Translational Research Working Group

Envisioning the Future of NCI's Investment in Translational Research

Interim Report to the National Cancer Advisory Board

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Bethesda, Maryland

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NIH Mission Statement

"Science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability."

http://www.nih.gov/about/index.html#mission.htm

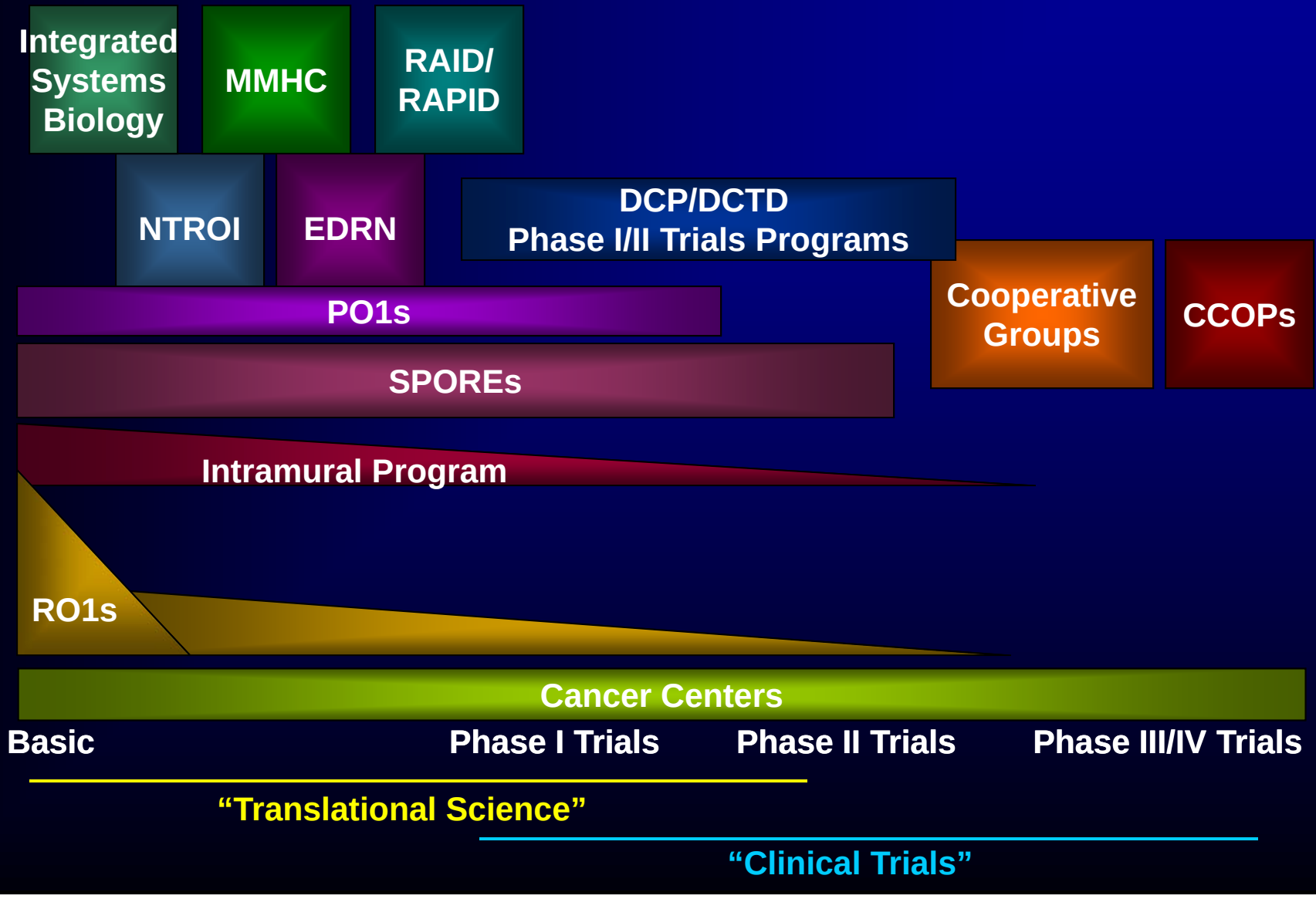
Medicine's Emerging Transformation

Transition will be fueled by translational science

20th Century	21st Century	Implications
Treat disease when symptoms appear & normal function is lost	Intervene before symptoms appear & preserve normal function for as long as possible	Prevention of disease & health preservation
Cross-sectional, morphologic definition & understanding of disease	Dynamic, cellular/molecular understanding of disease processes	Prediction of risk earlier & better; more effective, less toxic interventions
Expensive in financial & disability costs	Improved opportunities for effectiveness & efficiency	Personalization of risks & interventions

Adapted from presentations by A von Eschenbach, L Hood & E Zerhouni, 2005

NCI's "Bench to Bedside & Back" Research Infrastructure



Rationale for Change

- Advances in cancer biology offer enormous opportunities to improve cancer treatment & prevention
- Translation of these new concepts into drugs, devices & interventions that can be tested in the clinic or population has not kept pace with advances in fundamental research
- Expanding opportunities & high expectations coupled with limited resources require a translational research system that can identify & pursue the most promising opportunities efficiently & productively

Translational Research Working Group

Charge:

Evaluate the current status of NCI's investment in translational research & envision its future in an inclusive, representative & transparent manner

Objectives for Today's Presentation

- Define translational research (TR) & the TRWG's focus
- Review TRWG activities to date & its future plans
- Review Phase I draft recommendations
  - Organization
  - Funding
  - Prioritization
  - Core Services Coordination
  - Project Management
- Seek guidance from the NCAB on Phase I draft recommendations prior to embarking on Phase II activities & developing implementation plans

TRWG Membership

Abbruzzese, James	Dubinett, Steven	Limburg, Paul	Perez-Soler, Roman
Alberts, David	DuBois, Raymond	Look, A. Thomas	Rabkin, Charles
Anderson, Kenneth	Emanuel, Peter	Lubenow, Anne	Reid, Brian
Bast, Robert	Esserman, Laura	Lyerly, H. Kim	Scheinberg, David
Bigner, Darell	Fenton, Laurie	Maslow, David	Schilsky, Richard
Buetow, Kenneth	Gilmer, Tona	Matrisian, Lynn	Schlom, Jeffrey
Caligiuri, Michael	Gomez, Jorge	McGrath, Gail	Schnall, Mitchell
Cheever, Martin	Gordon, Gary	McLeod, Howard	Sellers, Thomas
Collins, Jerry	Gray, Joe	McTiernan, Anne	Sidransky, David
Cote, Richard	Gritz, Ellen	Mohla, Suresh	Sigal, Ellen
Courtneidge, Sara	Hait, William	Moore, Ida “Ki”	Simon, Richard
Cowan, Kenneth	Hawk, Ernest	Nelson, William	Srivastava, Sudhir
Dennis, Phillip	Hong, Waun Ki	Nichols, Cherie	Sullivan, Daniel
Di Bisceglie, Adrian	Jacks, Tyler	Olopade, Olufunmilayo	Tlsty, Thea
Doroshow, James	Kerr, David	Oberholtzer, John Carl	Weiner, Louis
Downing, Gregory	Lawrence, Theodore	Pazdur, Richard	

Programmatic Representation on the TRWG

(CRISP Database, 2000-2006)

- **Cancer Centers (8)**
  - David Alberts
  - Michael Caligiuri
  - Kenneth Cowan
  - Raymond Dubois
  - Peter Emanuel
  - William Hait
  - Tyler Jacks
  - H. Kim Lyerly
- **Industry (4)**
  - Martin Cheever
  - Sara Courtneidge
  - Tona Gilmer
  - Gary Gordon
- **EDRN (2)**
  - David Sidransky
  - Sudhir Srivastava
- **Advocates (3)**
  - Laurie Fenton
  - Gail McGrath
  - Ellen Sigal
- **SPOREs (14)**
  - James Abbruzzese
  - Kenneth Anderson
  - Robert Bast
  - Darell Bigner
  - Richard Cote
  - Steven Dubinett
  - Laura Esserman
  - Joe Gray
  - Waun Ki Hong
  - Lynn Matrisian
  - William Nelson
  - Olufunmilayo Olopade
  - David Sidransky
  - Thea Tlsty
- **Clinical Study Consortia (5)**
  - David Alberts
  - Michael Caligiuri
  - James Doroshow
  - Paul Limburg
  - Richard Schilsky
- **P01s (18)**
  - David Alberts
  - Kenneth Anderson
  - Robert Bast
  - Michael Caligiuri
  - Richard Cote
  - Steven Dubinett
  - Raymond Dubois
  - Gary Gordon
  - Joe Gray
  - Waun Ki Hong
  - Tyler Jacks
  - Theodore Lawrence
  - A. Thomas Look
  - H. Kim Lyerly
  - Brian Reid
  - David Scheinberg
  - Mitchell Schnall
  - Thomas Sellers

Programmatic Representation on the TRWG

(CRISP Database, 2000-2006)

- **R01s (30)**
  - Kenneth Anderson
  - Robert Bast
  - Michael Caligiuri
  - Martin Cheever
  - Richard Cote
  - Sara Courtneidge
  - Adrian DiBisceglie
  - James Doroshow
  - Steven Dubinett
  - Raymond Dubois
  - Peter Emanuel
  - Ellen Gritz
  - William Hait
  - Theodore Lawrence
  - Paul Limburg
  - A. Thomas Look
  - H. Kim Lyerly
  - Lynn Matrisian
  - Anne McTiernan
  - Ida “Ki” Moore
  - William Nelson
  - John Carl Oberholtzer
- **R01s (cont.)**
  - Olufunmilayo Olopade
  - Roman Perez-Soler
  - Brian Reid
  - David Scheinberg
  - Thomas Sellers
  - David Sidransky
  - Thea Tlsty
  - Louis Weiner
- **Training/Education (15)**
  - David Alberts (R25, T32)
  - Robert Bast (K12, T32)
  - Michael Caligiuri (T32)
  - James Doroshow (K12)
  - Raymond Dubois (T32)
  - Peter Emanuel (T32)
  - Waun Ki Hong (T32)
  - H. Kim Lyerly (K12, T32)
  - Lynn Matrisian (T32)
  - Ida “Ki” Moore (T32)
  - Olufunmilayo Olopade (T32)
  - David Scheinberg (K12)
  - Mitchell Schnall (T32)
- **Training/Ed (cont.)**
  - Thomas Sellers (R25)
  - Louis Weiner (K12)
- **Federal Gov’t (17)**
  - Kenneth Buetow (CB)
  - Jerry Collins (DCTD)
  - Phillip Dennis (CCR)
  - James Doroshow (DCTD)
  - Gregory Downing (OTIR)
  - Jorge Gomez (OCTR)
  - Ernest Hawk (OCTR)
  - Anne Lubenow (OC)
  - David Maslow (DEA)
  - Suresh Mohla (DCB)
  - Cherie Nichols (OSPA)
  - John Carl Oberholtzer (OCTR)
  - Richard Pazdur (FDA)
  - Charles Rabkin (DCEG)
  - Jeffrey Schlom (CCR)
  - Richard Simon (DCTD)
  - Sudhir Srivastava (DCP)
  - Daniel Sullivan (DCTD)

TRWG Expertise in Various Populations

- Head & Neck
  - Waun Ki Hong
  - David Sidransky
- Lung
  - Phillip Dennis
  - Steven Dubinett
  - Laurie Fenton
  - Waun Ki Hong
  - Roman Perez-Soler
- Stomach/Esophagus
  - Ernest Hawk
  - Paul Limburg
  - Brian Reid
- Pancreas
  - James Abbruzzese
- Liver
  - Adrian DiBisceglie
  - Theodore Lawrence
  - Charles Rabkin
- **Colorectum**
  - James Doroshow
  - Raymond Dubois
  - Ernest Hawk
  - Paul Limburg
  - Richard Pazdur
  - Jeffrey Schlom
- **Breast**
  - Kenneth Cowan
  - Laura Esserman
  - Joe Gray
  - William Hait
  - H. Kim Lyerly
  - Anne McTiernan
  - Olufunmilayo Olopade
  - Mitchell Schnall
  - Thomas Sellers
  - Thea Tlsty
- Ovary/Gyn
  - David Alberts
  - Robert Bast
  - Thomas Sellers
- GU
  - Richard Cote
- Prostate
  - William Nelson
- Brain
  - Darrel Bigner
- Skin
  - David Alberts
- Leukemia/Lynphoma
  - Michael Caligiuri
  - Peter Emanuel
  - A. Thomas Look
  - David Scheinberg
- Myeloma
  - Kenneth Anderson

TRWG Expertise in Special Scientific Areas

- **Prevention**
  - David Alberts
  - Adrian DiBisceglie
  - Steven Dubinett
  - Raymond Dubois
  - Laura Esserman
  - Gary Gordon
  - Ellen Gritz
  - Ernest Hawk
  - Waun Ki Hong
  - Paul Limburg
  - Lynn Matrisian
  - Anne McTiernan
  - William Nelson
  - Olufunmilayo Olopade
  - Charles Rabkin
  - Brian Reid
  - Thomas Sellers
  - David Sidransky
  - Sudhir Srivastava
  - Thea Tlsty
- **Pediatrics**
  - Peter Emanuel
  - A. Thomas Look
- **Survivorship**
  - Ida “Ki” Moore
- **Genetics**
  - Kenneth Buetow
  - Joe Gray
  - Olufunmilayo Olopade
  - William Nelson
  - Charles Rabkin
  - Thomas Sellers
  - David Sidransky
- **Imaging**
  - Daniel Sullivan
  - Mitchell Schnall
- **Drugs/Immunologics**
  - James Abbruzzese
  - David Alberts
  - Kenneth Anderson
  - Martin Cheever
  - Jerry Collins
  - Michael Caligiuri
  - Sara Courtneidge
  - Kenneth Cowan
  - James Doroshow
  - Tona Gilmer
- **Drugs/Immunologics (cont.)**
  - Gary Gordon
  - William Hait
  - Ernest Hawk
  - Waun Ki Hong
  - Paul Limburg
  - H. Kim Lyerly
  - William Nelson
  - Richard Pazdur
  - Roman Perez-Soler
  - David Scheinberg
  - Jeffrey Schlom
  - Richard Schilsky
  - Ellen Sigal
  - Richard Simon
  - Louis Weiner
- **Biobehavior**
  - Ellen Gritz
  - Anne McTiernan
- **Preclinical Models**
  - Tyler Jacks
  - Lynn Matrisian
  - Suresh Mohla
  - Thea Tlsty

TRWG Progress to Date (1)

- Recruited TRWG leadership & members
- Reviewed foundational documents
- Analyzed Clinical Trials Working Group process for ideas, challenges & lessons learned
- Developed web-based communication platform
- Gathered public comment on key questions
- Analyzed NCI's current investments in TR
  - Portfolio analysis
  - Process analysis
- Mapped 5 developmental pathways to clinical goals
- Constituted 4 Phase I subcommittees
  - Organization & funding
  - Core services
  - Prioritization
  - Project management

TRWG Progress to Date (2)

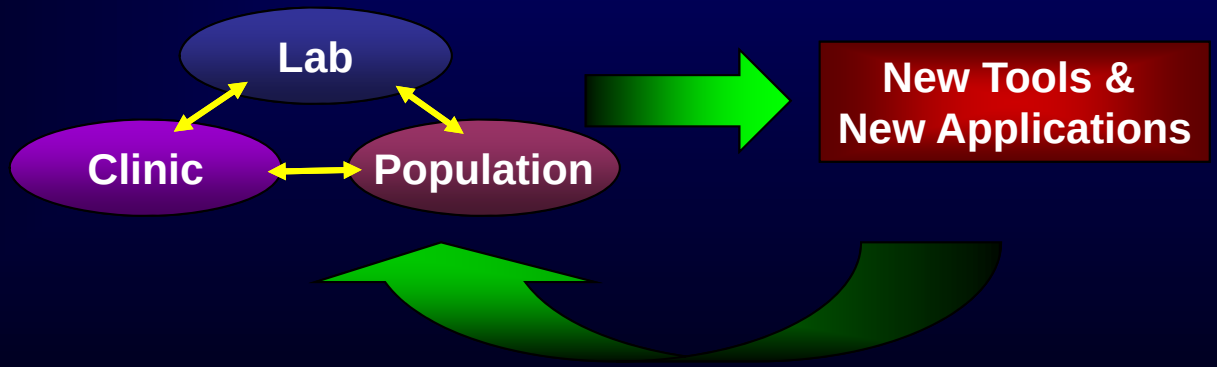
- Organized subcommittee conference calls
- Convened plenary meetings (Dec. ’05, Mar. ’06, May ’06)
- Convened a public roundtable (Feb. ‘06) focused on:
  - Developmental pathways to clinical goals
  - Cross-cutting themes
  - Populations intended to benefit
- Convened an industry/foundation roundtable (Apr. ‘06) focused on:
  - Resources
  - Collaboration
  - Developmental pathways
  - Management
- Today’s charge: Present draft Phase I recommendations

TRWG Products to Date

- TR definition
- Five developmental pathways to clinical goals
- Portfolio analysis
  - Review of NCI's current TR activities
- Process analysis
  - Case studies of 20 examples of translation in practice
- Draft Phase I recommendations

TRWG's Definition of Translational Research

- Research that transforms scientific discoveries arising in the lab, clinic or population into new clinical tools & applications that reduce cancer incidence, morbidity & mortality



The Translational Continuum

Basic Science Discovery

- Promising molecule or gene target
- Candidate protein biomarker
- Basic epidemiologic finding

Early Translation

- Partnerships & collaboration (academia, government, industry)
- Intervention development
- Phase I/II trials

Focus of TRWG

Late Translation

- Phase III trials
- Regulatory approval
- Partnerships
- Production & commercialization
- Phase IV trials – approval for additional uses
- Payment mechanism(s) established to support adoption
- Health services research to support dissemination & adoption

Dissemination*

- To community health providers
- To patients & public

Adoption

- Adoption of advance by providers, patients, public
- Payment mechanism(s) in place to enable adoption

**New drug, assay, device, behavioral intervention, educational materials, training*

President's Cancer Panel, 2004-2005 Annual Report

Five Pathways to Clinical Goals

- Agent
- Immune Response Modifier
- Interventive Device
- Risk Assessment Device
- Lifestyle Alteration

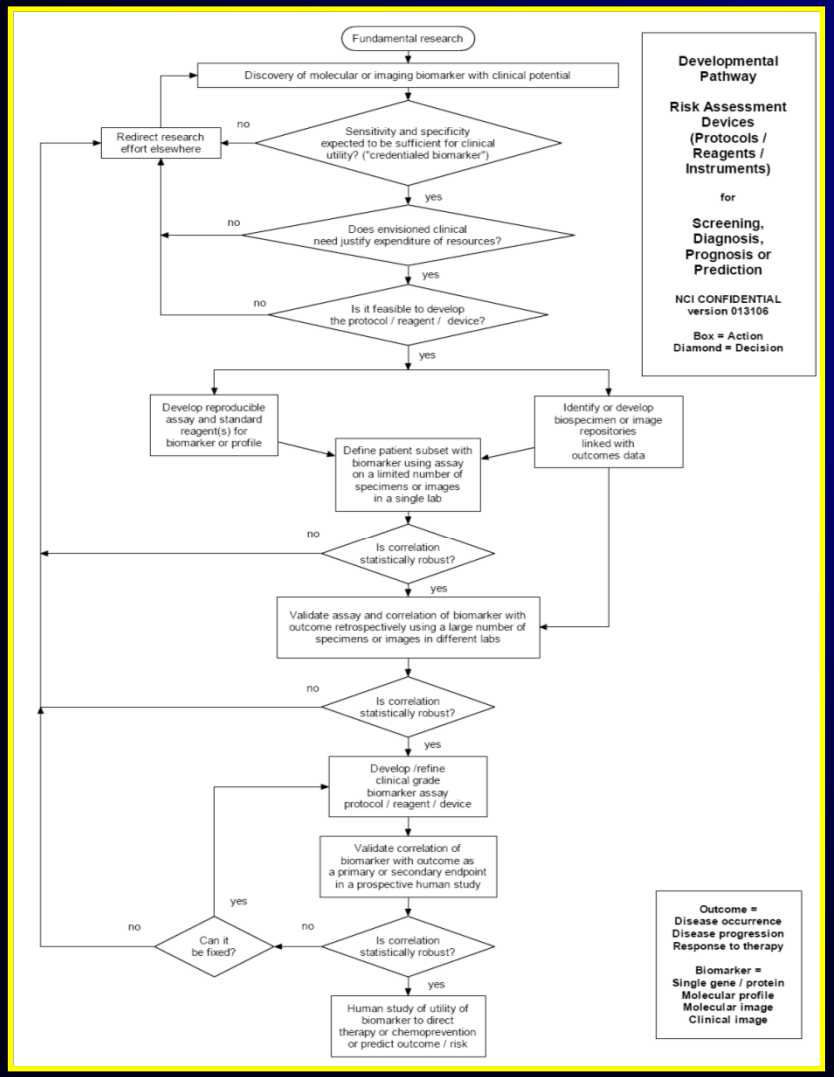
Portfolio Analysis: Key Findings

- Awards not adequately categorized for translational content to provide meaningful quantitative assessment
- TR is funded by most NCI Divisions, Offices & Centers
- TR is funded by a range of mechanisms - collaborative, facilitated & individual
- The majority of TR awards are to NCI-designated Cancer Centers

Process Analysis: Key Findings

- Translation Occurs via Diverse Mechanisms
  - Single facilitated program
  - Series of individual-investigator awards
  - NCI intramural research program
  - Combination of mechanisms
  - Mechanisms from NCI & other Institutes
- Translation Occurs via Diverse Stakeholder Interactions
  - Academia with industry funding
  - Traditional hand-off from academia to industry
  - Public/private partnership
  - Industry discoveries advancing with NCI-funded resources

The Challenge of Early Translation



- How can we best assure that
  - The most promising concepts enter the developmental pathway?
  - Concepts that enter advance to the clinic or to productive failure?
  - Progress is as rapid, efficient & effective as possible?

Obstacles to Meeting the Challenge

- Insufficient coordination & integration across NCI results in a fragmented TR effort that risks duplication & may miss important opportunities
- Absence of clearly designated funding & adequate incentives for researchers threatens the perceived importance of TR within the NCI enterprise
- Absence of a structured, consistent review & prioritization process tailored to the characteristics & goals of TR makes it difficult to direct resources to critical needs & opportunities

Obstacles to Meeting the Challenge

- TR core services are often duplicative & inconsistently standardized, with capacity poorly matched to need
- Multidisciplinary nature of TR & the need to integrate sequential steps in complex development pathways warrants dedicated project management resources
- Insufficient collaboration & communication between basic & clinical scientists & the paucity of effective training opportunities limits the supply of experienced translational researchers
- Inadequate collaboration with industry delays appropriate developmental hand-offs

TRWG Phase I Recommendation Subcommittees

Organization & Funding	Core Services Coordination	Prioritization	Project Management
Gray, Joe	Cowan, Kenneth	Tlsty, Thea	Lawrence, Theodore
Reid, Brian	Schnall, Mitchell	Schilsky, Richard	Limburg, Paul
Bast, Robert	Alberts, David	Abbruzzese, James	Anderson, Kenneth
Caligiuri, Michael	Bigner, Darell	Cheever, Martin	Collins, Jerry
Cote, Richard	Buetow, Kenneth	Downing, Gregory	Courtneidge, Sara
Dennis, Phillip	Doroshow, James	Emanuel, Peter	DiBisceglie, Adrian
Gomez, Jorge	Dubinett, Steven	Hong, Waun Ki	Esserman, Laura
Gordon, Gary	DuBois, Raymond	McGrath, Gail	Fenton, Laurie
Gritz, Ellen	Gilmer, Tona	McTiernan, Anne	Lubenow, Anne
Hait, William	Jacks, Tyler	Mohla, Suresh	Lyerly, H. Kim
Kerr, David	Look, A. Thomas	Oberholtzer, John Carl	Moore, Ida “Ki”
Scheinberg, David	Maslow, David	Olopade, Olufunmilayo	Nichols, Cherie
Sigal, Ellen	McLeod, Howard	Perez-Soler, Roman	Sellers, Thomas
Simon, Richard	Pazdur, Richard	Rabkin, Charles	Sidransky, David
Sullivan, Daniel	Schlom, Jeffrey	Weiner, Louis	Srivastava, Sudhir

Flexible Organizational Approach

Obstacle Addressed

Insufficient coordination & integration across NCI results in a fragmented TR effort that risks duplication & may miss important opportunities

Draft Recommendation

Establish a flexible, integrated organizational approach that coordinates early TR opportunities across the Institute

Flexible Organizational Approach

Goals of Draft Recommendation

- Enhance portfolio management & coordination
- Identify & advance the most promising opportunities
- Reduce fragmentation & redundancy
- Accelerate progress by ensuring that resources are adequately focused
- Coordinate the setting of TR goals
- Ensure dynamic balance of investigator-initiated & prioritized projects

Flexible Organizational Approach

Implementation Concepts Under Discussion

- Matrix organizational structure integrating all NCI programs & mechanisms that support TR
- Leadership for TR with authority over the matrix structure
- External advisory committee to advise the NCI Director on TR conduct, oversight, prioritization & funding
- Role of advisory committee & matrix structure in prioritization process
- Nature & scope of coordination of investigator-initiated projects

Designated Funding

Obstacle Addressed

Absence of clearly designated funding & adequate incentives for researchers threatens the perceived importance of TR within the NCI enterprise

Draft Recommendation

Designate a specific portion of the NCI budget for early TR

Designated Funding

Goals of Draft Recommendation

- Recognize importance of TR
- Manage TR as an enterprise
- Demonstrate enduring commitment to TR

Designated Funding

Implementation Concepts Under Discussion

- Nature & scope of TR activities covered by such designated funding
- Percentage of NCI budget to be designated
- Balance between funds for investigator-initiated projects & major projects prioritized through a comprehensive, system-wide process
- Nature of coordinated budget management process

Distinctive Prioritization Process

Obstacle Addressed

Absence of a structured, consistent review & prioritization process tailored to the characteristics & goals of TR makes it difficult to direct resources to critical needs & opportunities

Draft Recommendation

Establish a distinctive prioritization process for early TR to prioritize research goals & select specific projects to realize those goals

Distinctive Prioritization Process

Goals of Draft Recommendation

- Identify emerging concepts & translational opportunities that warrant a prioritized effort
- Focus sufficient resources on high priority projects to assure they are advanced efficiently & rapidly to the clinic
- Prioritize projects through a dynamic, systematic & iterative process involving all key stakeholders

Distinctive Prioritization Process

Implementation Concepts Under Discussion

- Translational Research Prioritization Committee as an external advisory body
- Membership encompassing all key stakeholders, term-limited to promote dynamism & adaptability
- Transparent decision process, drawing on broad community input
- Subcommittee structure to address varied TR vantage points (e.g., organs, mechanisms, clinical products, populations, developmental pathways)
- Candidate project concepts proposed by investigators, NCI staff, industry, etc.
- Criteria for prioritization to include scientific quality/validity, technical feasibility, clinical need

Tailored Funding/Review Mechanisms

Obstacle Addressed

Absence of a structured, consistent review & prioritization process tailored to the characteristics & goals of TR makes it difficult to direct resources to critical needs & opportunities

Draft Recommendation

Tailor funding & review mechanisms for early TR projects to facilitate & incentivize researcher participation

Tailored Funding/Review Mechanisms

Goals of Draft Recommendation

- Provide investigators with incentives for risk-taking & to reward “productive failure” as well as successful completion
- Provide avenues for flexibly forming teams & collaborations
- Reduce lag time between phases of research process
- Ensure TR applications are treated appropriately in review

Tailored Funding/Review Mechanisms

Implementation Concepts Under Discussion

- **Funding Mechanisms**
  - Goal-oriented, large-scale, flexible team awards encompassing one or more projects with incentives for collaboration & multi-institution network formation
  - Milestone-based funding to reward successful completion or productive failure
  - Translational R01's with both a discovery & a translational component

- **Review**
  - TR projects directed to designated study sections/review groups, potentially based on developmental pathways
  - Review criteria / processes tailored to TR objectives
  - Review criteria to reward collaborations & co-funding from industry
  - "Rolling tenure" review model based on a 3+3 year approach

Core Services Coordination

Obstacle Addressed

TR core services are often duplicative & inconsistently standardized, with capacity poorly matched to need

Draft Recommendation

Establish a system to coordinate core services & other infrastructure components essential for early TR

Core Services Coordination

Goals of Draft Recommendation

- Facilitate & accelerate access to a broad range of core services
- Increase standardization, quality assurance & cross-core reliability
- Minimize redundancy & assure efficiency & economy of scale by operating services at optimal capacity
- