Translational Research Acceleration Initiative

Lynn M. Matrisian, Ph.D.
Coordinating Center for Clinical Trials
National Cancer Institute
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?
15 TRWG 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

www.cancer.gov/trwg
Select several projects/year that are “ripe” for translation

• Translational Research Acceleration Process DOES:
  • Gather information on translational opportunities
  • Prioritize translational research opportunities
  • Develop a funding & project management plan to accelerate prioritized opportunities

• Translational Research Acceleration Process DOES NOT:
  • Impact Discovery research
  • Replace existing infrastructure or mechanisms for clinical or translational research
CTAC recommended that NCI proceed with establishing a process to accelerate translational cancer research (Dec 08):

1. Gather information
2. Prioritize
3. Fund & Manage
NCI Translates
NCI-wide Translational Science Meeting

- November 7-9, 2008, Washington, DC
  - 513 abstracts
    - Grants/PIs selected by NCI Program Staff
  - **800 invited participants**
    - NCI-funded scientists/clinicians
    - Advocates
    - NCI staff

- **TSM2: November 5-7, 2009, Vienna, VA**
  - Maximum of 1000 participants
    - Added Cancer Centers, HIV, CAM, SBIR
    - Additional junior investigators from CCs, SPOREs
2009 NCI Translates
NCI-wide Translational Science Meeting

Goal:
The overarching goal of the 2009 NCI Translational Science Meeting is the collective pursuit of innovative methods of rapidly and efficiently moving the most promising new scientific discoveries from the laboratory into development and early-phase clinical testing.

Objectives:
• Enhance scientific collaborations and interactions among all of the investigators NCI supports through its translational research funding
• Assist NCI in identifying scientific opportunities most worthy of support from the Institute’s new Process to Accelerate Translational Science initiative
A translational idea or project that:

- **Focuses on a clinical goal**
  - Develops a modality (drug, device, biomarker, etc) that can be tested in people – one of the 6 TRWG pathways
  - Identifies the population/cancer type in which it is tested

- **Describes scientific validity**

- **Provides information on feasibility**
  - Identifies individuals/research groups with projects or capabilities relevant to all pathway domains
Translational Research Opportunities piloted at the first Translational Science Meeting

- Poster Discussion Sessions organized by Pathway and scientific area or organ site

- Co-chairs educated how abstracts could coalesce into a Translational Research Opportunity

- Translational Research Opportunity Information Guides
  - 6 pathway specific guides

http://ncittranslates.nci.nih.gov/Purpose_Goals.htm
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 cite
- 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
Pilot Project: Immune Response Modifier Pathway

- Piloting information gathering and prioritization with Immune Response Modifier Pathway
  - Most complex of the Pathways
  - Previous prioritization of Immune Response Modifiers (summer 2007)
  - A group of committed immunologists/immunotherapists could be identified (Mac Cheever, Seattle Cancer Care)

- Phase I: Focused on Antigen development only
- Phase II: Expanded to entire IRM Pathway
Purpose: To develop a well-vetted ranked priority list of cancer vaccine target antigens based on pre-defined and pre-weighted objective criteria

Process
- Developed list of “ideal” cancer antigen criteria/characteristics
  - Email
  - 36 experts
- Prioritized and weighted criteria using pair-wise comparisons
  - Web-based, Sept 2008
  - 20 experts
- Selected 100 representative antigens
- Assembled information on pre-defined criteria from experts for each antigen
  - ~79 experts, final 75 antigens
- Ranked antigens based on the pre-defined pre-weighted criteria
  - Face-to-face, Oct 2008
  - 16 reviewers

Clin Can Res, in press
Purpose: To pilot the prioritization of IRM Pathway Translational Research Opportunities using pre-defined and pre-weighted objective criteria

