has already been performed, funds requested are anticipated to be well below the maximum amount. For funds for which characterization work is proposed, Year 2 funding should be less than Year 1 funding, as most characterization work should be performed within the first 6 months of the supplement award.
- Applicants should budget for one meeting of Childhood Cancer TARGET investigators (up to 5 members of the research team) in the Washington, DC area in FY 2010.
- In addition, domestic U.S. institutions planning to submit supplement requests that include foreign components should be aware that requested funding for any foreign components should not exceed 10% of the total requested direct costs or \$25,000 per year (per subcontract/subaward or in aggregate for multiple subcontracts/subawards), whichever is less.

Application Review:

Administrative supplement requests will not undergo peer review. They will be reviewed for scientific merit and for meeting the ARRA goals by a panel of NCI staff with expertise in the disciplines pertaining to childhood cancer and/or molecular characterization of cancer tissues. External experts may serve as consultants to NCI staff in this process. Requests will undergo initial administrative review by grants management staff from the NCI Office of Grants Administration (including the Grants Management Specialist assigned to the parent grant) to ensure administrative eligibility and that all required items are submitted.

Specific review criteria will include the following:

- Merit of proposed science
- Suitability and quality of tissue specimens (both tumor and normal) for the relevant characterization and sequencing studies,
- Expertise of the research/scientific team proposed to conduct and achieve the goals of the TARGET Initiative for the cancer type proposed,
- Clinical need and relevance of specimens to clinical need, and
- ARRA job creation and retention criteria:
 - Supplement will accelerate the research proposed in the parent grant
 - Supplement will enable hiring of additional staff
 - Supplement will enable increased hours of current part-time staff
 - Supplement enables recruitment for additional skills

The funding decision will be provided within 8-10 weeks of application submission.

Award Date:

Awards will be made by September 30, 2009.

Points of Contact:

Malcolm Smith, MD, PhD; Malcolm.Smith@nih.gov, and (301) 496-2522
Daniela S. Gerhard, Ph.D.; gerhardd@mail.nih.gov, and (301) 451-8027

How to Apply:

Requests for Childhood Cancer TARGET Initiative administrative supplements must be submitted to NCI (see address below) as described in these program guidelines. This is a one-time announcement and formal requests must be received on or before June 12, 2009. Late applications will not be accepted. Note the NIH Center for Scientific Review (CSR) IS NOT involved in receipt and processing of these requests.

Submit a signed, typewritten original of the proposal and five photocopies in one package to Dr. Malcolm Smith:

General Mail:

Malcolm Smith, MD, PhD
Assoc Branch Chief, Pediatrics
Cancer Therapy Evaluation Program, NCI
6130 Executive Boulevard MSC 7412
Room 7025
Bethesda, MD 20892-7412
Bus: 301-496-2522

FED-X (or comparable overnight delivery):

Malcolm Smith, MD, PhD
Assoc Branch Chief, Pediatrics
Cancer Therapy Evaluation Program, NCI
6130 Executive Boulevard
Room 7025
Rockville, MD 20852-4910
Bus: 301-496-2522

Applicants are also strongly encouraged to submit applications electronically as an e-mail attachment in PDF format (email address is Malcolm.Smith@nih.gov). DO NOT submit applications via Grants.gov as the NIH Center for Scientific Review (CSR) IS NOT involved in receipt and processing of these requests.

Appendix I – Suggested Application Procedures for Administrative Supplements for the Childhood Cancer TARGET Expansion

In addition to the instructions for applications provided by NIH Announcement Number [NOT-OD-09-056](#), inclusion of the following information in the “Research Project Plan” section of the application is suggested. This section should be limited to 20 pages.

- a) With regard to the **characteristics of each biospecimen collection**, include the following information:
 - i) numbers of unique patient tumor specimens (unique cases) included in the collection;
 - ii) anatomic sites and histopathologic types (WHO classification) represented in the collection;
 - iii) numbers of tumors by stage and/or risk group within the collection;
 - iv) if known, the proportion of patients with distinctive and clinically-relevant biological subtypes (e.g., embryonal and alveolar rhabdomyosarcoma; MYCN-amplified and non-amplified neuroblastoma, etc.);
 - v) the proportion of the specimens that represent tissue from primary, untreated tumor sites and the proportion of tumor specimens from metastatic lesions;
 - vi) the proportion of the specimen collection that is from treatment-naïve patients (NOTE: primary diagnosis specimens prior to treatment are preferred, and if other specimens are proposed then scientific justification should be provided);
 - vii) the length of follow-up for patients in the biospecimen collection (median and range); and
 - viii) the proportion of patients that have had a tumor-related event (e.g., failure to achieve remission, progressive disease, or tumor relapse) and the proportion of patients that are likely to have a tumor-related event at the time of final follow-up for the clinical protocol(s).

- b) With regard to the **contents of each biospecimen collection**, provide the following information (NOTE: formalin fixed and paraffin-embedded tissues are not suitable for the purposes of this FOA) :
 - i) the percentage of biospecimens that are > 200 mg in weight;
 - ii) the method of storage (e.g., fresh frozen, with or without embedding in OCT);
 - iii) the existence and characteristics (including source) of case-matched normal tissue biospecimens (NOTE: normal tissue biospecimens are required for the primary DNA sequencing component of the TARGET Initiative);
 - iv) if nucleic acids have already been extracted from the tissue specimens, the quantity of DNA and RNA available for specimens (median and range). Preference is given for DNA and RNA isolated from the same

- tissue specimen (e.g., Qiagen AllPrep or comparable methods).
- c) Concerning whether the biospecimens were from patients treated in **clinical trials**, provide the following information:
 - i) the protocol(s) on which the patients were treated;
 - ii) whether the samples and data were or are collected as part of a “linked” or “coded” protocol (meaning that the patients can be anonymously tracked for the purpose of attaching longitudinal and outcomes data to the samples in accordance with adherence to Federal patient privacy regulations and protections);
 - iii) the current status of the protocol(s) from which the specimens were collected (e.g., enrolling patients, closed to accrual but in follow-up, or closed to accrual and final analysis completed).
 - d) With regard to **annotation** of biospecimens, provide the demographic, clinical, and pathologic data elements associated with the specimens. (NOTE: During the first 6 months of the funding period, all data elements relevant to the TARGET initiative for each tissue collection must be made Cancer Data Standards Registry and Repository (caDSR) compatible.)
 - e) With regard to **standard operating, quality control, and quality assurance procedures**, indicate the following:
 - i) whether the time from cut-off of blood supply to stabilization (i.e., warm ischemia time) is documented as a data element for each specimen;
 - ii) whether there is central pathology review confirmation of diagnosis;
 - iii) whether the cellular composition of each sample is documented;
 - iv) whether the proportion of biospecimens that are greater than 80 percent tumor is documented and, if so, what fraction of the biospecimens are greater than 80 percent tumor; and
 - v) the quality control processes used to evaluate each biospecimen.
 - f) **Biological characterization** may have been performed on the biospecimens. If gene expression profiling or copy number/LOH or epigenomic evaluations have been performed on the specimens, address the following:
 - i) the technology and methods employed for the biological characterization;
 - ii) the genomic analysis tools;
 - iii) the quality control measures that were applied at all steps during the biological characterization of the specimens; and
 - iv) a succinct summary of relevant genomic, transcriptomic, and/or epigenomic findings.
 - v) NOTE: Existing characterization work must be deposited into the TARGET molecular characterization database upon receipt of the award so that it can be shared with other TARGET researchers collaborating on study of this childhood cancer. Once these existing data are published, then they will be made available through the TARGET website under the TARGET

Initiative data access policy.

- g) With regard to **additional characterization studies** for which the applicant requests support, the type of genomic characterizations and the technology platform(s) that are proposed for application to the tissue specimens should be described as should the experience of the applicant for the platforms proposed. The technology platforms must employ high throughput genomic, transcriptomic or epigenomic characterization technology. For the purposes of this FOA, a technology platform is considered validated if it has been utilized in the TCGA Pilot Project to generate genomic data or as long as a new version of a technology is documented to generate data that meet the quality standards of the earlier version used in the TCGA Pilot Project. Technologies not investigated during the TCGA Pilot Project are eligible, provided that the technology has been developed to the level of generating reproducible results in a high throughput fashion and demonstrates a clear advantage over other technologies. If alternative platforms are proposed, then validation measures should be provided. The applicant must be able to complete most of the characterization work within 6 months of the award. Molecular characterization needs to be done using appropriate Standard Operating Procedures to minimize the variability in laboratory processes, and the information relating to the procedures documented.
- h) **Data processing, deposition, and reporting standards.** Characterization data generated (raw, normal and analyzed), will be deposited to the TARGET Data Coordinating Center (DCC). The project will use the definition of data levels as defined at http://tcga-data.nci.nih.gov/docs/TCGA_Data_Primer.pdf. In addition, to ensure that the characterization data can be integrated for analysis a quality control process together with metadata annotation needs to be developed and made available to the community through the DCC. The proposal should contain a plan to address statistical and bioinformatics aspects of the analyses as well as data processing, standards for deposition to the DCC and reporting. Areas that may require particular attention include but are not limited to: sources of experimental variability, measures of confidence limits, quality control and quality assurance procedures and measures. The initial processing of the experimental data should be described.
- i) **The research project plan should discuss how the supplement will accelerate the tempo of scientific research and/or allow for job creation and retention.** In order to ensure that all expenditures in support of an administrative supplement advance the objectives of the Recovery Act, all applications must address Recovery Act justifications, including how the supplement is expected to stimulate the economy by:
- i) Enabling hiring of additional staff;
 - ii) Enabling increased hours of current part-time staff; and/or
 - iii) Recruiting for additional needed skills.