



TRWG Implementation Update

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National Cancer Institute

15 Initiatives with Implementation Plans



Optimize and enhance NCI functions that are critical for translational research

- **Coordinated Management**

- Integrated NCI management
- Budget designation
- TR coding
- Prioritization process

- **Tailored Funding**

- Modify TR award mechanisms
- Improve investigator-initiated TR awards
- STRAP awards
- Academic/industrial collaborations

- **Operational Effectiveness**

- Project management
- Core services coordination
- Enhance biorepositories
- Improve IP negotiations
- Enhance foundation/advocate group collaborations
- Enhance training/incentives

Develop a new process to accelerate translational cancer research

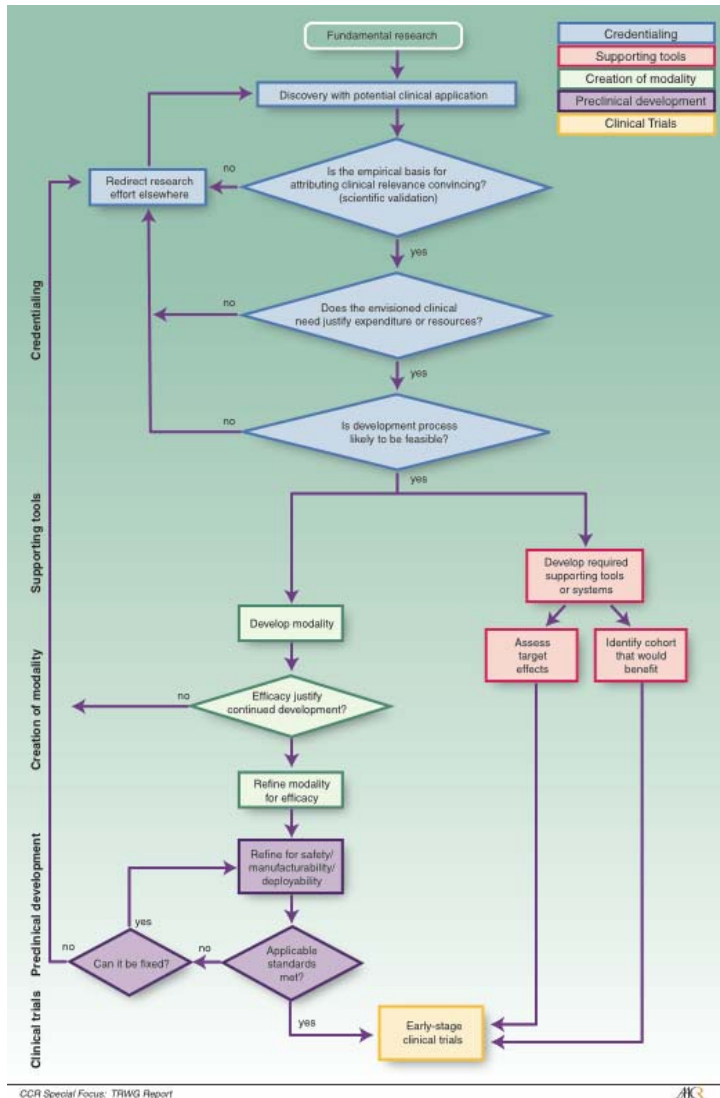


The Challenge of Early Translation

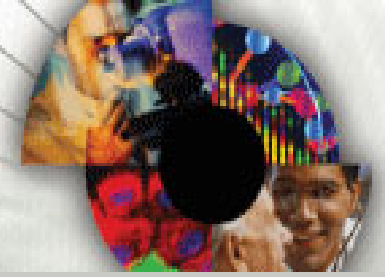


How can we best assure that:

- The most promising concepts enter the developmental pathways?
- Concepts that do enter advance to the clinic or to productive failure?
- Progress is as rapid, efficient and effective as possible?



TRWG Recommended Process for Accelerating Translational Research



Select several projects/year that are “ripe” for translation

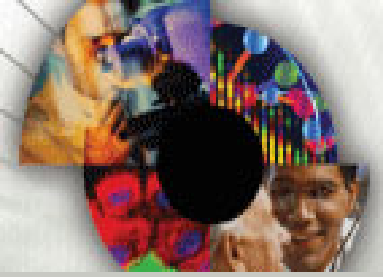
New Translational Research Acceleration Process:

- Gather information on translational opportunities
- Prioritize translational research opportunities
- Develop a funding plan to accelerate prioritized opportunities

New Translational Research Acceleration Process DOES NOT:

- Impact Discovery Research
 - Replace existing infrastructure and/or mechanisms for translational or clinical research

Implementing the TRWG Process for Accelerating Translational Research



New Translational Research Acceleration Process:

- **STEP 1: Gather information** on translational opportunities
- **STEP 2: Prioritize** translational research opportunities
- **STEP 3: Develop a *fund*ing plan**

In February, 2008, CTAC asked the NCI to demonstrate that there were sufficient translational research opportunities to warrant developing a new translational research prioritization process and funding strategy

Step 1: Gather Information



NCI Translates *NCI-wide Translational Science Meeting*

- **November 7-9, 2008, Washington, DC**
- **Coordinating Center for Clinical Trials,**
 - Sheila Prindiville, M.D., M.P.H.
 - Lynn Matrisian, Ph.D.
- **513 abstracts**
 - Grants/PIs selected by NCI Program Staff
- **800 invited participants**
 - NCI-funded scientists/clinicians
 - Advocates
 - NCI staff

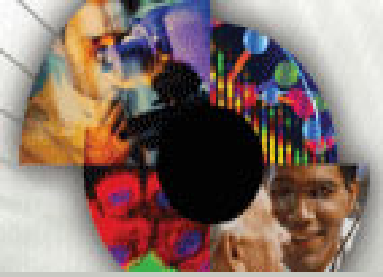
Purpose and Charge



To Accelerate Translational Cancer Research

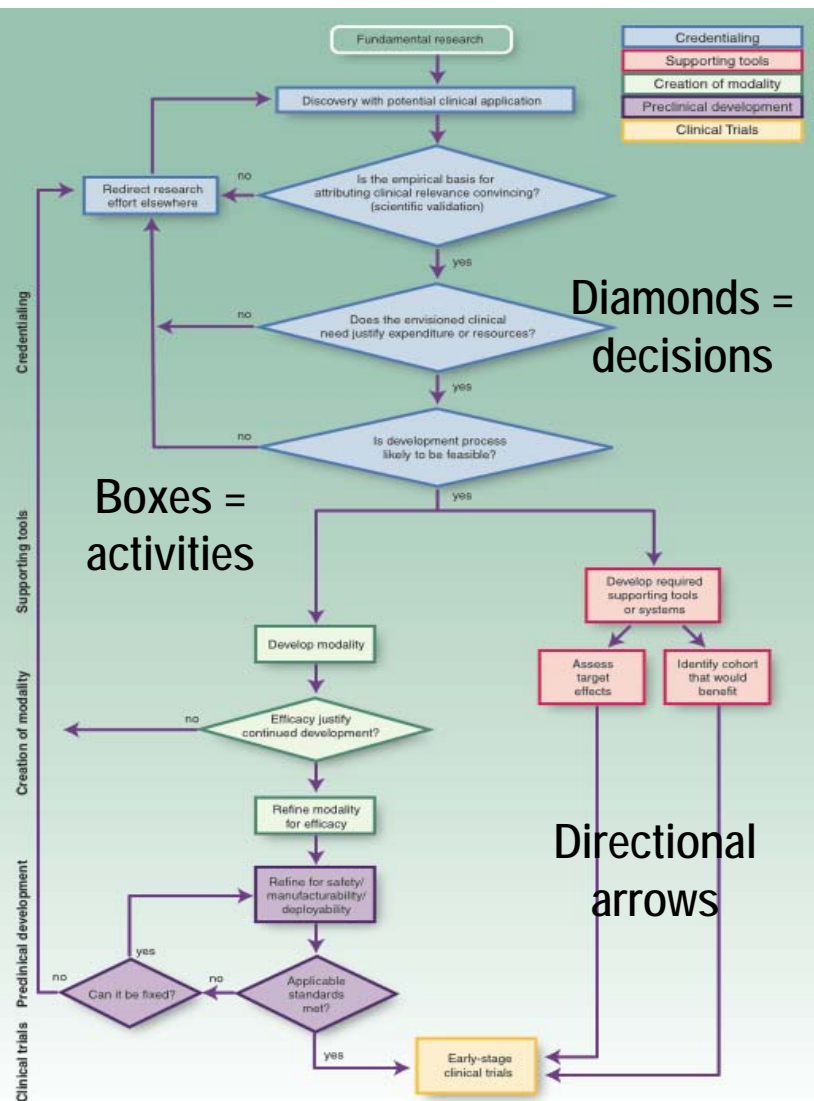
- Convene experts for a trans-NCI translational science discussion
 - Showcase NCI-supported translational research
 - Expand range of collaborations and interactions between NCI-supported investigators and mechanisms
- Explore potential for translational research prioritization and acceleration as recommended by the Translational Research Working Group (TRWG)
 - Enhance knowledge and use of the TRWG pathways
 - Discuss example “Translational Research Opportunities” and the information necessary to evaluate and prioritize translational research projects
 - Demonstrate that there are compelling translational research opportunities that warrant acceleration

Implementation Progress



1. Enhance knowledge and use of the TRWG pathways (*NCI Translates*)
2. Discuss example “Translational Research Opportunities” and the information necessary to evaluate and prioritize translational research projects (*NCI Translates*)
3. Demonstrate that there are compelling translational research opportunities warranting acceleration (*NCI Translates*)
4. Develop and initiate prioritization process
5. Develop funding and project management process for project acceleration

Organizational principle: *Pathways to Clinical Goals*



Assessment Modalities

(for screening, diagnosis, prognosis, or prediction)

- **Biospecimen-based** (protocols, reagents, instruments)
- **Image-based** (agents, techniques)

Intervention Modalities

(treatment and prevention)

- **Agents** (drugs or biologics)
- **Immune response modifiers** (vaccines, cytokines)
- **Interventive devices** (radiation, surgical devices)
- **Lifestyle alterations** (exercise, nutrition)

5 Domains per Pathway

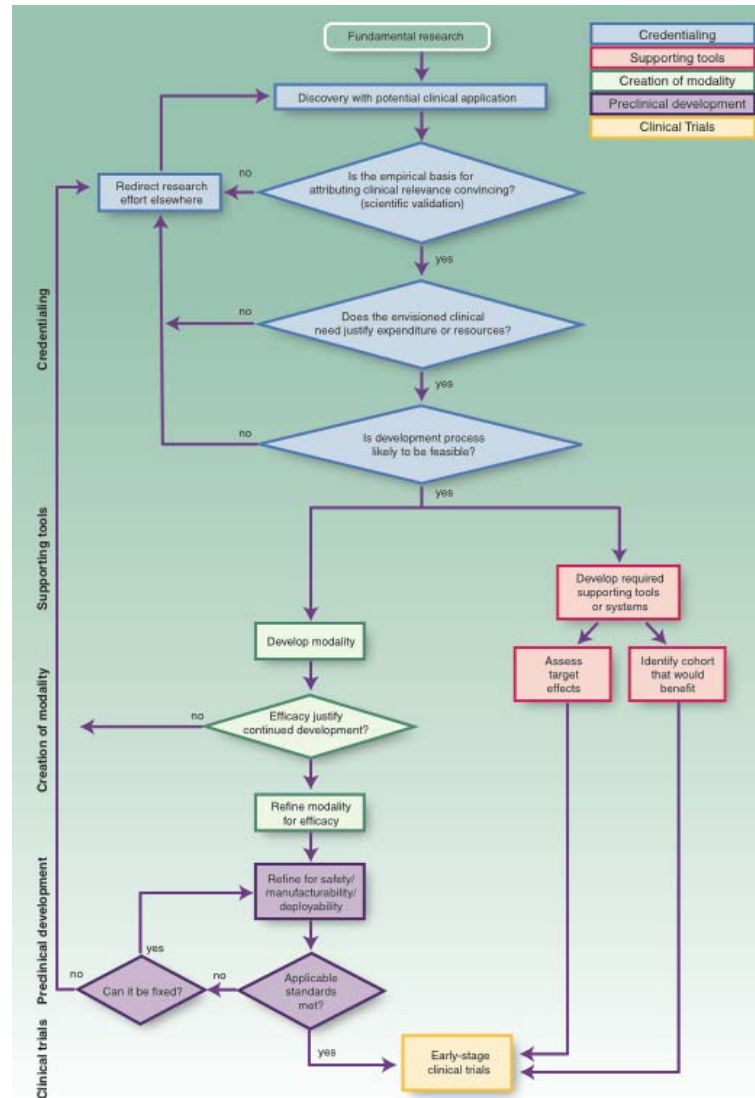


Credentialing

assessment of scientific validity, clinical need & feasibility

Creation of Modality

e.g., medicinal chemistry, multi-lab validation



Supporting Tools

e.g., animal model, cohort, specimen repository

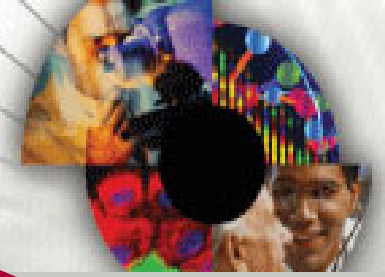
Preclinical Development

e.g., toxicology, test on phantoms

Early Phase Clinical Trials

Clinical Cancer Research

Sept 15th, 2008



SPECIAL FOCUS

The Translational Research Pathways: Introduction and Overview
Ernest T. Hawk, Lynn M. Mamasian,¹ Will Joyce Vree,² Judith Habalala,³ and Owen G...

Abstract The Translational Research Working Group (TRWG) was convened as a national initiative to evaluate the current status of the National Cancer Institute's investment in translational research and to propose a new model for translational research. The TRWG was organized to address the challenges of translational research as a set of developmental processes or pathways focused on various clinical goals, with an individual's cancer-related (or modeled) and top-addressing health status (stage or baseline) as the starting point.

Background Advances in... Improve... and...

clincancerres.aacrjournals.org

CCR 14: 5663-5713 (2008)

Abstract Coding



Abstracts were coded to pathways, populations, and organ sites

Step 1: TRWG Developmental Pathways

Please select at least **one** below.

	ASSESSMENT		INTERVENTIVE			
	Biospecimen	Imaging	Agents	Immune	Devices	Behavioral
Credentialed discovery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Supporting Tools	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Creation of Modality	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Preclinical development	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ph/II Clinical trials	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Step 2: Select Your Population

Please select at least **one** below.

- At Risk
- Early disease
- Late disease
- Pediatric
- Minorities & Underserved

Step 3: Select Your Organ Sites

Please select at least **one** below.

