Translational Research Acceleration Initiative

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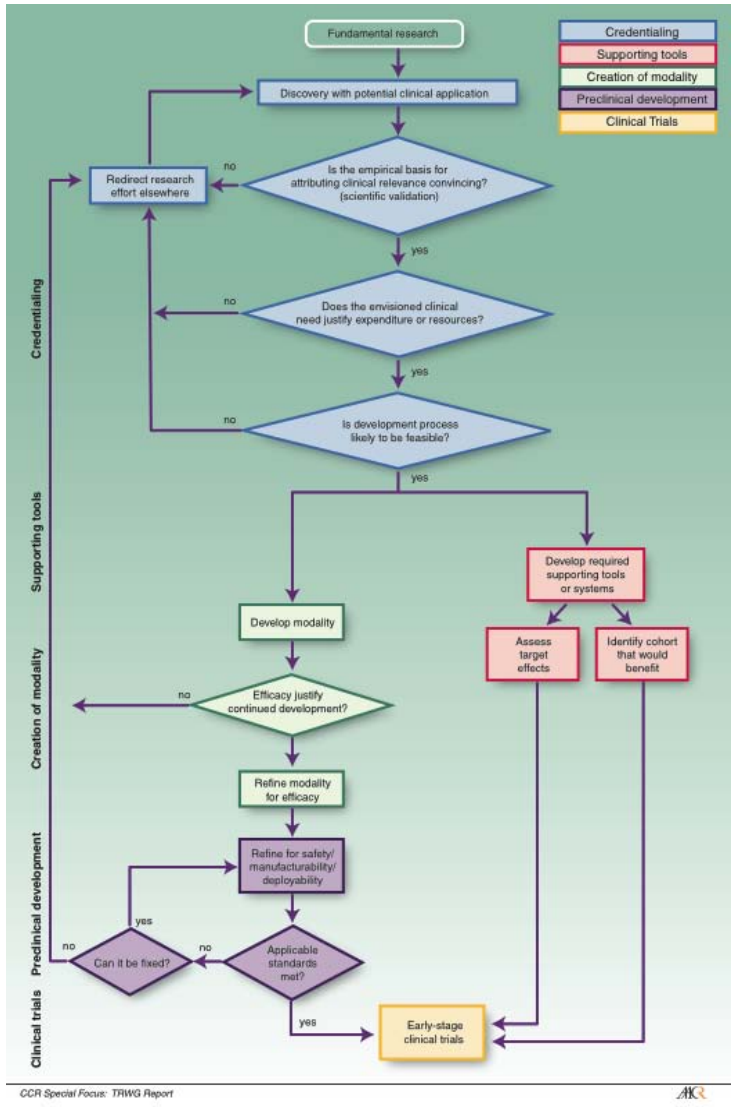
National Cancer Institute

TRWG: 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?

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

Translational Research Acceleration Initiative

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

Process to Accelerate Translational Science Initiative

CTAC recommended that NCI proceed with establishing a process to accelerate translational cancer research (Dec 08):

Gather information

↓

Prioritize

↓

Fund & Manage

Gather Information

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

Gather Information

2009 NCI Translates NCI-wide Translational Science Meeting

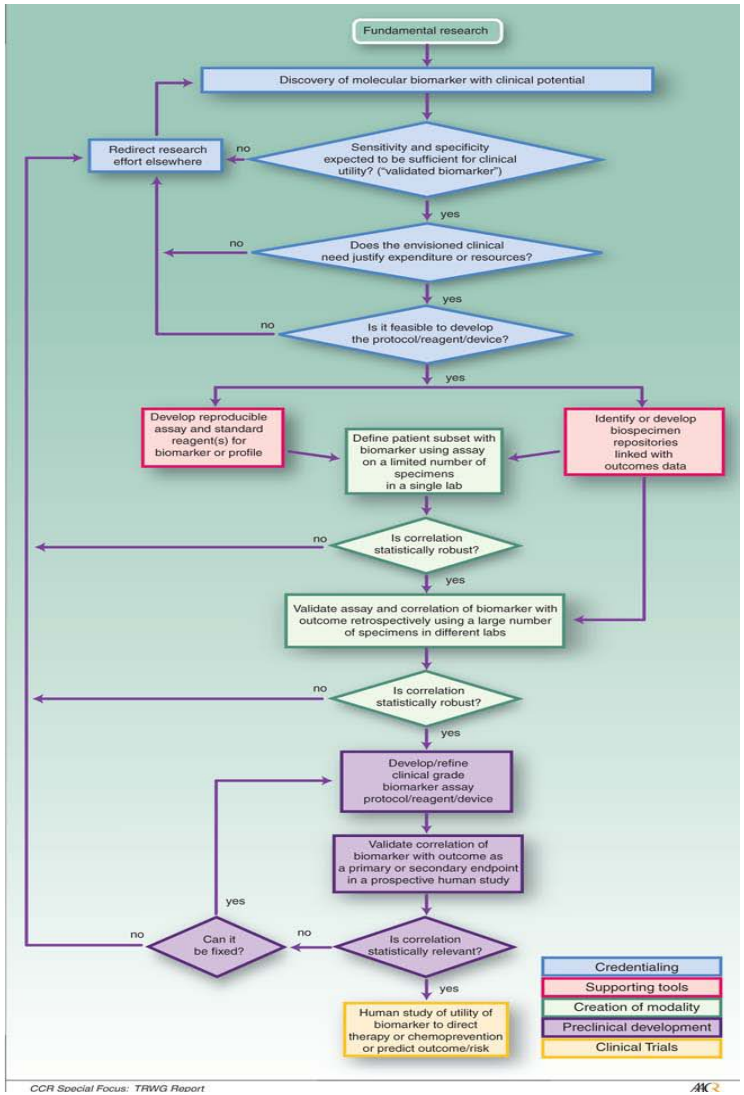
Goal:

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***

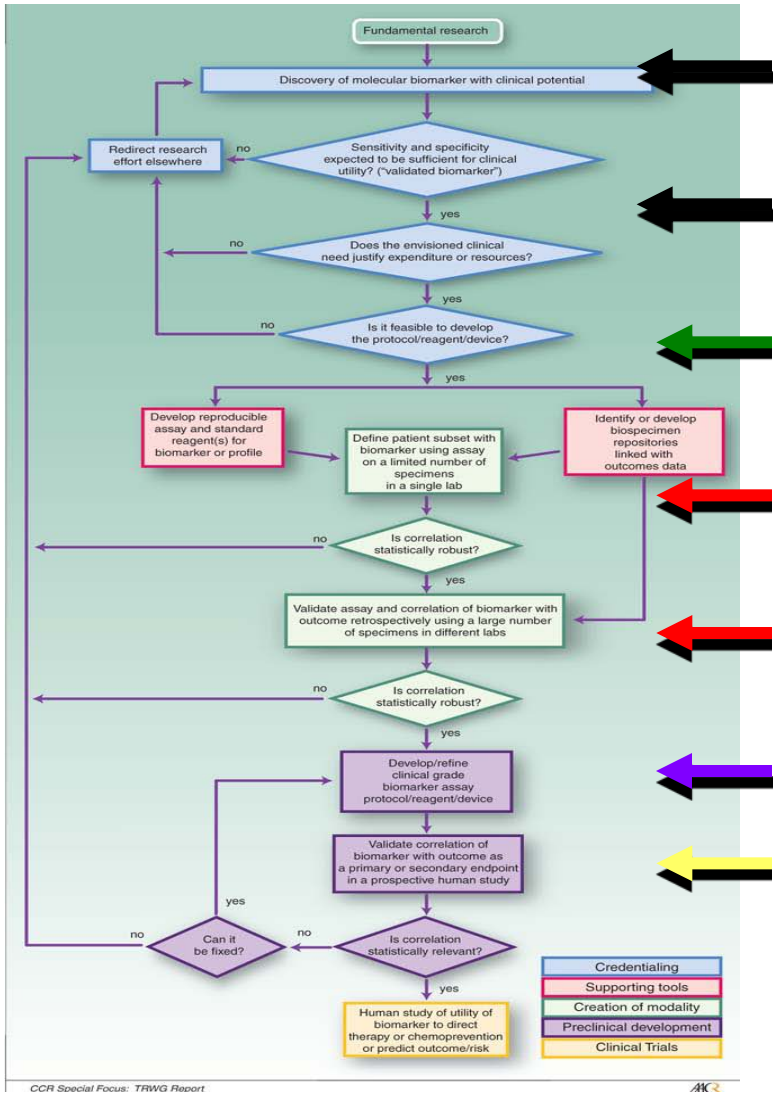
Translational Research Opportunities introduced at first TSM



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

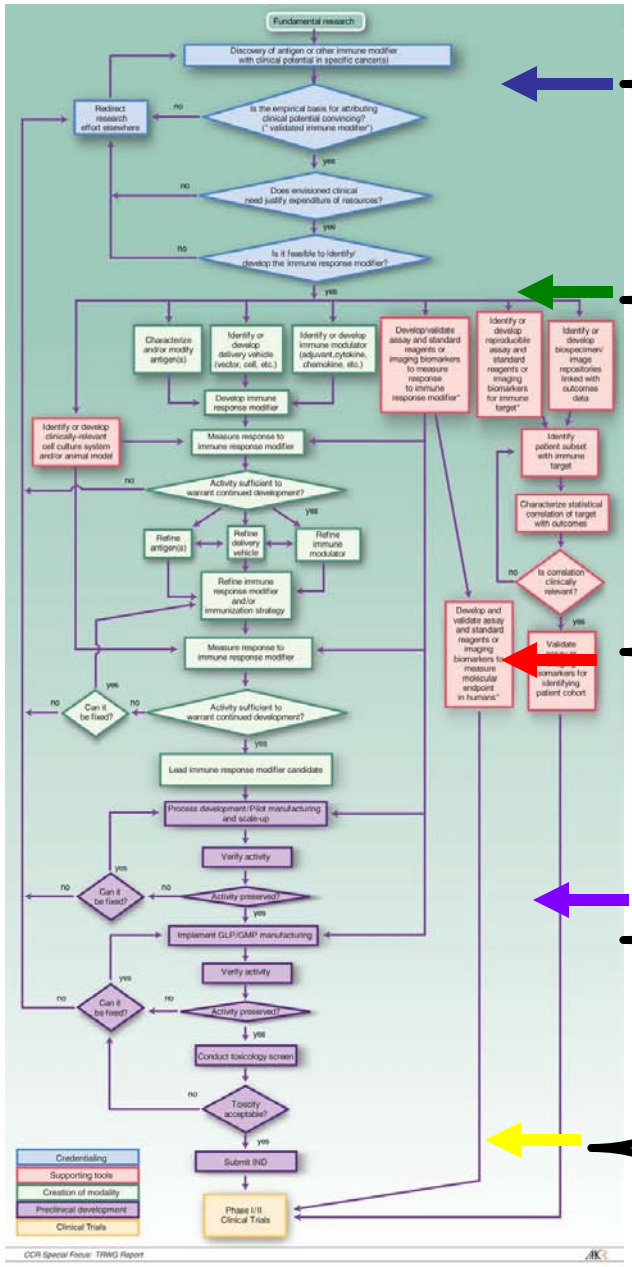
Translational Research Opportunities piloted at the first Translational Science Meeting



- 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://ncitranslates.nci.nih.gov/Purpose_Goals.htm