Process
- Developed list of “ideal” criteria/characteristics for IRM Pathway Translational Research Opportunities based on the IRM Pathway and the previous Antigen Prioritization experience
- Prioritized and weighted criteria using pair-wise comparisons
  - Web-based pilot prioritization (4 extramural investigators)
  - Face-to-Face meeting April 19, 2009 at AACR (21 investigators)
  - Subsequent facilitated or asynchronous web sessions (15-21 votes/category)
• Identify the most important boxes (things to do) within each domain

• Request level of evidence on **Scientific Validity**
  – Experiments in humans
  – Experiments in animals
  – In vitro experiments

• Request demonstrated **Feasibility** of that domain
  – Full scale manufacturing
  – Piloted manufacturing
  – Laboratory product
IRM Pathway Criteria and Subcriteria

- Antigen
- Formulation (cell preparation, delivery vehicle, adjuvant, etc)
- Immune Modifier Agent (cytokines, etc)
- Combination Regimen
- Assay for Immune Response
- Assay to select patient population
- Availability of Patients for Trials

**SUBCRITERIA:**
Scientific Validity & Feasibility for each component
- Identify the most important boxes (things to do) within each domain
- Request level of evidence on **Scientific Validity**
  - Experiments in humans
  - Experiments in animals
  - In vitro experiments
- Request demonstrated **Feasibility** of that domain
  - Full scale manufacturing
  - Piloted manufacturing
  - Laboratory product
Form for submission of IRM
Translational Research Opportunities

ANTIGEN

Levels of evidence

Levels of evidence

Cheever et al, Clin Can Res in press (Pilot Phase I)
Form for submission of IRM
Translational Research Opportunities

Scientific validity

Feasibility

Levels of evidence
- Human
- Animal
- In vitro

Evidence for feasibility
- Clinical grade
- Class-related clinical grade
- Laboratory product
Form for submission of IRM
Translational Research Opportunities

Level of development
- Clinical validation
- Standardization
- In development

Validity & Feasibility

**Component: Assay for Immune Response**

If entire component is not applicable to this Opportunity, enter "not applicable" in the adjacent comment box. If component is relevant but there is no data available, enter "no data available" in the adjacent comment box.

<table>
<thead>
<tr>
<th>Validity &amp; Feasibility</th>
<th>Assay to quantify immune response has been clinically validated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assay to quantify immune response has been developed and standardized</td>
</tr>
<tr>
<td></td>
<td>Assay to quantify immune response is in development</td>
</tr>
</tbody>
</table>

**Comments / Literature**
Form for submission of IRM
Translational Research Opportunities

![Flowchart](image)

<table>
<thead>
<tr>
<th>COMPONENT: AVAILABILITY OF PATIENTS FOR TRIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scientific validity</strong></td>
</tr>
<tr>
<td><strong>Feasibility</strong></td>
</tr>
</tbody>
</table>

**COMMENTS / LITERATURE**
Process to Accelerate Translational Science Initiative

Gather information

Prioritize

Fund & Manage

Request for Information for IRM Translational Research Opportunities release pending
Process to Accelerate Translational Science Initiative

Gather information

Prioritize
Which Opportunities are most “ripe” for acceleration?

Fund & Manage
March 2009

**Process to Accelerate Translational Science (PATS)**

- **PATS WG of CTAC**
  - NCI Division Directors
  - Extramural members

Determine interpathway criteria

Determine pathway-specific criteria
• Web-based version of the Analytical Hierarchy Process (AHP) for dealing with complex decisions provided by *Decision Lens®*
• Criteria weighting accomplished by pair-wise comparisons, asynchronously or face-to-face

---

**Prioritization Tool used by IRM Pilot**

- Jan 29, 2009, CTROC recommended proceeding with AHP/Decision Lens® prioritization tool
- Presented to CTAC March 4, 2009
AHP/Decision Lens Prioritization Tool

- Web-based platform facilitates webinar discussion or asynchronous input
- Logical organization and tracking of alternatives
- Facilitates updates in information
- Facilitates transparency, discussion of disparate viewpoints
- Integrates objective and subjective evaluation
- Allows “what if” scenarios to increase confidence in ranking
- Allows evaluation of components in isolation
- Does NOT make decisions – facilitates evaluation of information
IRMM Pathway Criteria and Subcriteria