- Breast
- Brain
- Colorectal
- Gastrointestinal (other than CR)
- Genitourinary (other than prostate)
- Gynecologic
- Head and Neck
- Hematopoietic
- Lung
- Prostate
- Skin
- Rare (Sarcoma, etc)
- All or most organ sites

Program Committee



Placed abstracts into Poster Discussion Sessions

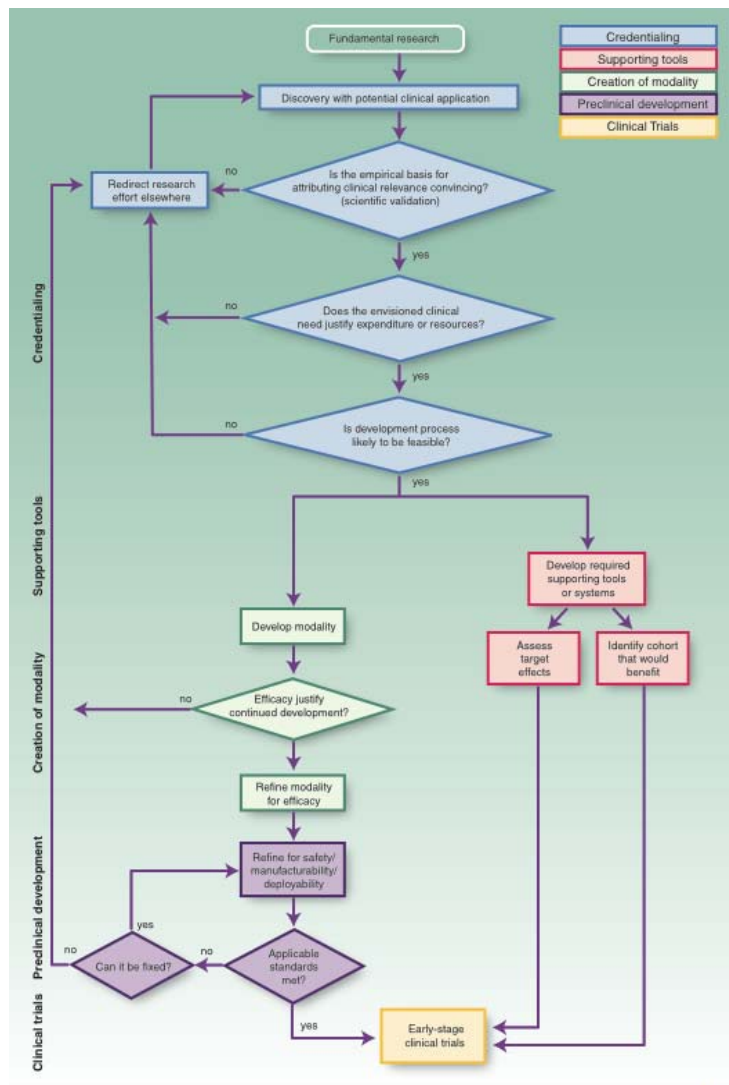


25 Poster Discussion Sessions



- **Agents**
 - Biochemical Targets & Drug screening
 - Stem Cells, Gene Expression, & Epigenetics
 - Drug Delivery & Gene Therapy
 - Integrative Biology
 - Prostate Cancer
 - Pancreatic and Breast
 - Hematological Malignancies
 - Head/Neck & Lung
- **Biomarkers**
 - “Omic “ Technologies
 - Prognostic & Predictive
 - Early Detection
 - Breast Cancer
 - Prostate & Bladder Cancers
 - Esophagus, Colon & Liver
 - Lung Cancer
 - Hematological & Pediatric Cancers
- **Imaging**
 - Early Detection
 - Imaging & Therapeutics
- **Immune Response Modifiers**
 - Antibodies, Cytokines, & Viruses
 - Vaccines
 - Cellular Therapies
- **Interventive Devices**
 - Ionizing & Non-ionizing radiation
 - Devices for surgical ablation & biopsy
- **Lifestyle Alterations**
 - Dietary components
 - Biobehavioral mechanisms

TRWG Pathways to Clinical Goals



Uses of the TRWG Pathways:

- Research project management
- Research program management
- Coordination of research efforts
- Teaching

Implementation Progress



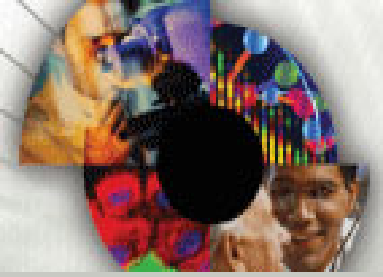
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Translational Research Opportunity



- Focuses on a ***clinical goal***
 - Develops a modality (drug, device, biomarker, etc) that can be tested in people
 - Identifies the population/cancer type in which it is tested
- Describes ***scientific validity***
- Details ***clinical need***
- Provides information on ***feasibility***
 - Identifies individuals/research groups with projects or capabilities relevant to pathway domains

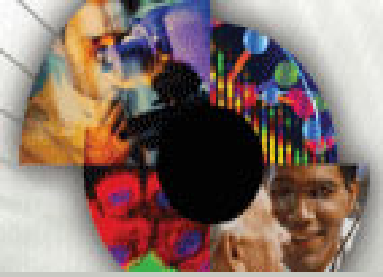
Information Guide to Translational Research Opportunities



Translational Research Opportunity Information Guides

- Pathway-specific (6 Information Guides)
- Provided to all NCI Translates Participants
- Available at <http://ncitranslates.nci.nih.gov>
 - Provides a strawman template for information required for Translational Research Opportunities

Information Guide to Translational Research Opportunities

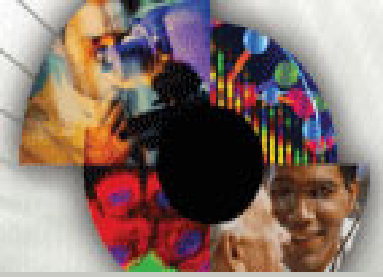


1. Informative Title of Opportunity

Define the opportunity concisely, identifying the modality to be created and the primary clinical target.

Example: “Proteasome inhibitor for the treatment of multiple myeloma”

Information Guide to Translational Research Opportunities



2. Scientific basis of the proposed opportunity

- 3 – 5 key points (1-3 sentence summaries)
- Type of evidence
 - Epidemiologic
 - Expression
 - Cell culture
 - Animal model
 - Clinical
 - Other
- Literature cited where possible



Information Guide to Translational Research Opportunities

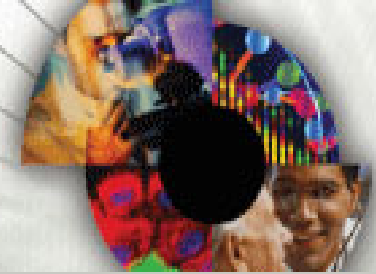


3. Importance of clinical or public health need

- Annual incidence of condition addressed by this modality (U.S.)
- Five year survival rate
- Alternatives
 - Currently available
 - In development
- Other factors



