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Update on Implementation of Recommendations of the Guidelines Harmonization Working Group

Clinical Trials and Translational Research Advisory Committee (CTAC)

November 9, 2011

Presenters: Toby T. Hecht, Anna T. Levy

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Guidelines Harmonization Working Group: GOALS

- Harmonize program guidelines and develop incentives to foster collaboration among all components of the clinical trials infrastructure including Cancer Centers, SPOREs, and Cooperative Groups

- Promote collaborative team science:
  - Ensure that guidelines for different clinical trials funding mechanisms are aligned
  - Eliminate redundancy and duplication while proactively encouraging collaboration

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Guidelines Harmonization Working Group: Approach

- Define collaboration
- Identify model collaborative efforts
- Examine current guidelines for clinical & translational research infrastructures and disincentives to collaboration
- Develop a vision document with recommendations
- Presented to CTAC (July 2009)
- Implementation Plan & Progress to CTAC (December 2010)

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Toward a Fully Integrated Clinical Trials System Recommendations

- Revise Guidelines
  - Describe collaborative efforts across mechanisms in specified sections of application
  - Provide meaningful guidance on what is needed to receive credit for collaboration across NCI translational and clinical trials system.
  - Credit should be reflected in priority score.
  - Incentivize trans-mechanism collaborations that will move novel interventions from pre-clinical to early clinical to phase III trials.
- SPOREs: Guidelines Updated – August 2011
- Cancer Centers, Cooperative Groups – in progress

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Implementation Updates: November 2011

Incentives to Collaboration:

- Cancer Clinical Investigator Team Leadership Award
- CTSU Harmonization Opportunity for Collaborative, Multi-center Phase II trials led by Cancer Centers & SPOREs
- Organ Site Specific Meetings
- Grand Opportunity ("GO" Grants) for Clinical & Translational Research

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How the New SPORE Guidelines have Implemented the Recommendations of the GHWG Report

- Collaborative efforts across mechanisms should be described in a specified section of the application
  - A new independent section called "Scientific Collaboration" has been established. This section includes:
    - Description of collaborative efforts that have as their goal moving studies of cancer therapeutics, biomarkers, prevention, or epidemiology for the discovery/laboratory phase to early clinical trials/studies to later phase studies and beyond
      - Within the SPORE community
      - Across NCI-supported clinical trial and translational science mechanisms
      - With other government and non-government programs
    - Description of leadership related to collaboration
    - Description of collaborative arrangements, where appropriate, such as separate grants, contracts, or CRADAs with industry, for the continued development of concepts originating in SPOREs

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How the New SPORE Guidelines have Implemented the Recommendations of the GHWG Report

- How will collaborative efforts be defined?
  - Horizontal Collaboration: Where groups work together coordinately to accomplish a set of research aims or goals on a single level, that is, in the laboratory, or at the clinical trial stage, or as a population clinical study.
  - Vertical Collaboration: Where groups work together sequentially or with some overlap, to move up the translational research pathway, that is, from discovery to preclinical development, to Phase I trials or studies, to later phase studies, and possibly to a final hand-off to a commercial company.
  - Each SPORE must demonstrate a commitment to both *horizontal* and *vertical* collaboration in completing preclinical projects and moving promising results along the pathway of translational/clinical development.

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How the New SPORE Guidelines have Implemented the Recommendations of the GHWG Report

- Credit should be reflected in the priority (overall impact) score
  - This section will receive an independent numerical score (1-9) in peer review.
  - A new paradigm for *overall impact* scoring has been established
    - Instead of the previous 70:30 ratio between scientific projects and procedural elements, reviewers are being asked to focus on the translational impact of the scientific research projects as they are supported by the cores and in the context of the program organization and capabilities, the developmental programs, and the scientific collaboration procedural sections of the SPORE.

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How the New SPORE Guidelines have Implemented the Recommendations of the GHWG Report

- Collaborative activities should be promoted between programs
  - Collaborative activity has *always* been a key feature of the SPOREs but it was reviewed as one of 7 elements in the Program Organization and Capabilities section of the application.
  - Now the Scientific Collaboration section is independently scored.
  - Most organ sites have monthly teleconferences for sharing information, data, and for initiating collaborations.
  - Institutions with several SPOREs have initiated meetings across organ sites where signaling pathways common to several organ sites, and technologies (e.g., oncolytic viruses) are shared.

