National Cancer Institute

CANCER.GOV/RECOVERY

NCI Guidelines for Administrative Supplements in Support of Early Phase Imaging in Therapeutic Clinical Trials - Cancer Imaging Program

Title of Announcement: Early Phase Imaging in Therapeutic Clinical Trials - Cancer Imaging Program

Announcement Number: n/a

Available Funds: **$6,300,000 (total costs)**

Release Date: **April 29, 2009**

Receipt Date: **May 27, 2009**

Purpose:

The Cancer Imaging Program (CIP) of the National Cancer Institute (NCI) announces a unique funding opportunity for CIP early phase clinical trials. This initiative provides funding to enhance the scientific tempo and goals of the most promising early phase imaging clinical trials through the provision of adequate resources. Specifically, in support of prospective, standardized imaging clinical trials that will, in the context of standard therapies, evaluate the preliminary efficacy of an advanced imaging agent/modality within the context of a multi-site clinical trial.

This initiative is one of several being offered by NCI to help fulfill the goals of the American Recovery and Reinvestment Act (ARRA) to help stimulate the economy through support of biomedical and behavioral research. Additional information the Recovery Act and related NIH opportunities is available through the Office of Extramural Research.

Eligibility Requirements:

This opportunity is open to NCI-sponsored grant mechanisms currently supporting imaging clinical trials being conducted under approved protocols (i.e., U01 & U10-Cooperative Group Programs, R01, P01, P30-Cancer Center Support Grants) or protocols that will be approved shortly that address early phase evaluations within the following focused scientific areas.

- Development of FLT-PET as a predictive marker in cancer therapy of solid-tumors (single-site ready for expansion to a multi-site study)
- NaF – PET as a pharmacodynamic biomarker (single-site ready for expansion to a multi-site study)
- Application of USPIOs to direct brain cancer therapy

Applicants may apply for an administrative supplement providing the following conditions are met:

- The applicant is the Principal Investigator (PI) of the original award.
- Costs for the proposed research imaging clinical trial or clinical trial support activities are not included in the original grant award.
- Protocols considered highest priority must fall into one of the following categories:
    - Any protocol "in-review" **IF** it is submitted to an IRB for approval within 90 days. Any protocol "approved" but not yet open **IF** it can be open to enrollment within 90 days.
- Applicants must have access to 'trial ready' sites. Specifically, sites that are capable of both conducting clinical trials in which there is an integral advanced imaging endpoint and qualifying for participation in such a trial through submission of appropriate core laboratory images (phantoms or patients) and site specific data required for the qualification and administration process.
- Studies must comply with the current Terms of Award (TOA) for ARRA applicants, as well as those standard TOA of NCI-sponsored clinical trials mechanisms of support.

Background/Objectives:

- **Development of FLT-PET as a predictive marker in cancer therapy of solid-tumors:**

The ability to evaluate the effectiveness of a given therapy during the treatment cycle at time point's early enough to impact treatment selection and overall management will provide definitive information that could advance both clinical management and cancer research.

Promising evidence exists that mid-therapy 18-F FDG-PET imaging may be predictive of tumor response. However, interpretation of the data is complicated by the fact that 18-F FDG-PET has a tendency to accumulate in inflammatory tissues. Preliminary 18-F FLT-PET data promises to better predict response to therapy as a superior correlate to cellular proliferation without accumulation in inflammatory tissues. Establishing the utility of a radiolabeled imaging agent that has been proposed for investigating cellular proliferation with positron emission tomography (PET) will advance existing scientific understanding of which uptake parameters of 18-F FLT best correlate with early tumor response to chemotherapy with a direct comparison to standard of care 18-F FDG-PET imaging parameters to determine their predictive value. This information will advance scientific understanding, advance clinical management of solid-tumor cancer patients and ultimately may lead to a decrease in mortality.

- **NaF – PET as a pharmacodynamic biomarker**

30-40% of prostate cancer patients will experience a relapse after local surgery or radiation therapy. Most will develop osteoblastic bony metastasis. Therapies include androgen deprivation for hormone-sensitive disease, chemotherapy for more advanced castration-resistant disease and intravenous biphosphonates. There is also a strong

constant osteolytic component to prostate cancer metastases that correlates to an elevated N-teopeptide of type I collagen excretion into the urine---a biomarker of bone turnover with prognostic ability for both SREs and death, as well as defines a sub-population that will benefit from biphosphonate therapy. Current methods of imaging bone cannot detect the therapeutic impact of existing therapies, let alone differentiate therapeutic effects between varying therapies. Standard imaging methods such as CT and MRI scans (measure via RECIST) and bone scintigraphy fall short of being useful tools to determine tumor activity and therapeutic response that would assist in treatment selection and prognostics for patients with bone metastasis.

18-F-Fluoride PET in patients undergoing treatment with various biphosphonatess will allow for the advancement of scientific understanding of the effect of the drug (effect of regional bone metabolism (Ki) and fluoride delivery (K1)) on bone metabolism and blood flow, as an indirect measure of angiogenesis. Preliminary data in breast cancer suggest that fluoride K1 and Ki can be independently and accurately measure for both normal bone and bone metastases. The ability to quantify the changes in fluoride kinetics in response to therapy is critical to better evaluate response to treatment.