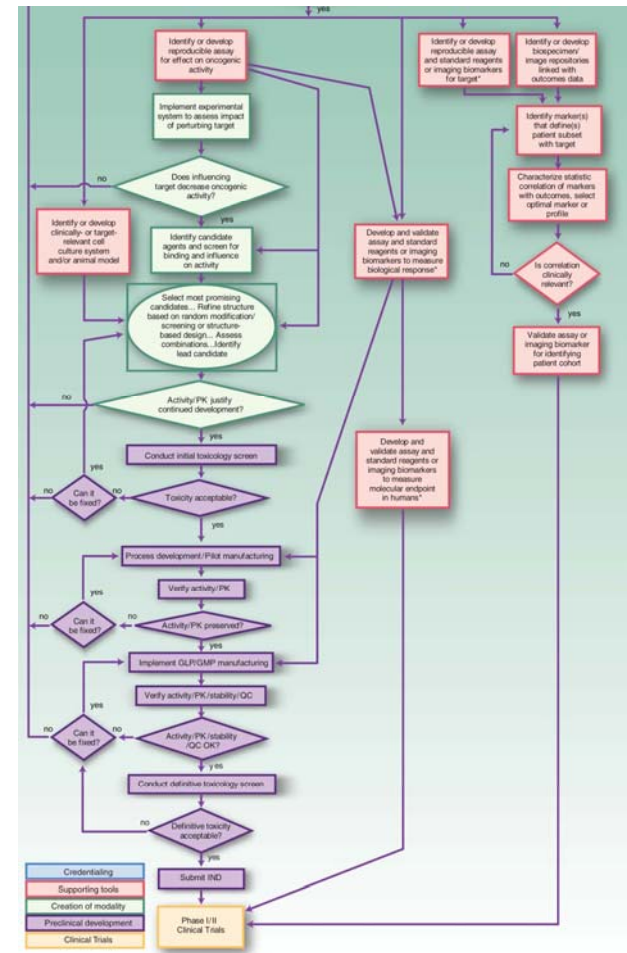
Information Guide to Translational Research Opportunities



Feasibility = the capability to perform every step in the pathway

3rd pathway diamond

Is it feasible to identify/develop an agent against the target?



Information Guide to Translational Research Opportunities



4. Activities and resources needed to realize the Opportunity

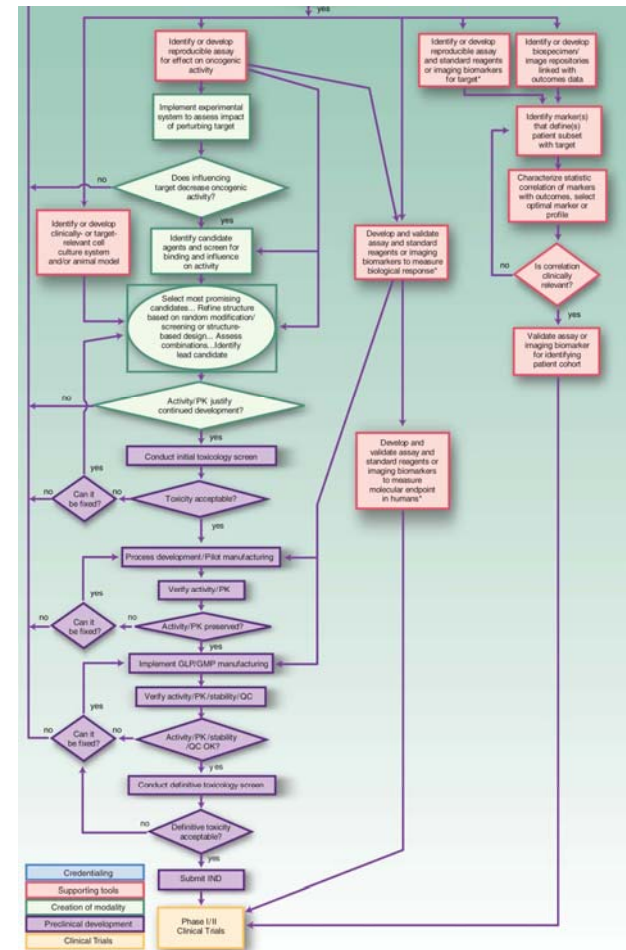
SUPPORTING TOOLS

CREATION OF MODALITY

PRECLINICAL DEVELOPMENT

CLINICAL TRIALS

Every box in each domain!



Information Guide to Translational Research Opportunities



4. Activities and resources needed to realize the proposed opportunity (cont.)

- Title or brief description of specific resource
- Status of activity/resource
 - completed/available
 - minimal effort needed to complete
 - substantial effort needed to complete
 - activity or resource not necessary
- Specific individuals, laboratories, companies, etc. capable of providing the required resource or conducting the necessary studies or developmental activities

Information Guide to Translational Research Opportunities



5. Suitability for NCI investment

- Estimated years required to advance modality to early stage clinical trials
- Likelihood that industry will develop the modality without NCI investment
- Likelihood that industry will commercialize the modality if NCI demonstrates preliminary efficacy in early stage trials
- Likelihood that the modality will be incorporated into routine clinical practice if shown to be efficacious

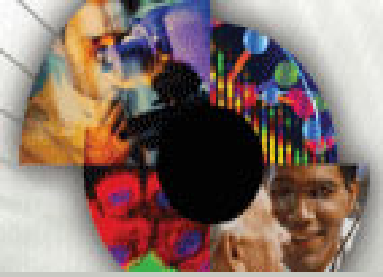
Information Guide to Translational Research Opportunities



5. Suitability for NCI investment (cont.)

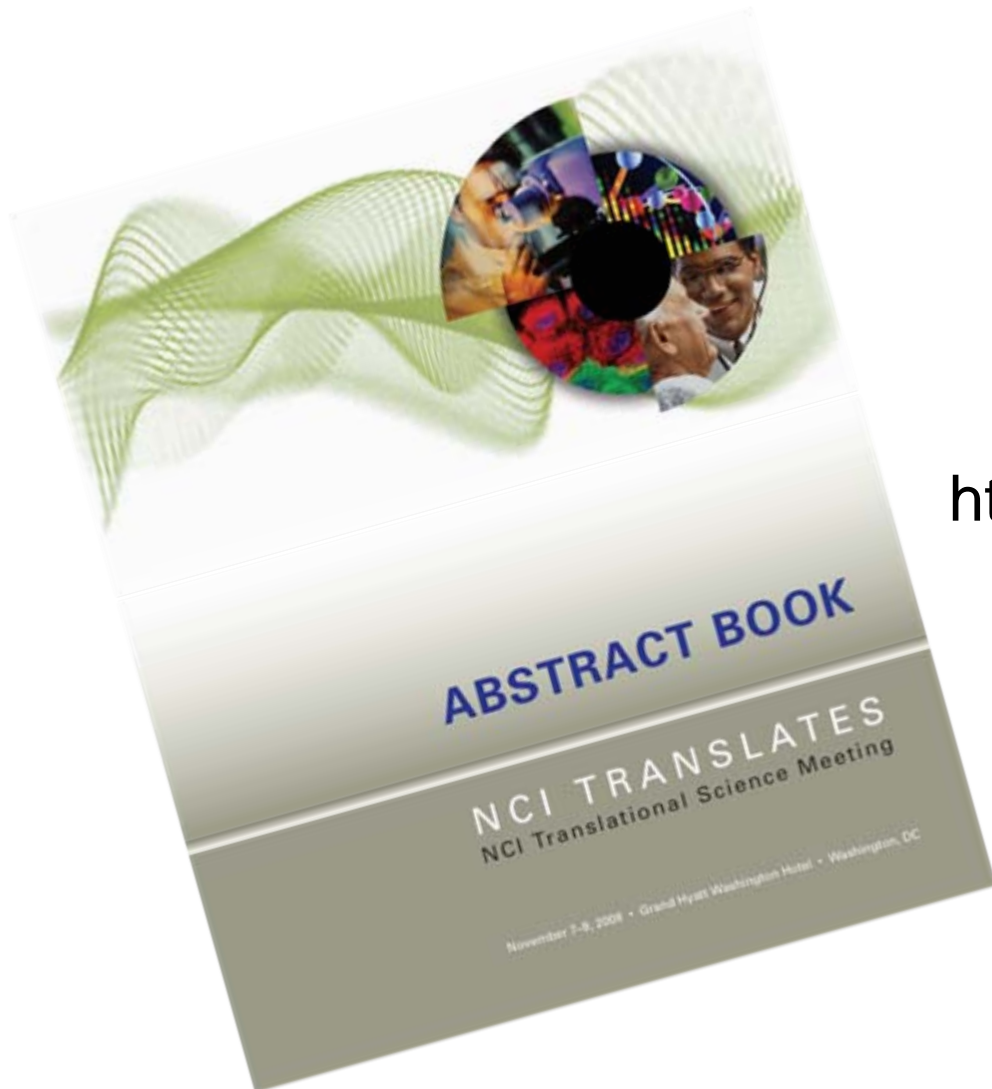
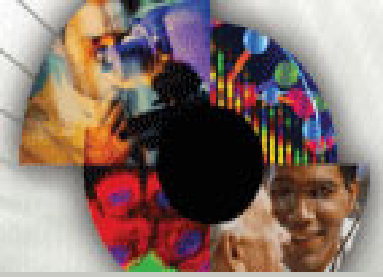
- Collaboration among investigators in academia and/or government important for timely and efficient progress
- Collaboration with industry or foundation-driven research initiatives
- Industry financial and/or infrastructure resources
- Financial support from foundations or other philanthropic sources

Implementation Progress



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Compelling Opportunities

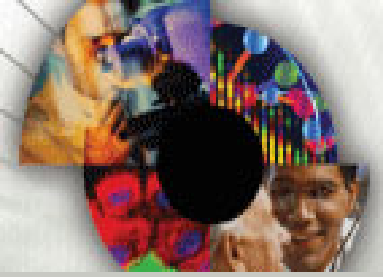


513 abstracts

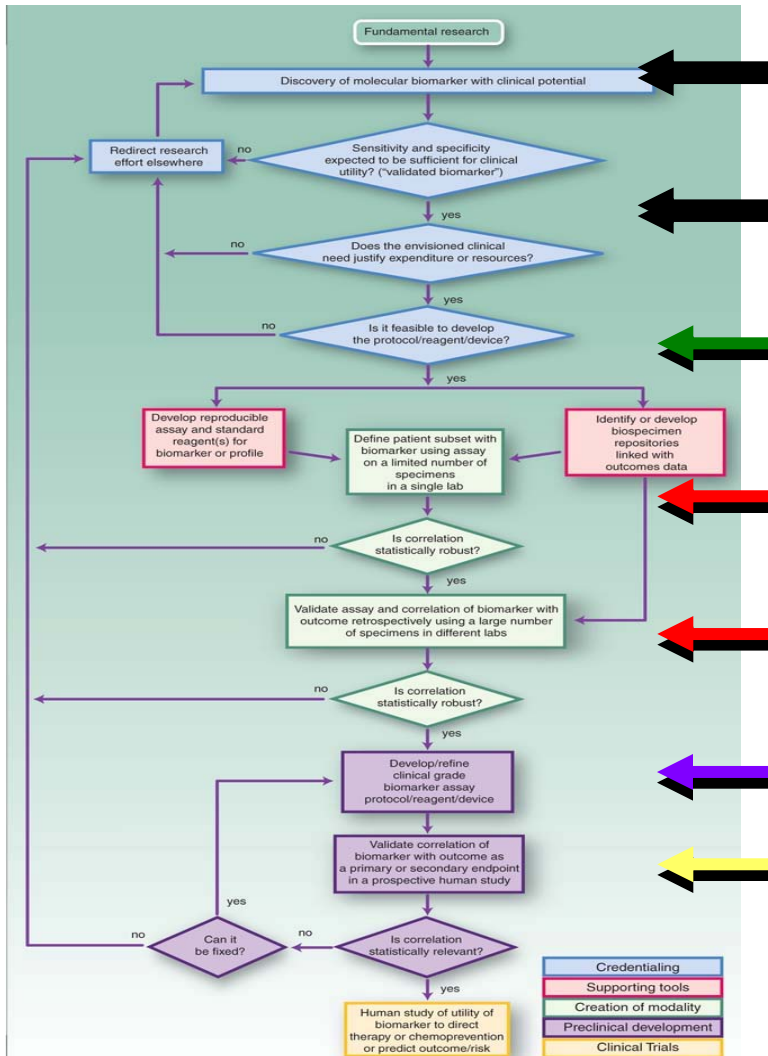
<http://ncitranslates.nci.nih.gov>

Poster session tab

Poster Discussion Sessions



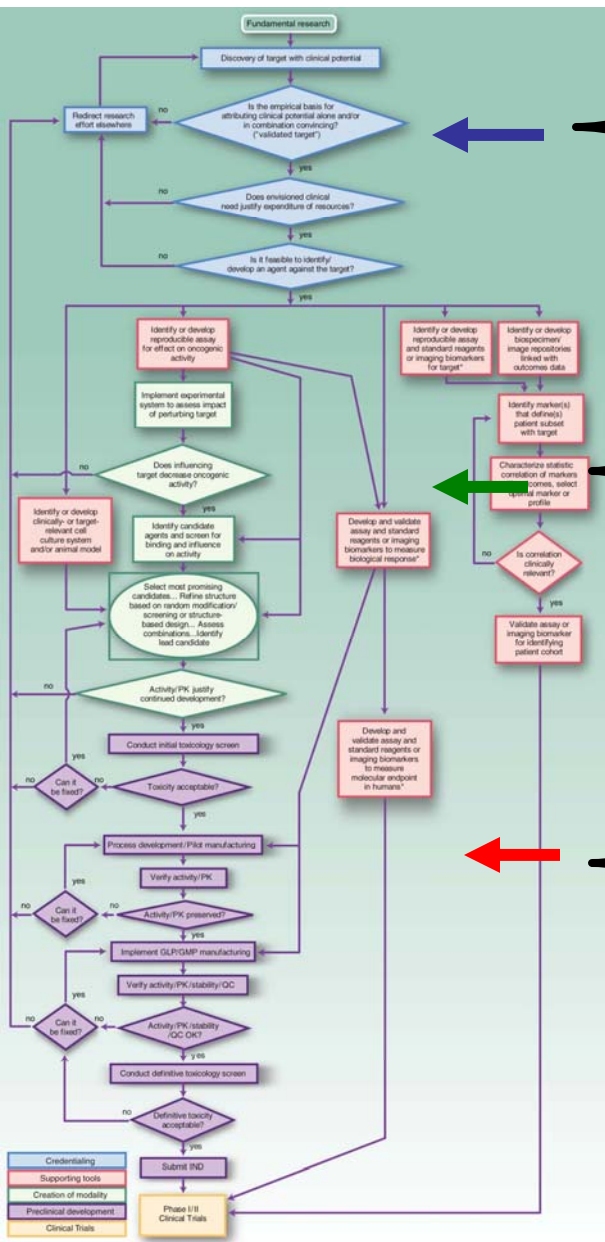
Compelling Opportunities



Example Opportunities:

- presented by Poster Discussion Session Co-chairs based on session abstracts
- educated how abstracts could coalesce into a translational research opportunity
- NOT prioritized
- 1 example/pathway presented at closing session