Immunotherapy: WT-1 vaccine in AML and ovarian cancer



- oncogenic protein
- expressed at high levels in AML & OvCa

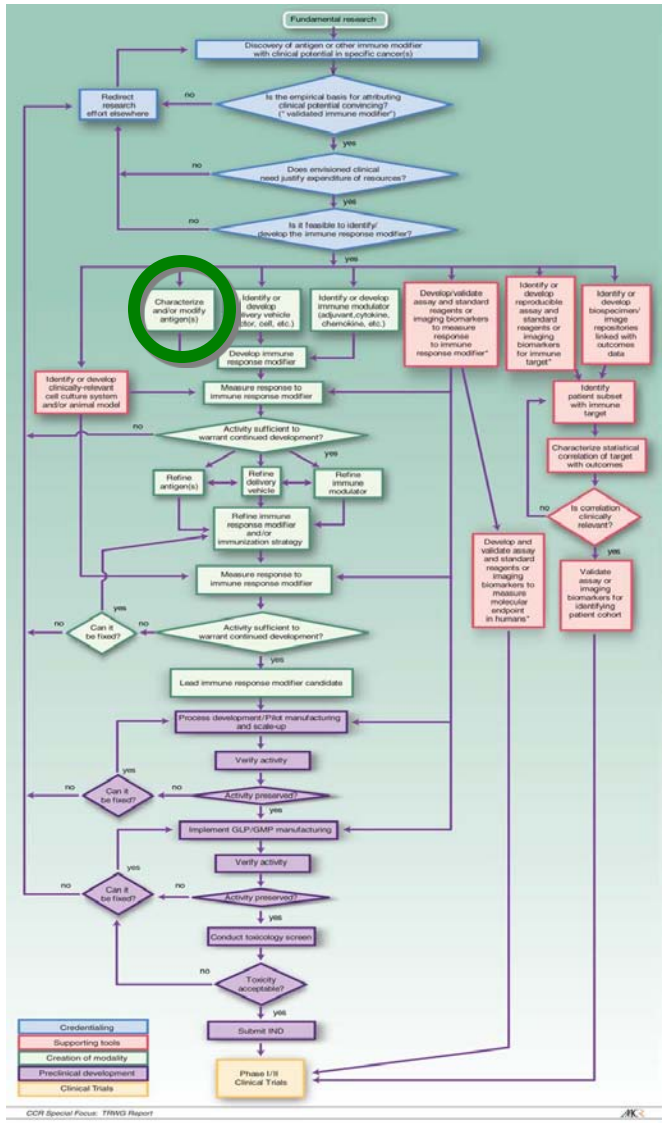
- Peptide antigen
- Delivery vehicle w/ CpG&MPL adjuvants
- IL-7 and anti-PD1 as immune modulators

- 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 manuftd

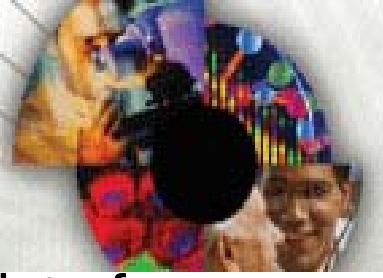
- Iterative Phase I with marker endpoints
- Phase II when immunity achieved in Ph I
- Network of preselected sites

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

Immune Response Modifier Pilot Prioritization Process Project (IRM P5): Antigens (Phase I)



- 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

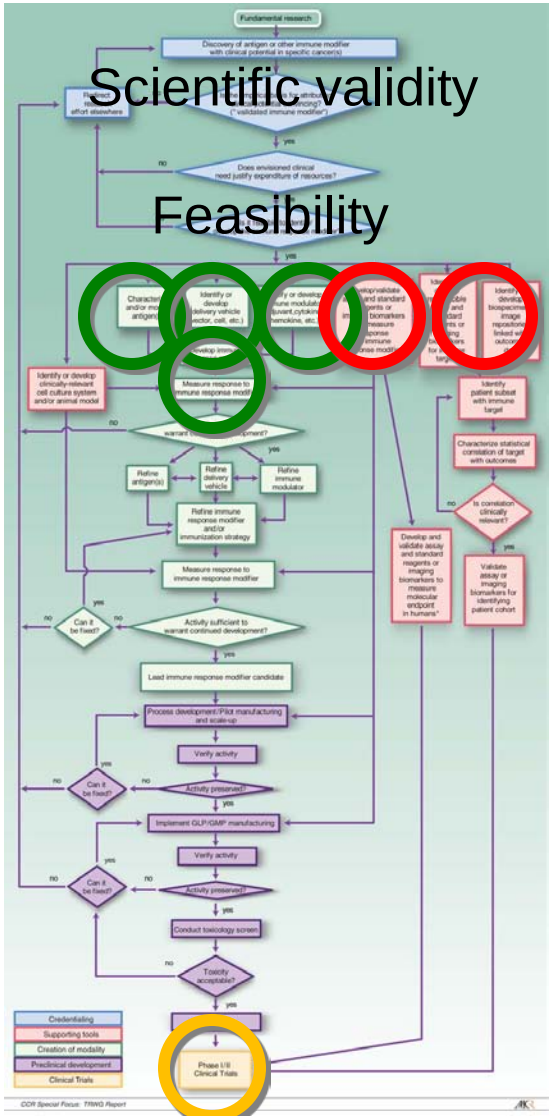
Clin Can Res, in press

Immune Response Modifier Pilot Prioritization Process Project (IRM P5): IRM PATHWAY (Phase II)

- Purpose: To pilot the prioritization of IRM Pathway Translational Research Opportunities using pre-defined and pre-weighted objective criteria

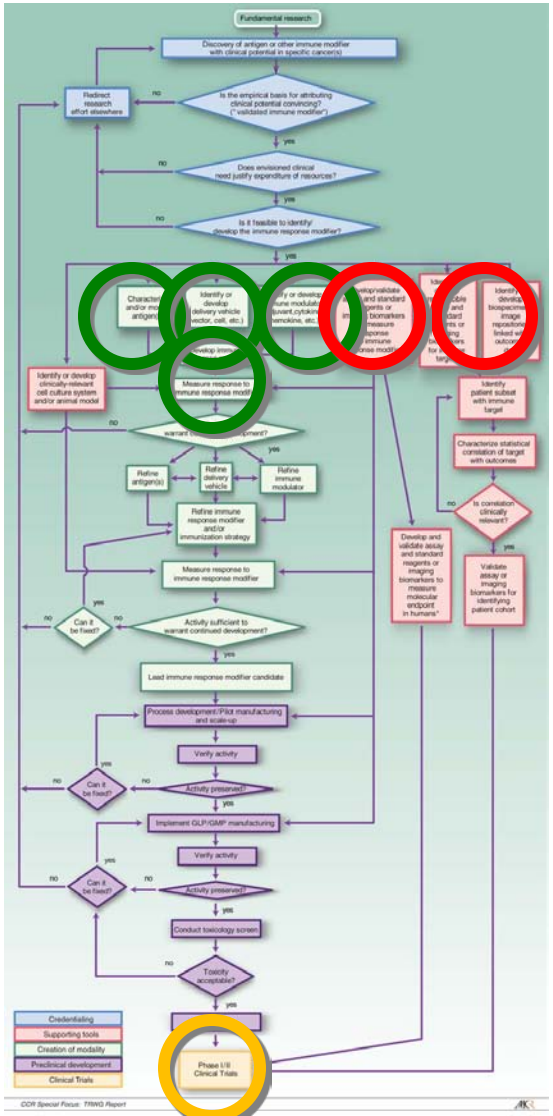
- Process
  - Developed list of “ideal” criteria/characteristics for IRM Pathway Translational Research Opportunities based on the IRM Pathway and the previous Antigen Prioritization experience
  - Prioritized and weighted criteria using pair-wise comparisons
    - Web-based pilot prioritization (4 extramural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

Evolution/Simplification of Translational Research Opportunities: IRM pilot Phase II



- 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

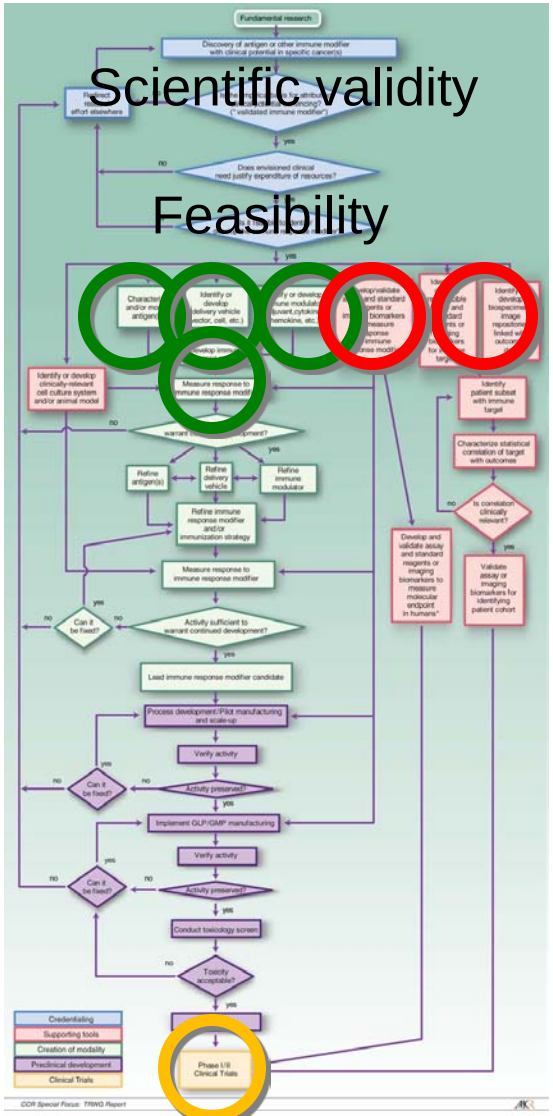
IRM Pathway Criteria and Subcriteria



- 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

Evolution/Simplification of Translational Research Opportunities: IRM pilot Phase II



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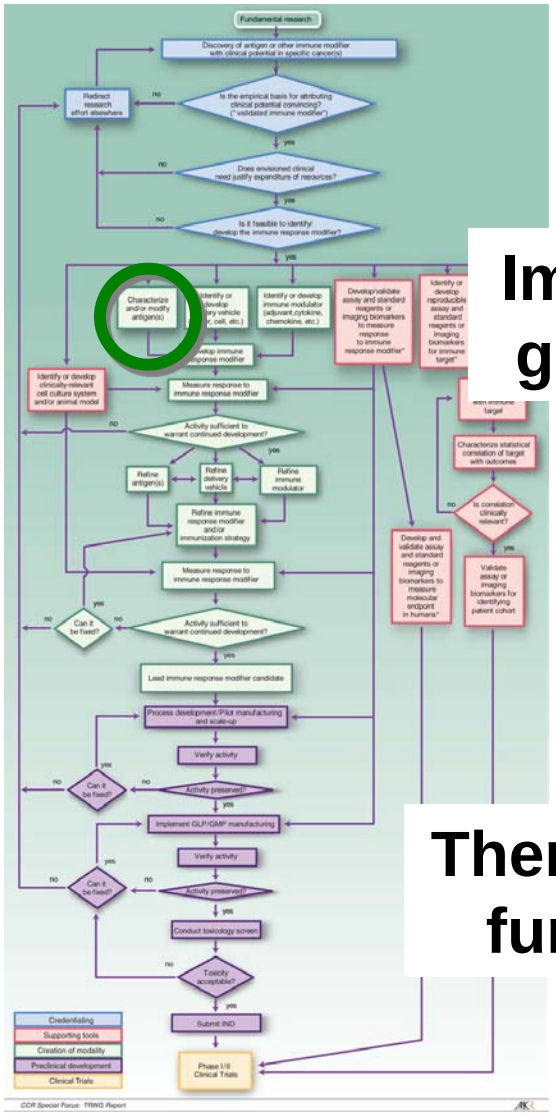
Form for submission of IRM Translational Research Opportunities