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How the New SPORE Guidelines have Implemented the Recommendations of the GHWG Report

- Incentivize trans-mechanism collaborations that will move novel interventions from preclinical to early clinical to Phase III trials
  - Only Phase I and early Phase II (<100 patients) may be supported by the SPORE.
  - Hand off to Clinical Trials Cooperative Groups: For collaboration (with other SPOREs, Cancer Centers, and other NCI grant mechanisms) on randomized Phase II therapeutic trials (≥ 100 patients), SPOREs are being advised to use the appropriate NCI Disease Specific Steering Committee and their Task Forces and work together to develop clinical concepts from early SPORE trials that could move forward to the Cooperative Groups. May include correlative studies.
  - Hand off to the NCI Cancer Trials Support Unit (CTSU): An alternative, but limited collaborative opportunity for large Phase II trials is access to CTSU resources on recommendation by a Steering Committee when it is not possible to use the Cooperative Groups.
- Additional information is in the new Guidelines.

Implementation Timeline

SPORES
Tentative Timeline

Approval of New Guidelines	Amended Program Announcement	Applications Receipt	Funding
• August 2011	• September 2011	• January 2012	• FY2013
• Completed August 2011	• Completed September 2011	• Letters of intent due December 2011	

http://trp.cancer.gov/investigator_resources/docs/spore_guidelines_20120120.pdf

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Incentives for Collaboration—Organ Site Workshops—Updates

- Goal of the Workshops
  - To provide a venue for investigators working in all areas of cancer translational research to come together in small groups to focus on new goals in translational science:
    - To facilitate investigator-initiated interactions
    - To foster collaborations across grant mechanisms
    - To forge new collaborations or to consolidate ones that have just started
- Conditions
    - Must have co-chairs from more that one NCI-supported mechanism (active funding required)
    - Must have a unique collaborative purpose with follow-up
    - Must have stated objectives and outcomes aligned with the scientific priorities of the specific organ site disease
    - A similar meeting must not be scheduled in that organ site in the near future or past.
    - Outcomes must be reported by co-chairs.

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Incentives for Collaboration—Organ Site Workshops—Updates

- Summary of Initiative
  - 10 applications
  - 3 approved for support:

  - Prostate Cancer Genetics Workshop: 11/10
  - Targeting Lymphoma Metabolism and Oncogenic Pathways: 7/11
  - Novel Neoadjuvant Therapy for Bladder Cancer: 9/11

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Incentives for Collaboration—Organ Site Workshops—Updates

Prostate Cancer Genetics Workshop (Nov. 4, 2010)

William Catalona and William Isaacs: co-chairs

Purpose:

- To bring together experts in the field of prostate cancer genetics to develop a strategy to study the genetics of aggressive prostate cancer.
- To discuss consistency in specimen and data collection

Participants:

- Urologists, medical oncologists, geneticists, epidemiologists, statisticians, NCI staff
- Funded by: SPOREs, NHGRI, EDRN, SPECS, International Consortium of Prostate Cancer Genetics, Prostate Cancer Foundation, MADCap

Outcome:

- Multi-institutional collaboration for acquisition and analysis of data for a case-case association study to identify SNPs that are associated with aggressive prostate cancer
- Meeting report on workshop published in Cancer Research, May 10, 2011 DOI:10.1158/0008-5472.CAN-11-0314
- Follow-up activities: Genetics Working Group formed; 23,000 cases (enough for analysis of Caucasians and African Americans); 35 SNPs identified. Analysis ongoing.

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Grand Opportunity ("GO") Grants

A model mechanism for team science research

Toby T. Hecht
Translational Science Program

November 9, 2011

CTAC

Guideline Harmonization Working Group Report

Recommendations: Incentives for Collaboration

- Build on "GO" grants (ARRA, in April 2009) for Clinical/Translational Research
  - Evaluate the effectiveness of the "GO" grants: *"Coordination of Clinical/Translational Research across the NCI"* with the intent of developing a mechanism for long-term support of similar grants.
  - Use as a model to develop a new mechanism that will move exciting, novel, clinically applicable ideas from bench to bedside through the clinical trials system—transcending cultural barriers and research silos.

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GO Grant PI Qualifications

- Must include PIs from different institutions, with diverse expertise, who are already supported by different NCI/NIH funding mechanisms (SPOREs, P01s, R01s, U01s, N01s, Cooperative Groups, Cancer Centers, etc.) to form a team that can perform intensive, high impact, and, if possible, paradigm-shifting studies associated with clinical trials.
- Must propose translational cancer research projects of significant scope and consequence that, nonetheless, can be completed within 2 years.
- Must propose focused, evidence-based, hypothesis-driven correlative studies associated with either an ongoing clinical trial or a new (ready to proceed) clinical trial in multi-institutional settings.
- Industrial and foundation partners may participate in the research but will not receive government support for these studies.