Ultimately, if 18-F-Fluoride PET proves to be a useful prognostic tool in the treatment of bony metastases, sub-set populations that will and will not benefit can be indentified at time-points early enough to make a difference by saving lives and dollars.

- **Application of USPIOs to direct brain cancer therapy**

Differentiation between pseudoprogression and true tumor progression is critical in decision-making for treatment options in patients with brain tumors, so that patients can be maintained on therapies that are effective and can be switched to other therapies if a tumor is progressing. In the US, approximately 150,000 new cases of primary and metastatic brain cancers occur each year, so an improvement in evaluating treatments will improve the lives of cancer patients. Making this judgment currently can be very difficult. Distinguishing true tumor progression from pseudoprogression is crucial in management decisions for brain cancer patients, e.g. continuation or cessation of chemotherapeutic drugs such as temozolomide based on tumor response.

Additionally, since gadolinium agents should never be given to patients with impaired kidney function and this nanoparticle drug has been extensively tested and found to be safe in this population, it will provide a route to use of this agent as the sole contrast agent in the large population of patients with impaired kidney function when they are in need of MR imaging as part of their clinical care.

Trials that will assess the capability of dynamic susceptibility-weighted contrast-enhanced magnetic resonance imaging (DSC-MRI) using the ultra-small super-paramagnetic iron oxide contrast agent ferumoxytol in comparison to gadolinium-based contrast agent (GBCA) gadoteridol to distinguish these two pathologies will advance scientific understanding of ferumoxytol MRI as a useful tool in the evaluating the treatment of malignant brain tumors. Ultimately, if ferumoxytol MRI proves to be a useful tool in evaluating the treatment of malignant brain tumors, sub-set populations that are and are not responding to therapy can be identified at time-points early enough to make a difference by saving **lives and dollars.**

Allowable Costs:

Note: Only one administrative supplement for a project period of 2 years will be awarded per institution. However, multiple projects may be requested within a single administrative supplement within the focused scientific areas noted above.
Each individual applicant project budget request may not exceed $1,500,000 total costs over 2 years (24 months).

Application and Submission:

Letter of Intent **by 5pm EDT on May 6, 2009**

Application **by 5pm EDT on May 27, 2009**

Applicants are encouraged to discuss their administrative supplement request with the Branch Chief or Program Director of the Clinical Trials Branch, Cancer Imaging Program, National Cancer Institute prior to submission.

Use the PHS 398 research grant application instructions and forms (rev.11/07). Follow standard PHS 398 instructions for font size. NIH will return applications that are not submitted on the 9/04 version. For further assistance contact GrantsInfo at 301-435-0714 or via email at GrantsInfo@nih.gov

All requests must include the following:

Letter of Intent (LOI): To expedite the review process, you are requested to notify the Cancer Imaging Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute of your interest to submit an application for this administrative supplement. This notification should be provided either by email or letter no later than **May 6, 2009** to the contact listed below.

Contact Information:

Barbara A. Galen - Program Director, Cancer Imaging Program, National Cancer Institute
General Mail:
6130 Executive Blvd MSC 7412
Suite 6050
Bethesda, MD 20892-7412
Phone: (301)-594-5225

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6130 Executive Blvd.,
Suite 6047A
Rockville, MD. 20852-4910
Phone: (301) 594-5225 Fax: (301) 435-3507 Email: bgalen@mail.nih.gov

The LOI should include a descriptive title of the proposed research, collaborations, and/or collaborative agreements, the name and address of the Principal Investigator, the names of other key personnel, the participating institutions. **Note:** No signatures are required on electronic files submitted as Letters of Intent (LOI). The documents must be in MS Word Format and PC compatible. A contact phone number and email address for the project leader must be provided.

Cover letter: Request the administrative supplement and provide the name and contact information for both the Principal Investigator (PI) of the application. Please include the parent grant number and title; the amount of the requested supplement; name, title, phone, email and address of the authorized institutional official. Include the following statement: "Per supplement instructions, a detailed budget request is enclosed for the total amount of _____."

The cover letter must be signed by the authorized institutional business official of the institution.

PHS 398 Face page (PHS 398, Form Page 1):

- Item 1: The request must have the same title as the original award. Please include the number of the original grant.
- Item 2: Identify the supplement as **'*Early Phase Imaging in Therapeutic Clinical Trials – Cancer Imaging Program*'.**
- Item 3: The request must have the same PI as the original grant.
- Item 4: Request a period of 24 months of support. There must be an active original award during the entire funding period.
- Items 7A-8b: Denote the direct and total costs for the first year, as well as for the entire period of support. Total costs should not exceed those stated under Allowable Costs above.
- All remaining items on the face page should be filled out in accordance with the PHS 398 application instructions.