Immuno-genicity

Therapeutic function

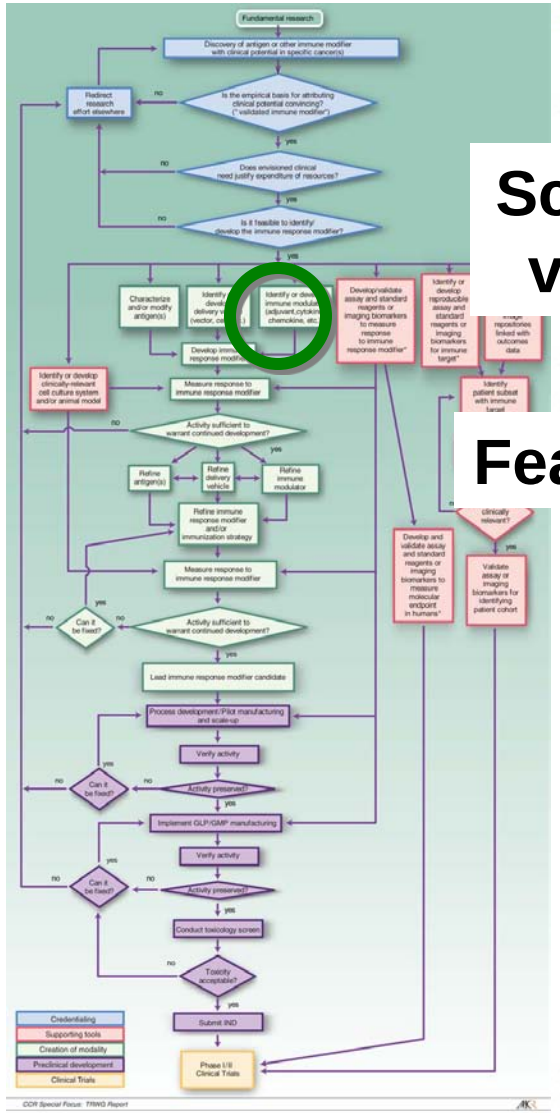
		COMMENTS / LITERATURE
COMPONENT: ANTIGEN	**ANTIGEN**	
If entire component is not applicable to this Opportunity, enter "not applicable" in the adjacent comment box. If component is relevant but there is no data available, enter "no data available" in the adjacent comment box.		
Immunogenicity	T cell and/or antibody responses elicited to this antigen in clinical trials	
	Spontaneous T cell responses to this antigen observed in some patients	
	Antigen is immunogenic in animal models with natural levels of antigen expression similar to humans	
	Spontaneous antibodies to this antigen are observed in some patients	
Therapeutic function	This antigen has shown efficacy in a controlled vaccine clinical trial	
	This antigen has shown responses in T cell therapy	
	Pre existent immunity to this antigen has shown a correlation with survival	
	This antigen has shown efficacy in appropriate animal	

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

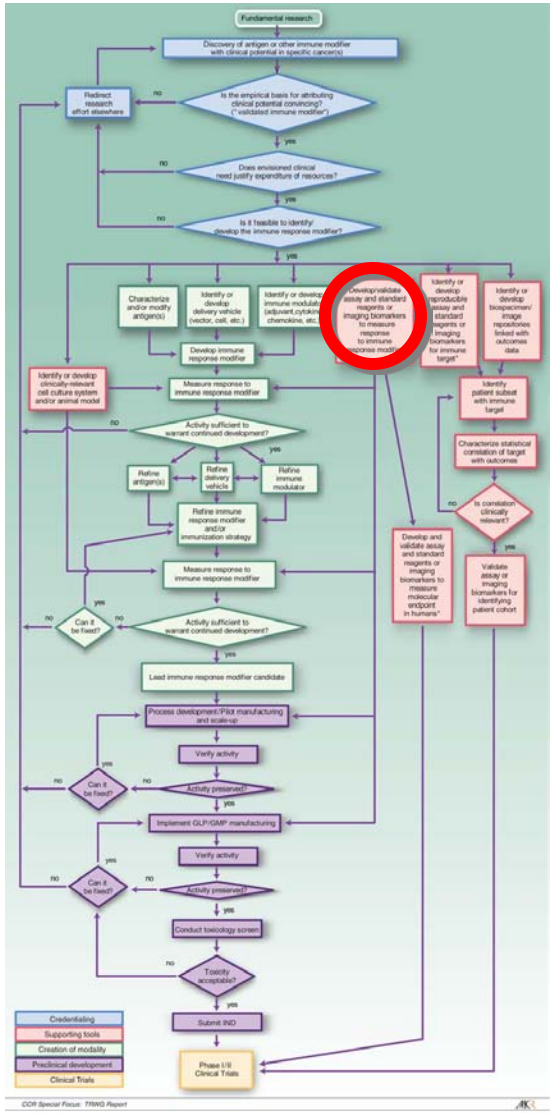
Feasibility

COMPONENT: **IMMUNE MODIFIER AGENT**		
If entire component … in the adjacent comment box. If component is relevant but there is no data available, enter "no data available" in the adjacent comment box.		
	Augments specific immunity in human trials	
	Augments specific immunity in animals	
	Augments specific immunity in vitro	
	Manufacturing of clinical grade agent (include information on stage of development, scale, reproducibility, etc)	
	Manufacturing of clinical grade class-related modifier (include information on stage of development, scale, reproducibility, etc)	
	Available as a laboratory grade product	

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

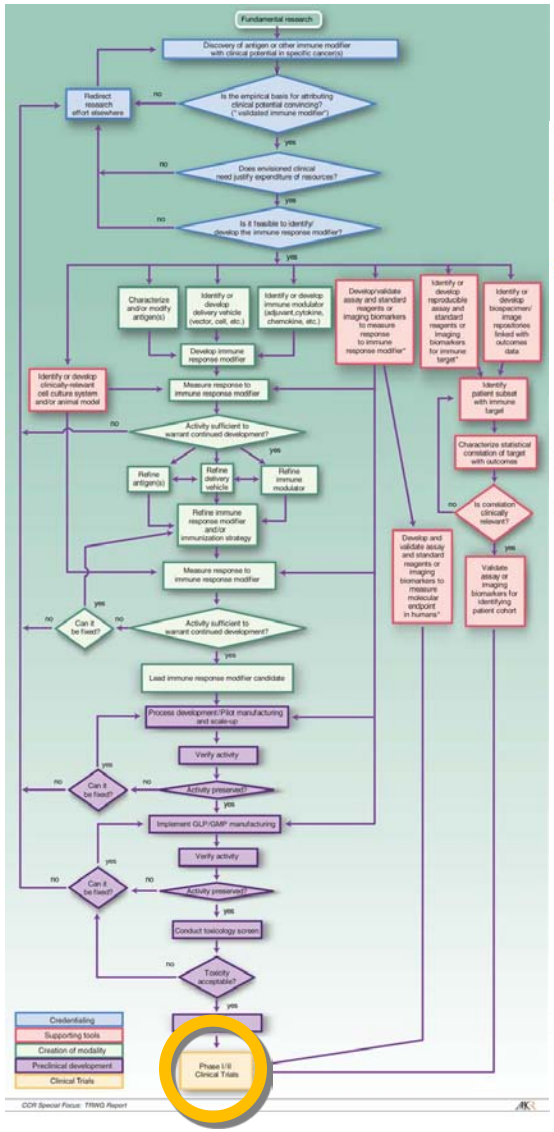


Validity & Feasibility

Level of development
- Clinical validation
- Standardization
- In development

		COMMENTS / LITERATURE
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.		
Validity & Feasibility	Assay to quantify immune response has been clinically validated	
	Assay to quantify immune response has been developed and standardized	
	Assay to quantify immune response is in development	