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Results of the "GO" Initiative

32 Applications were submitted in response to this specific RFA

9 were funded (across NCI Divisions, Programs, and diseases.)

NCI Program	Investigator	Funded Grant
TRP	Goggins, Michael	Predicting pancreatic cancer responses for a PARP inhibitor-based clinical trial
CTEP	Reaman, Gregory	Targeted therapies for childhood acute lymphoblastic leukemia
CDP	Triche, Timothy	Translation of predictive rhabdomyosarcoma biomarkers into clinical practice
CDP	Curran, Walter	Refining a molecular recursive partitioning analysis model for glioblastoma
DCP	Willey, James	Validation of a multi-gene test for lung cancer risk
TRP	Trock, Bruce	Biomarker prediction of Gleason upgrading in prostate cancer
TRP	Grant, Steven	Proteasome/HDAC inhibition in leukemia/MDS; Phase I trial and correlative studies
DCP	Mallery, Susan	Clinical evaluation of a bioadhesive gel for oral cancer chemoprevention
TRP	Wolchok, Jedd	Defining the importance of immunity to NY-ESO-1 in melanoma therapy and prognosis

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“GO” grant status

- Each grant has been active for 2 years
- Each grant has been given a 1 year no-cost extension
- Progress reports are due after the end of the no-cost year
- Full evaluation is possible only after grants are completed
- A short synopsis of the work for selected grants will be given here

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Timothy Triche: Translation of Predictive Cancer Biomarkers into Clinical Practice

- Multiple PIs: T. Triche (Children's Hosp. of LA) and S. Skapek (U. Chicago)
- Institutions: USC, U. Nebraska, U. Penn, Nationwide Children's Hosp., COG
- Goal: To develop diagnostic gene expression profiles from formalin-fixed paraffin-embedded tumor tissues for the clinical classification of childhood rhabdomyosarcomas in order to determine treatment options, because conventional pathology and clinical criteria fail to predict outcome in most patients, particularly those classified as intermediate risk.
- Progress:
  - Analyzed outcome vs. 1.4 million RNA transcript expression values in 167 childhood rhabdomyosarcoma cases from COG Intermediate Risk treatment protocols to derive a multi-gene ('metagene') biomarker profile that predicts outcome better than histopathology, age, stage, and anatomical site.
  - Successfully translated a microarray-based prognostic profile extracted from 1.4 million coding and non-coding RNA features to a 78 feature metafeature on a cheaper, faster platform that works well on routine FFPE specimens.
  - NanoString platform selected as best technology to translate an RMS prognostic signature to a clinical assay. Excellent correlation between data generated at CHLA and NCH. Application for CLIA certification at both labs.
  - Will assess RNA expression in 400 corresponding FFPE tumors from COG D9803 (closed protocol, intermediate risk); refine by dropping under-performing RNAs.
  - Prospective validation on RMS patients in COG low, intermediate and high risk therapy protocols.

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Trock: Biomarker Prediction of Gleason Upgrading

- Institutions: JHU, FHCRC, Mayo Clinic, MSKCC, UCLA, UT San Antonio, U. Mich., Harvard.
- Goal: To develop a new biomarker-based diagnostic model to improve the diagnostic accuracy of prostate biopsies—a critical need to increase the safety of patients choosing active surveillance and who are determined to be Gleason Grade 3, but who may be Gleason 4. Biomarkers include: molecular indices of chromosome instability, mitotic spindle checkpoint integrity, centrosome function, proliferation, hypoxia, and epigenetic/DNA damage response. A predictive model will be proposed and validated in an independent cohort.
- Progress:
- 200 radical prostatectomy specimens (Gleason scores 3+3, 3+4, and 4+3) have been accessioned and 106 of biopsy cores (GS3+3) with corresponding prostatectomies tissues (GS 3+3 and GS 3+4 or 4+3) have been obtained. Tissue microarrays are complete. Biomarker analysis will be performed in 5 laboratories: MSKCC, Mayo, FHCRC, UCLA, JHU to find markers that discriminate Gleason grade 3 from Gleason grade 4.
- Biomarker assay optimization is complete. Analysis is continuing and will be completed by the end of the no-cost extension.