- Antigen
- Formulation (cell preparation, delivery vehicle, adjuvant, etc)
- Immune Modifier Agent (cytokines, etc)
- Combination Regimen
- Assay for Immune Response
- Assay to select patient population
- Availability of Patients for Trials

Scientific Validity & Feasibility for each component

Rating scales/level of evidence for each criteria
## Criteria for IRM Translational Research Opportunity prioritization

### IMMUNE MODIFIER AGENT (cytokines, etc)

<table>
<thead>
<tr>
<th>CRITERIA Subcriteria</th>
<th>RATING SCALE</th>
<th>LEVEL OF EVIDENCE in descending order</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scientific validity</strong></td>
<td>Augments specific immunity in human trials</td>
<td>Data for augmenting specific immunity in human trials is superb as judged by an informed expert</td>
</tr>
<tr>
<td></td>
<td>Augments specific immunity in animals</td>
<td>Data for augmenting specific immunity in animals is superb as judged by an informed expert</td>
</tr>
<tr>
<td></td>
<td>Augments specific immunity in vitro</td>
<td>Adequate data for augmenting specific immunity in human cells in vitro</td>
</tr>
<tr>
<td></td>
<td>No in vitro or in vivo data available</td>
<td>No in vitro or in vivo data available</td>
</tr>
<tr>
<td><strong>Feasibility</strong></td>
<td>Manufacturing of clinical grade agent</td>
<td>GMP/clinical grade manufacturing of the agent at scale is reproducible and reliable</td>
</tr>
<tr>
<td></td>
<td>Scalable clinical grade manufacturing process for the agent has been piloted</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manufacturing of clinical grade class-related modifier</td>
<td>Scalable clinical grade manufacturing process for the agent class has been demonstrated</td>
</tr>
<tr>
<td></td>
<td>Available as a laboratory grade product</td>
<td>Laboratory product only</td>
</tr>
<tr>
<td></td>
<td>Not developed</td>
<td>Not completely developed</td>
</tr>
</tbody>
</table>
IRM Pilot Prioritization Project

IRM SubGroup
Develop/Weigh Criteria

spring 2009

Request for Information

Release July 10, 2009
Due August 21, 2009

~100 Translational Research Opportunities?

Extramural & intramural content experts
NCI staff & extramural investigators without conflicts

Scientific Input

Computer assisted prioritization
• scientific validity
• feasibility

Scientific Prioritization

~10 Opportunities
Top 10-20%

Complete October 2009

NCI leadership
IRM Pilot Prioritization Project

Top Opportunities

NCI Leadership

Additional prioritization criteria:
• clinical need
• appropriateness for NCI investment

Other Pathways:
Inter-pathway prioritization

1-3 IRM Special Translational Research Acceleration Projects (STRAPs)

Request(s) for Supplements/Proposals/Applications
Process to Accelerate Translational Science Initiative

1. Gather information
2. Prioritize
3. Fund & Manage
Call for Supplements/Applications/Proposals for 1-3 IRM STRAPS

Supplements/existing mechanisms:
- NeXT
- R01
- Cooperative Groups
- P01
- RAPID
- EDRN
- SPOREs
- Cancer Centers
- etc

New (if necessary):
- RFAs
- RFPs
- Cooperative Agreements
- CRADAs
- etc

Scientific/Feasibility Review

NCI leadership

Setting up evaluation criteria for STRAPs and TRWG Report

Implementation

Funded STRAP

FY2010
Determine pathway-specific criteria

March 2009
PATS WG of CTAC

Pilot Projects for each of the Pathways

spring-summer 2009
IRM (Cheever)

summer-fall 2009
BM (Tlsty)
LA (Bruner, Ballard-Barbash)
In conjunction with NCI Experimental Therapeutics Program

Agents

fall-winter 2009
IM (Dorfman)
ID (Lawrence)