Form for submission of IRM Translational Research Opportunities



		COMMENTS / LITERATURE
COMPONENT: AVAILABILITY OF PATIENTS FOR TRIALS		
Scientific validity	Data supporting choice of cancer type and stage of disease for clinical testing	
Feasibility	Availability of patients/individuals with the required characteristics for clinical trials (include information on disease prevalence, competing protocols and status of standard therapy)	

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

Process to Accelerate Translational Science (PATS)

March 2009

PATS WG of CTAC

NCI Division Directors
Extramural members

Determine interpathway criteria

IRM

BM

Ag

IM

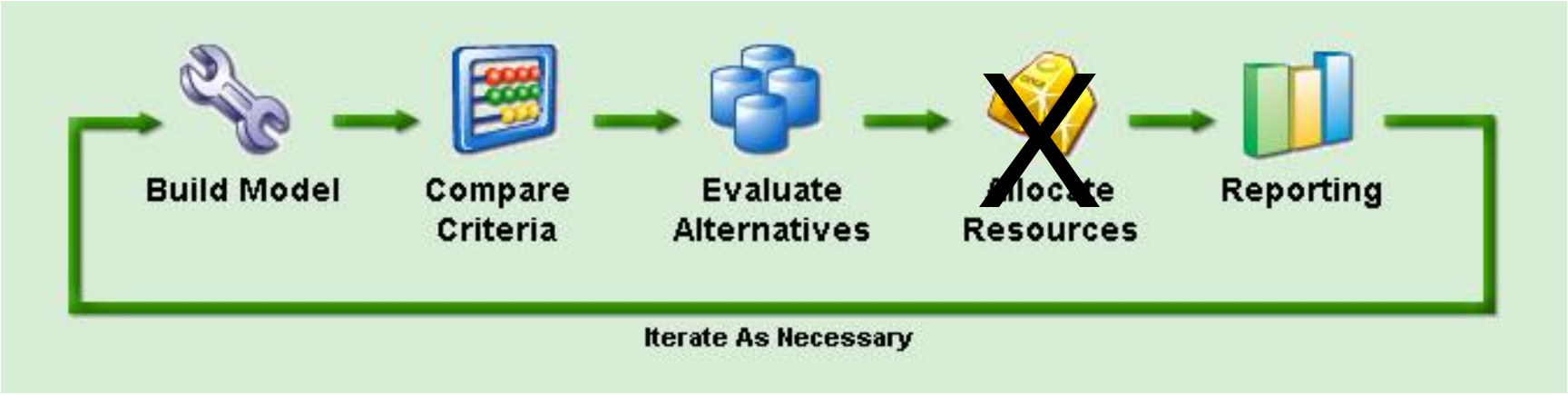
LA

ID

Determine pathway-specific criteria

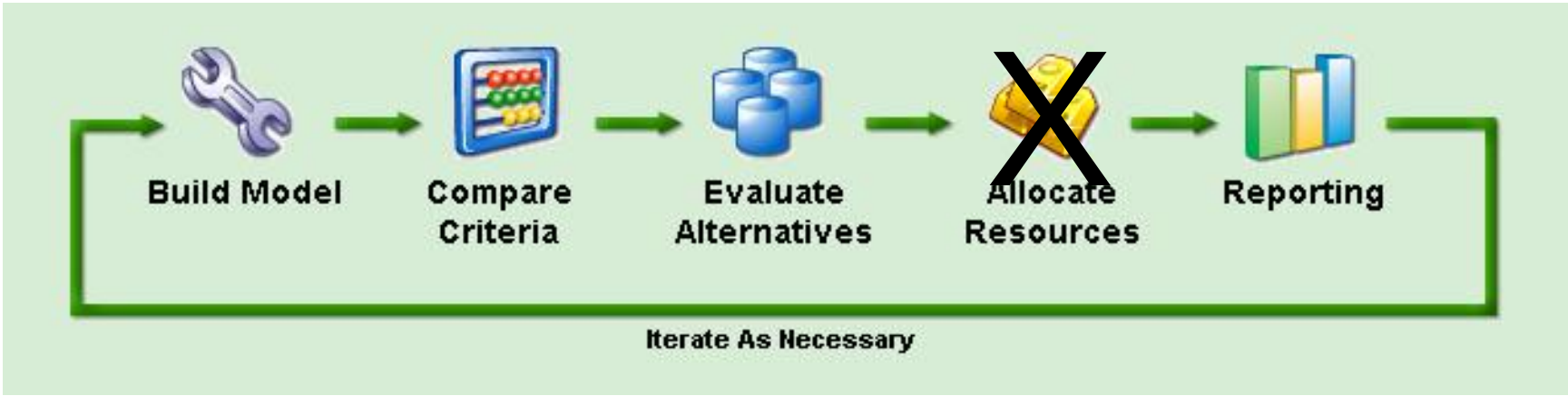
Prioritization Tool used by IRM Pilot

- 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



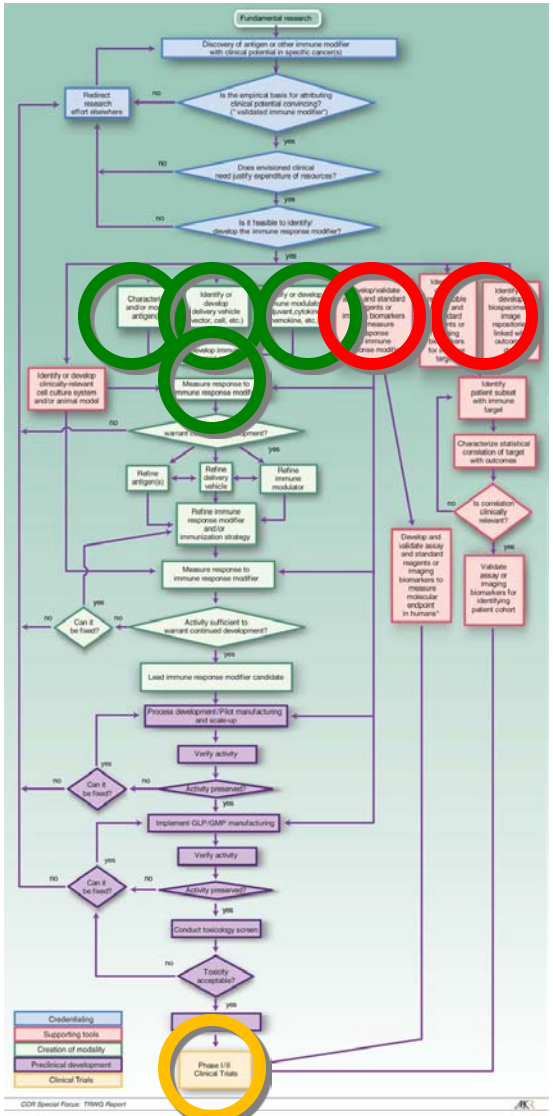
- Jan 29, 2009, CTROC recommended proceeding with AHP/*Decision Lens* prioritization tool
- Presented to CTAC March 4, 2009

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

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

Scientific Validity & Feasibility for each component

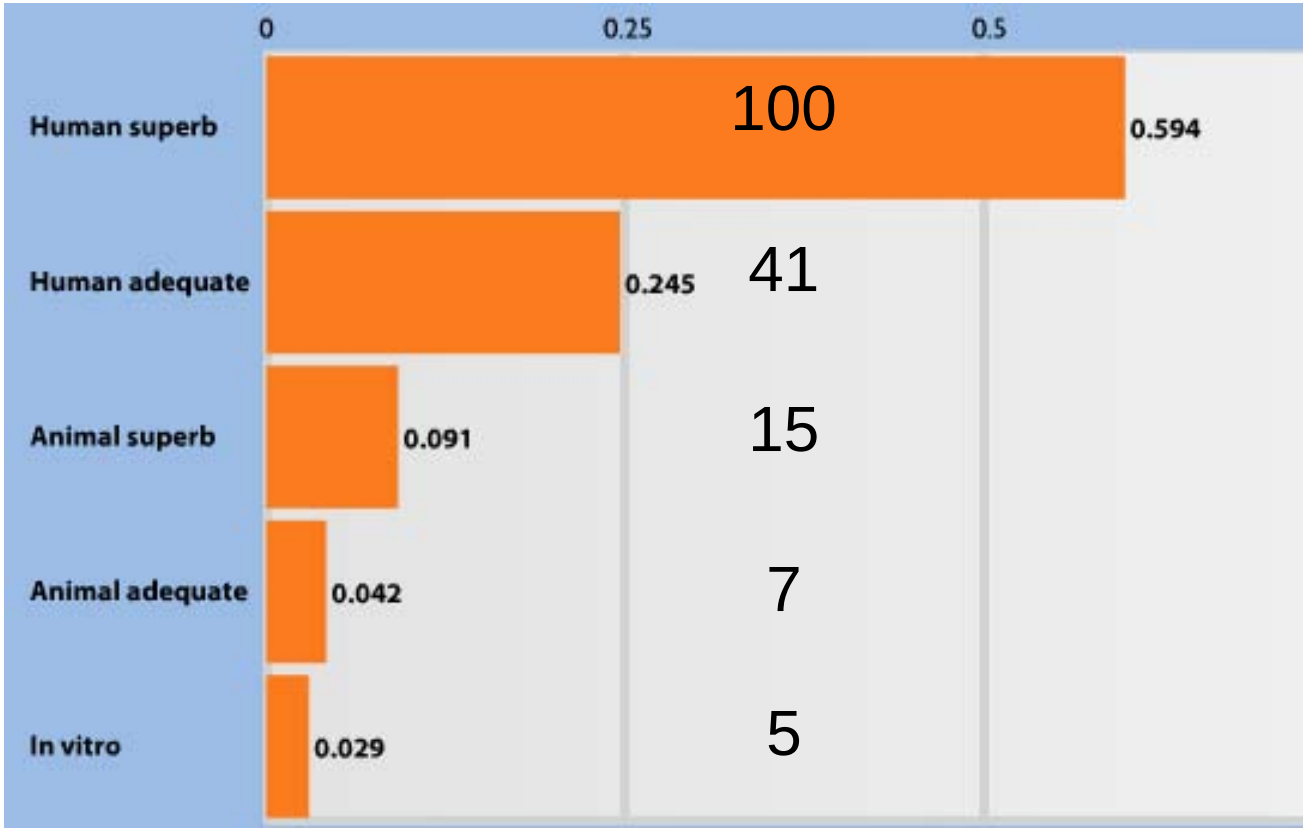
Rating scales/level of evidence for each criteria

Criteria for IRM Translational Research Opportunity prioritization

CRITERIA Subcriteria	RATING SCALE	LEVEL OF EVIDENCE in descending order
IMMUNE MODIFIER AGENT (cytokines, etc)		
Scientific validity	Augments specific immunity in human trials	Data for augmenting specific immunity in human trials is superb as judged by an informed expert
		Data for augmenting specific immunity in human trials is adequate
	Augments specific immunity in animals	Data for augmenting specific immunity in animals is superb as judged by an informed expert
		Data for augmenting specific immunity in animals is adequate
	Augments specific immunity in vitro	Adequate data for augmenting specific immunity in human cells in vitro
	No in vitro or in vivo data available	No in vitro or in vivo data available
Feasibility	Manufacturing of clinical grade agent	GMP/clinical grade manufacturing of the agent at scale is reproducible and reliable
		Scalable clinical grade manufacturing process for the agent has been piloted
	Manufacturing of clinical grade class-related modifier	Scalable clinical grade manufacturing process for the agent class has been demonstrated
	Available as a laboratory grade product	Laboratory product only
	Not developed	Not completely developed