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Steven Grant: Proteasome/HDAC inhibition in Leukemia/MDS; Phase I Trial and Correlative Studies

- Institutions: Massey Cancer Center (VCU); MD Anderson Cancer Center
- Goal: Study the antitumor activity of the combination of a pan-HDAC inhibitor (belinostat) and a proteasome inhibitor (bortezomib) (drugs that have little or no activity as single agents) in a clinical trial of refractory AML, high risk MDS, CML-blast crisis, and ALL patients. To perform correlative PD studies, in bone marrow and/or peripheral blood, on NF-**κB activation, down**-regulation of NF-**κB**-dependent proteins XIAP and Bcl-xL, up-regulation of pro-apoptotic protein Bim, and inhibition of 20S proteasome activity.
- Progress:
  - Clinical trial agreement and IND approval obtained.
  - Clinical trial opened in May 2010. 16 patients enrolled to 3 dose levels; ready to escalate to 4th dose level. No DLTs encountered so far.
  - Responses: 1 CR (dose level 1); 4 stable disease; 7 progressive disease
- Obstacles:
  - Patients have not met the criteria for correlative studies ($\geq$ 65% bone marrow or peripheral blood blasts) or have refused a second post-treatment bone marrow sample.
- Publications:
  - Blood (Suppl.) Am Soc Hematology 117, 2011
  - J. Biol Chem 286: 34036-34050, 2011.
  - Oncotarget 2: 284-6, 2011.

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Susan Mallery: Clinical Evaluation of a Bioadhesive Gel of Oral Cancer Chemoprevention

- Institutions: OSU (Colleges of Dentistry, Medicine, and Pharmacy), Med. Col. Wisconsin
- Goal: To extend previous work to a prevention trial with freeze-dried black raspberry (BRB) bioadhesive gel in dysplastic oral lesions which showed that 1/3 of participants were high responders (to anthocyanins in the preparation) and suggested that patient-specific differences in target tissue absorption, metabolic activation, and local retention of the BRB constituents affected chemopreventive response.
- Progress:
  - Assays have been established which identify the pharmacokinetic parameters and anthocyanin bioactivation pathways that are active in the human oral mucosa.
  - IND approved.
  - Study with normal volunteers support participant differences in gel absorption, distribution, and local retention of anthocyanins in the oral mucosa.
  - Oral cancer chemoprevention trial is proceeding; 16 patients accrued; studies to determine LOH indices (p53, p16, and FHIT) and p16 methylation (comparing pre to post tissues) are ongoing. Histologic and clinical results are promising.
  - 10 additional patients are in various stages of the study at this time.
  - One patient's dysplastic lesion completely resolved clinically; his light microscopic diagnosis decreased two histologic grades.
- Publications: Cancer Prev Res (Phila). 2011 Aug;4(8):1209-21. Epub 2011 May 10.

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Wolchok: Defining the Importance of Immunity to NY-ESO-1 in Melanoma Therapy and Prognosis

- Institutions: MSKCC, Yale, Moffitt Cancer Center, Washington U., Ludwig Institute, U. Nevada, U. New Mexico, Blumenthal Cancer Center (NC).
- Goal: To establish the importance of NY-ESO-1 as a biomarker in the immunotherapy of metastatic melanoma with anti-CTLA4 (blocking antibody).
- Progress:
- All patients treated with ipilimumab (ipi) in the adjuvant setting have been accrued.
- In studies with advanced melanoma patients treated with ipi, patients with an NY-ESO-1 antibody response experienced more frequent clinical benefit at week 24 than seronegative patients.
- Within a subset of seropositive patients, the induction in patients of specific CD8+ T cell responses to NY-ESO-1 correlated with a better clinical response compared with patients who did not have specific CD8+ T cells.
- B and T responses to NY-ESO-1 may have predictive value of ipi treatment.

- Publications: Proc. Natl. Acad. Sci. 108, 16723, 2011.

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The "GO" Concept for Team Science

- There are few, if any, mechanisms that *require* collaboration across institutions and across methods of grant/contract support.
- Collaboration is essential for studies of rare cancers, and those that are underrepresented in the NCI portfolio.
- Funding mechanisms do not commonly support *both* clinical trials and correlative studies.
- Studies could be completed in 3 years—less than the average R01.
- Better than competitive supplements/revisions:
  - Competitive revisions are appropriate for grants with enough years left in their funding period.
  - Many collaborators are out of synchrony in their funding periods.
  - Investigators who are co-PIs (with critical expertise) could not apply.
- Should the NCI consider using this type of grant mechanism in the future to encourage team science?

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