Agents: Targeting the Wnt pathway

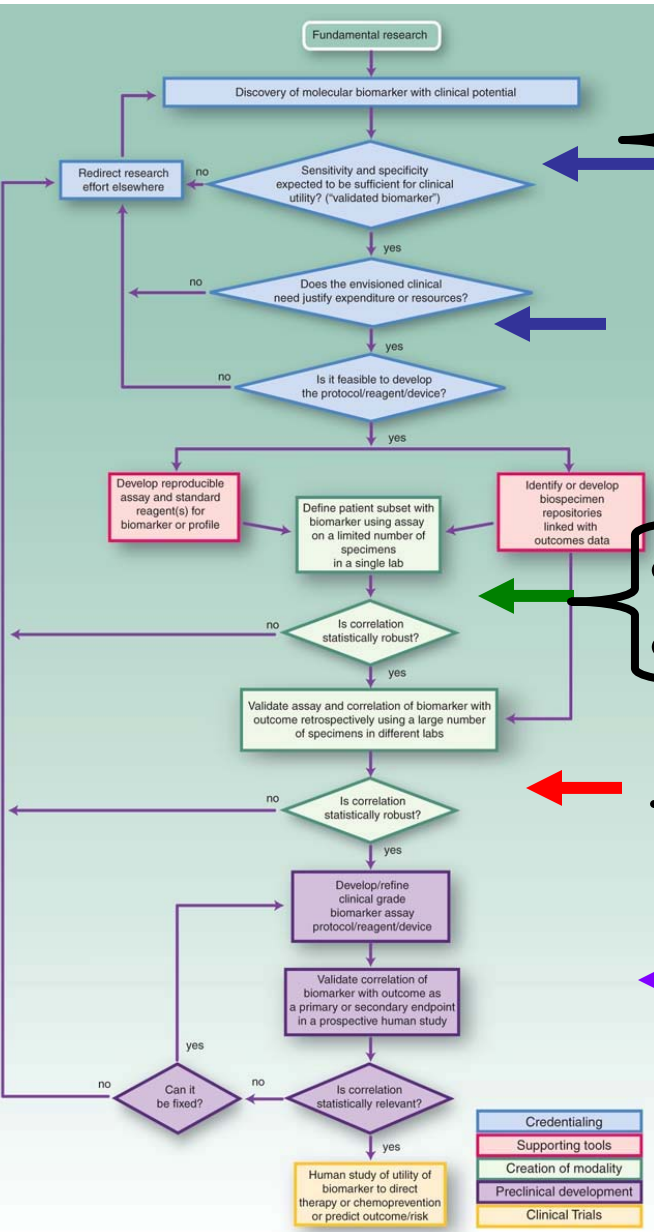


- Stem cell regulatory network
- Extensive evidence for causal role in CRC and others
- VU-WS30 (anti-helminth) identified in Xenopus egg assay to block Axin degradation & prevent Wnt signaling
- Modifications required to overcome limited systemic access
- Inhibits β -catenin induced proliferation of colon cancer cell lines
- Mouse models of CRC available
- Assays for Wnt signaling needed
- Tox, etc, needed on modified agent
- CRC for initial trials

Agents Pathway Opportunity Examples

- PI3Kinase inhibition in malignant glioblastoma
- C-VISA-BikDD proapoptotic gene therapy in pancreatic cancer
- Targeting the Wnt pathway in colorectal cancer
- FLT3 Inhibitors in combination with established chemotherapeutics for the treatment of FLT3mut Acute Leukemias
- Targeting the Hedgehog pathway in pancreatic cancer
- PMSA-targeted prodrug for the treatment of prostate cancer
- Anti-CCL2 in metastatic prostate cancer
- EGFR Inhibition in Combination with Molecular Targeting of Alternate Signaling Pathway(s) in head and neck cancer
- Green tea to reduce the risk of lung cancer
- RalGTPase inhibition in the treatment of pancreatic cancer
- Combined inhibition of the HER network to overcome resistance to HER2-targeted therapy
- Src as a successful target for solid tumors
- Molecular Identification and Preventive Elimination of Precursors of Triple Negative Breast Cancer
- Rationale targeted therapies in multiple myeloma
- Targeting Oncogenic Ras in Myeloid Malignancies

Biospecimen: Biomarkers for DCIS progression



- 14-3-3ζ in 40% BrCa, corr with survival
- Rb pathway markers Ki67, p16, COX2 corr with recurrence of DCIS as BrCa

5-10% of DCIS lesions progress to invasive cancer within 5 years, most women treated aggressively

- IHC techniques for all 4 markers available
- Independent lab validation needed

- Few small cohorts available
- Assay validation required

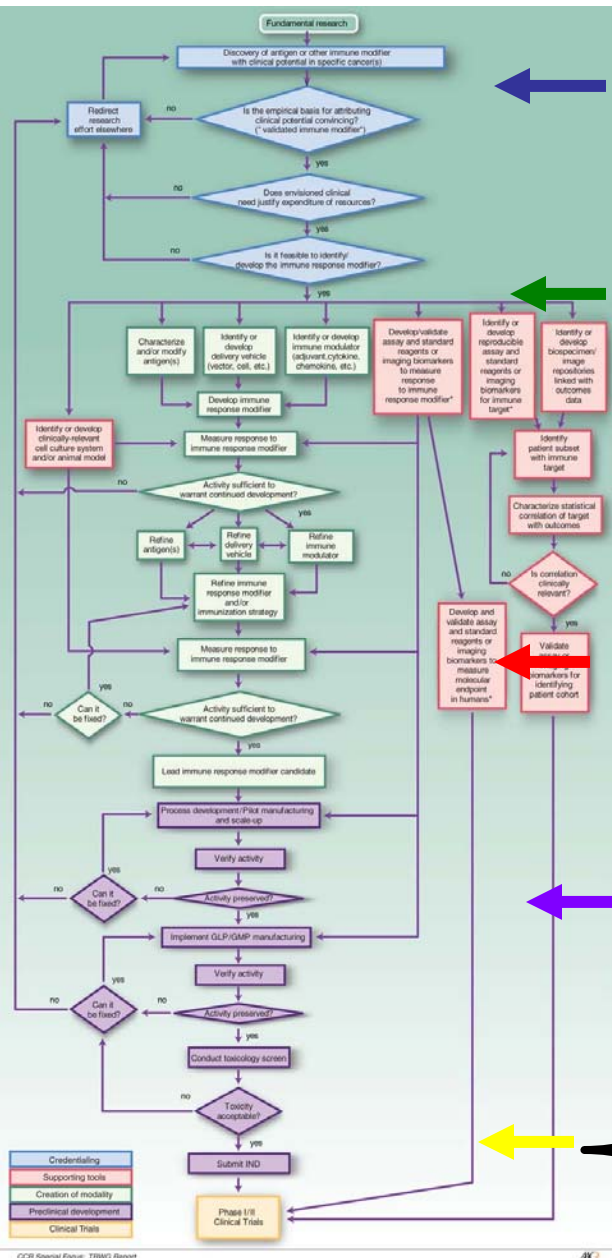
• Prospective studies required

• Large scale, long term effort required

Biospecimens Pathway Opportunity Examples

- Flt3/ITD biomarkers for risk and target identification in pediatric AML
- Multi-gene classifier predicts for MRD+ (EFS surrogate) and rhabdomyosarcoma risk class
- A Tissue Biomarker Panel Predicting Systemic Progression after PSA Recurrence Post-definitive Prostate Cancer Therapy
- NMP22 BladderChek in bladder cancer
- Development of a Predictive biomarker panel for patients undergoing neoadjuvant aromatase inhibitor therapy for ER+ breast cancer
- New molecular subsets of GBM: A TCGA Cancer Genome Project
- Detection of Circulating Tumor Cells in Pts Treated for Metastatic Breast CA
- Markers to predict subsequent events in women with early breast cancer
- Biomarkers for risk stratification of prostate cancer
- Development of a predictive biomarker panel for patients undergoing neoadjuvant aromatase inhibitor therapy for ER+ breast cancer
- Genomic and epigenomic profiling for early detection of colorectal cancer
- Genomic and epigenomic profiling of Barrett's esophagus and esophageal adenocarcinoma
- RRM1 & ERCC1 as biomarkers of treatment response in NSCLC
- Personalized Medicine for Lung Cancer
- Defining subgroups of melanoma and determining optimal targeted therapy

Immunotherapy: WT-1 vaccine in AML and ovarian cancer



- oncogenic protein
- expressed at high levels in AML & OvCa
- Peptide antigen
- Delivery vehicle w/ CpG&MPL adjuvants
- IL-7 and anti-PD1 as immune modulators
- T-cell response assay available
- RT-PCR measure WT1 in blood/BM
- Imaging for T cells at tumor site
- Cell/animal models available
- WT-1 expression assay required
- WT-1 peptides can be manufactured
- Adjuvants, modulators can be manufd
- Iterative Phase I with marker endpoints
- Phase II when immunity achieved in Ph I
- Network of preselected sites

Immune Response Modifier Pathway Opportunity Examples

- Targeting Dendritic Cells via Antibodies for Cancer Therapy
- Anti-Her2 and IL-12 therapy for metastatic breast cancer
- Mesothelin-based Immunotherapy in Pancreatic Cancer
- Adoptive T-cell transfer therapy
- WT1 vaccine in minimal residual disease in WT1+ solid tumors
- Muc1 as a prophylactic vaccine

Imaging: PSCA imaging of prostate cancer

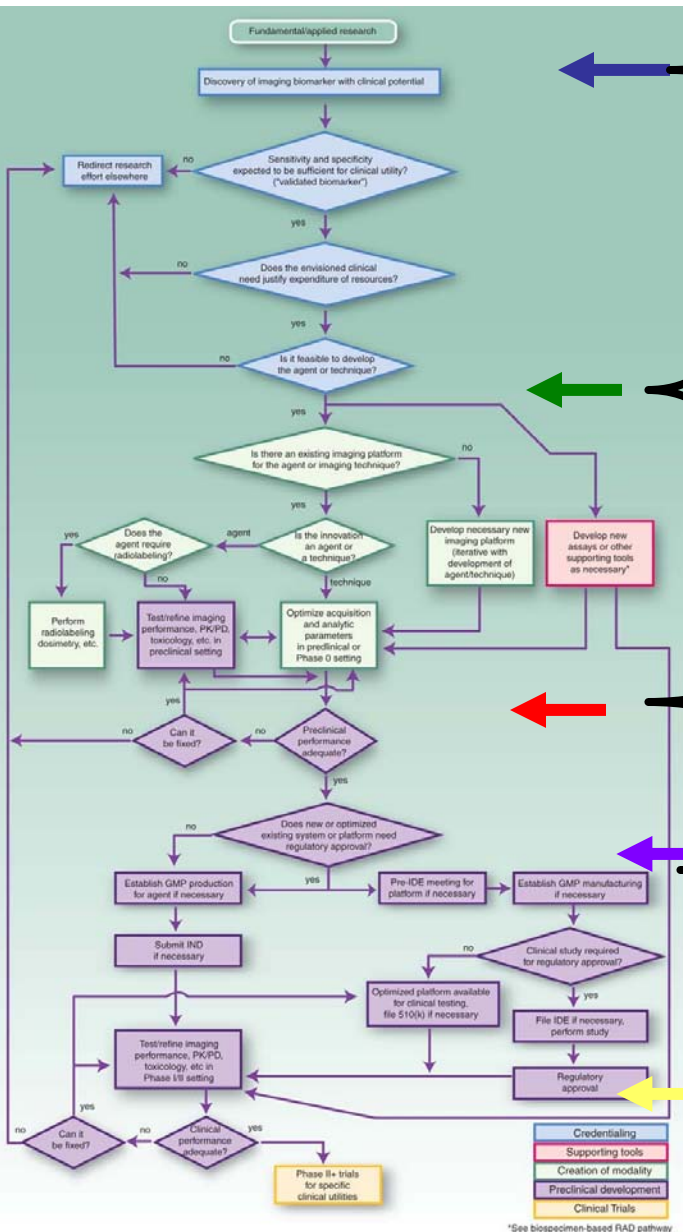
Prostate-specific glycoprotein expressed by normal and cancer cells

- Engineered antibody fragments labeled for PET or SPECT imaging
- Imaging platform exists, co-development not required
- Imaging protocols and Imaging acquisition standardized

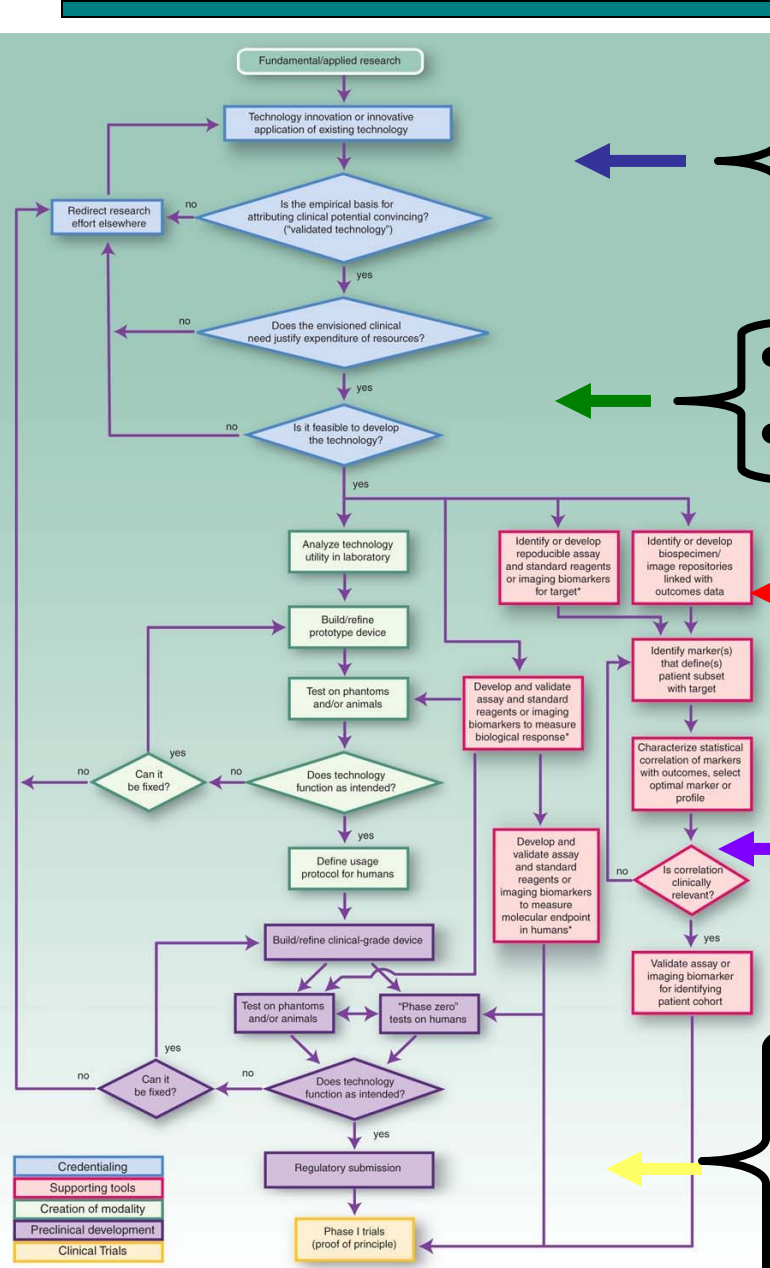
- Tracer kinetic models needed
- Physical phantoms needed

- GMP/GLP of Ab fragments needed
- Dosimetry and toxicology needed

- Metastatic prostate cancer
- Pancreatic cancer addtl possibility
- American College of Radiology Imaging Network

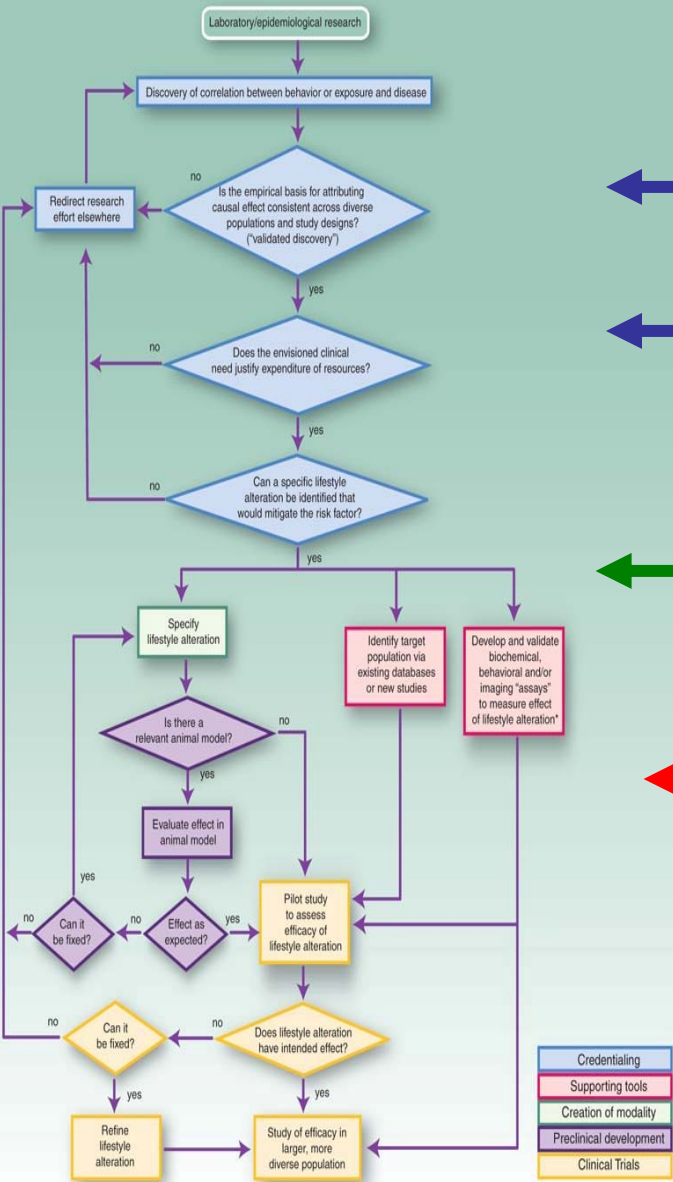


Interventive Device: IRE and imaging in hepatocellular CA



- Irreversible electroporation induces apoptosis
- Predictable ablation zone
- Preserves collagenous structures
- Available for clinical use, not optimized
- Integration with imaging
- ApoSense to monitor apoptosis
- MRI to monitor cell permeability
- Partnership between IRE and imaging
- Human studies to optimize performance required
- Dose-escalation for efficacy
- Validation of biomarkers as 2^{ary} endpt
- Ablation followed by resection

Lifestyle: Age-dependent diet and exercise to reduce BrCa risk



- Breast cancer risk tracks with country of origin during puberty
- Events during age 15-20 influence breast cancer risk
- Reducing the incidence of breast cancer would have enormous social and economic impact
- Diet/exercise interventions at puberty
- NIH National Children's Study
- Komen Fdn biospecimen repository
- Markers of puberty required
- Genetic/epigenetic changes
- Mouse models demonstrate age-dependent effects of carcinogens
- Interventional trials required

Imaging Pathway Opportunity Examples

- Molecular Imaging of PSCA in prostate cancer
- Breast CT
- ¹⁸F-FMISO imaging of hypoxia
- ¹⁸F-FES imaging of the estrogen receptor in breast cancer

Interventive Device Pathway Opportunity Examples

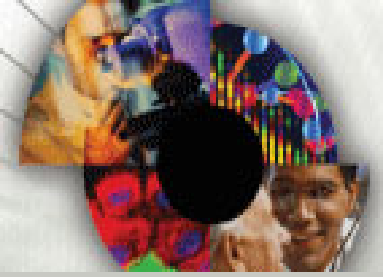
- Improving Radiation Therapy (Imaging, planning, delivery)
- Photodynamic therapy
- Development, Optimization, and Validation of Irreversible Electroporation (IRE) Integrated with Imaging Planning, Guidance, and Monitoring for the Treatment of Hepatocellular Carcinoma

Lifestyle Alterations Pathway Opportunity Examples

- Diet and exercise intervention at puberty to reduce breast cancer risk
- Metformin in breast cancer prevention in women with BMI>40
- Memantine and Procedural Memory Training For Prevention of Cognitive Dysfunction in Patients Receiving Whole-brain Radiotherapy
- Peri-surgical stress management in ovarian cancer patients

Implementation Progress

NEXT STEPS



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Proposed Components of a Prioritization Process



NCI solicits concepts (RFI)

Transparent and open process

Intra- and inter-pathway prioritization

CTAC Working Groups prioritize concepts
using specified criteria

CTAC review of prioritization plan

Concurrence of Working Group(s)' recommendations

Executive Decisions (NCI Leadership)

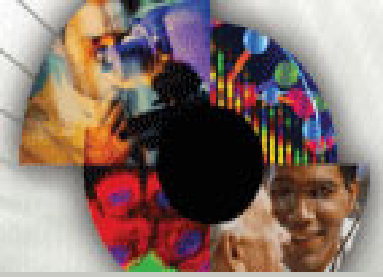
Competitive solicitation for priority projects; tailor funding strategy
depending on project needs

Concurrent NCI Activities



- Develop Project Management capabilities
 - Required to link new or existing teams/projects and to facilitate hand-offs between groups
- Develop customized funding strategies
 - Funding mechanisms and sources depend on project specifics
 - Range from expansion of existing activities to new activities
 - Require extraordinary coordination

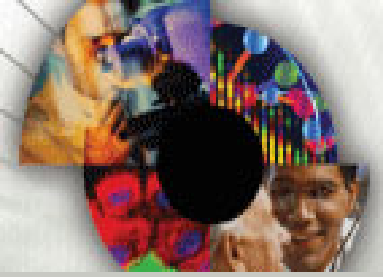
Proposed CTAC Working Group



Charge:

- Oversee development of prioritization process
 - Process options/straw men to be presented to Working Group by NCI staff
 - Define inter-pathway criteria; may need additional groups to define intra-pathway criteria
- Provide input on funding strategies developed by NCI (mechanisms)

Anticipated Timeline & Deliverables



Spring 2009

Prioritization process defined for presentation
at March CTAC meeting

Summer 2009

Funding strategies
RFI for concepts for prioritization

FY 2010

Concepts received by RFI prioritized
Competitive solicitation for prioritized projects

TRWG Implementation Plan



Comments and Questions

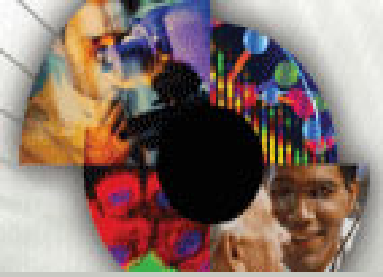
Next Step



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ACTION ITEM



CTAC will form a working group to advise NCI on the development of a prioritization process and provide input on funding strategies