Immune Response Modifier Criteria

Example rating scale weighting



For details on process (Phase 1 pilot): Cheever, M.A., Allison, J.P., Ferris, A.S., Finn, O.J., Hastings, B.M., Hecht, T.T., Mellman, I., Prindiville, S.A., Viner, J.L., Weiner, L.M., Matrisian, L.M. **The Prioritization of Cancer Antigens: A National Cancer Institute Pilot Project for the Acceleration of Translational Research.** *Clinical Cancer Research, in press*

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

Scientific Prioritization

Computer assisted prioritization
- scientific validity
- feasibility

~10 Opportunities
Top 10-20%

Complete October 2009

NCI leadership

IRM Pilot Prioritization Project

Other Pathways: Inter-pathway prioritization

Top Opportunities

NCI Leadership

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

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

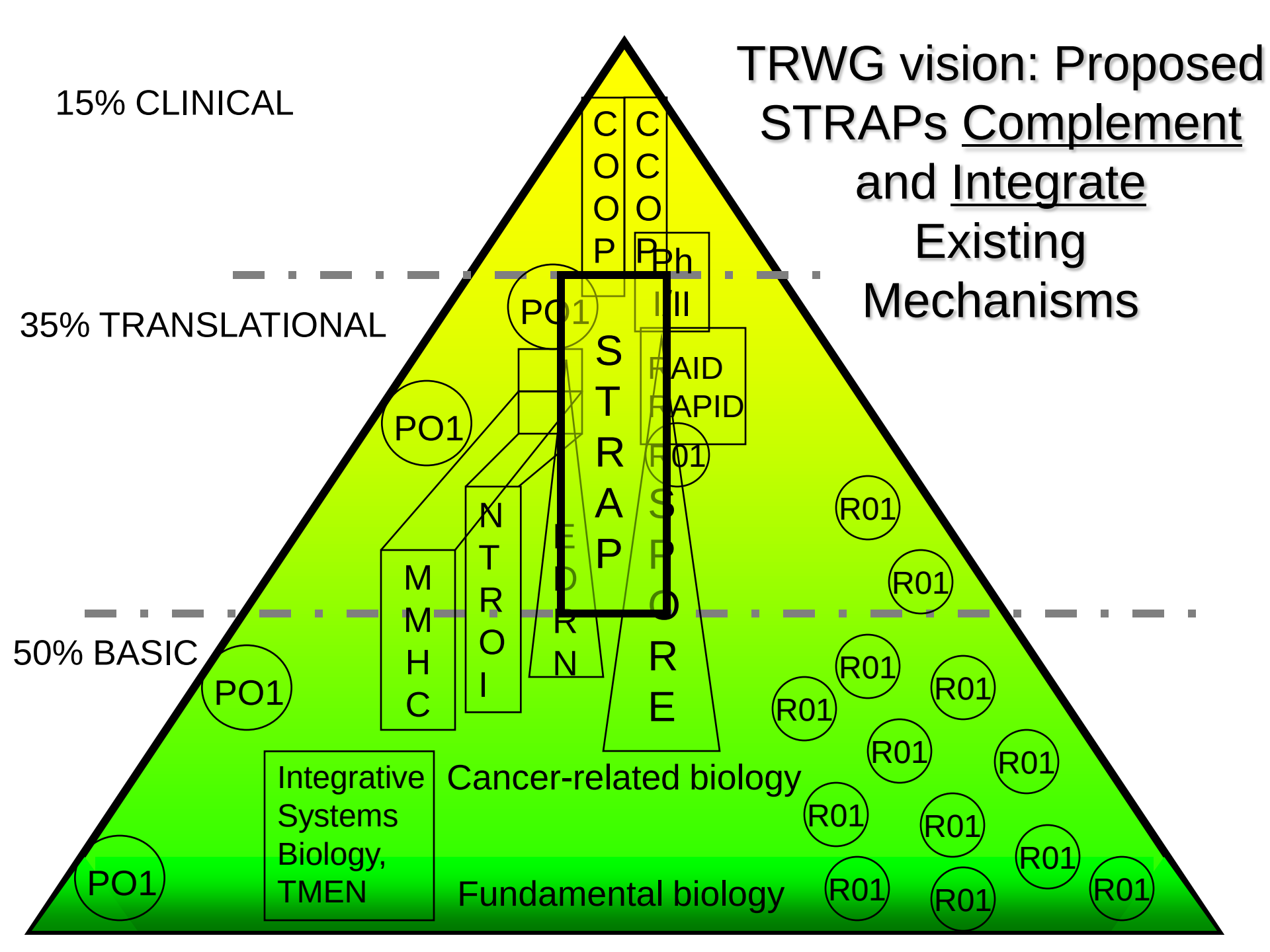
Request(s) for Supplements/Proposals/ Applications

Process to Accelerate Translational Science Initiative

Gather information

Prioritize

Fund & Manage


TRWG vision: Proposed STRAPs Complement and Integrate Existing Mechanisms
15% CLINICAL
35% TRANSLATIONAL
50% BASIC
COOP
CCOP
PhII
PO1
STRAP
RAID
RAPID
R01
PO1
MMHC
NTROI
NEURO
SPORE
R01
R01
PO1
R01
R01
R01
R01
R01
R01
R01
R01
PO1
Integrative Systems Biology, TMEN
Cancer-related biology
Fundamental biology

IRM STRAP

Call for Supplements/Applications/Proposals for 1-3 IRM STRAPS

Supplements/ existing mechanisms:

NeXT
R01
P01
Cooperative Groups
NCI clinical center
RAPID
EDRN
SPOREs
Cancer Centers
etc

New (if necessary):

RFAs
RFPs
Cooperative Agreements
CRADAs
etc

Scientific/Feasibility Review

NCI leadership

Funded STRAP

Setting up evaluation criteria for STRAPs and TRWG Report Implementation

FY2010

Staging of Process to Accelerate Translational Science (PATS) Subgroups

March 2009

PATS WG of CTAC

Pilot Projects for each of the Pathways

Determine pathway-specific criteria

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)*