PHS 398 (Form page 2)

- **Note:** The project "summary" is that of the administrative supplement, not the parent grant. All other information requested on Form Page 2 should be provided.
- A brief proposal describing the project (not to exceed 5 pages), including:
- Scope of the overall project and anticipated contribution of the requested supplement:
    - Summary of the activities that were included in the parent grant that encompass those proposed in the supplemental request.
    - Purposes of the supplement, including research design/proposed scientific activities and methods and plans for data analysis.
    - Relationship of the supplement to the parent grant.
- Research project plan
    - Should include a brief description of how the supplement will accelerate the tempo of scientific research and/or allow for job creation and retention.
    - All applications must address Recovery Act justifications, including how the supplement is expected to stimulate the economy by:
        - Enabling hiring of additional staff;

- Enabling increased hours of current part-time staff;
- Procuring additional needed equipment (costing under $100,000);
- Recruiting for additional needed skills

PHS Biographical Sketch Format Page: For all new Senior/key personnel.

Human Subjects/Vertebrate Animal documentation (if applicable). Include a current Human Subjects/IRB or vertebrate animals/IACUC approval letter, if applicable. Otherwise, this letter will be required at time of funding. All appropriate IRB and IACUC approvals must be in place prior to a supplement award being made. NOTE: no significant changes in the approved use of human subjects or vertebrate animals will be considered for administrative supplements.

PHS Other Support Format Page: Documentation of active research funding (i.e., NIH, other federal, private sources) for all collaborating investigators.

Detailed Budget for Initial Budget Period [PHS 398 (O9/2004), Form pages 4-6) All applicants can request up to $1,500,000 in total costs for a 24 month period per project and must provide an itemized budget, signed by the grantee institution's business office. **Note:** Actual awards will be based on availability of funds.

PHS 398 Checklist Form: per routine

Literature Cited Provide a listing of relevant publications.

Post Award Requirements *ARRA Related Reporting.* Post award, Phase I/II Therapeutic & Imaging Clinical Trials – Cancer Imaging Program awardees will be required to provide periodic reports for use by NCI/NIH to fulfill ARRA related reporting requirements. See the following announcement NOT-OD-09-080 I for specific Terms of award and reporting requirements. Details regarding the specific content and timeframes for these reports are yet to be determined. However, the expectation is that successful grantees would fully comply with these requests. *Final Report.* Within 90 days after the conclusion of the funded activity, the applicant must submit to their respective grant Program Official a Final Progress Report that constitutes the final Phase I/II Therapeutic & Imaging Clinical Trials – Cancer Imaging Program report**.**

Submission of Administrative Supplement Request Requests for this administrative supplement must be submitted to CIP as described in the program guidelines. **This is a one-time announcement and formal applications must be received on or before May 27, 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.

Applicants are strongly encouraged to submit their administrative supplement requests electronically as an e-mail attachment in PDF format; however, the scanned application must include the signature of the AOR.

Electronic Submission If sending an electronic PDF copy, the email address is **bgalen@mail.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.

Paper Submission:

Submit a signed, typewritten original of the proposal and **five** signed, single sided photocopies, Times Roman 12" pt in one package to:

Barbara A. Galen - Program Director, Cancer Imaging Program, National Cancer Institute
General Mail:
6130 Executive Blvd MSC 7412
Suite 6050
Bethesda, MD 20892-7412
Phone: (301)-594-5225

FED-X:
6130 Executive Blvd.,
Suite 6047A
Rockville, MD. 20852-4910
Phone: (301) 594-5225 Fax: (301) 435-3507 Email: bgalen@mail.nih.gov

Review Considerations:

All proposals will undergo administrative review by NIH Program and Grants Management staff with expertise relevant to the supplement request. Key administrative review criteria include, but are not limited to:

- Is the supplement request within the scope of the original application?
- Is there sufficient time left on the original grant to complete the propose work of the supplement?
- Is the proposed budget within the allowable costs of the announcement?

Applications judged to be responsive to the intent of this initiative will also be evaluated by an ad-hoc committee of NCI staff and external experts with relevant expertise. The scientific and technical review criteria below will be used and applications will be prioritized accordingly. It is expected that successful applicants will be awarded before September 30, 2009.

- **Scientific Relevance** (adequacy of preclinical and clinical data supporting prioritization of the proposed question/approach and adequacy of the clinical data supporting the ability to administer therapy as proposed in the proposal.)

- **Study Feasibility** (e.g., likelihood of achieving the stated accrual rates and proposed study duration and of collecting and testing the data as specified in the proposal.)

- **Importance of Research Question in advancing the scientific tempo of the scientific question at hand** (e.g., is the study likely to advance scientific understanding and/or make a meaningful contribution to the management of patients in the population under study.)

- **Research Team and Environment:** (e.g., is the expertise of the research /scientific team appropriate and sufficient to accelerate the tempo of scientific research and achieve the goals of the proposed supplemental work?)

Inquiries:

Inquiries concerning the Phase I/II Therapeutic & Imaging Clinical Trials – Cancer Imaging Program funding opportunity, application requirements and supplement and application process should be addressed to:

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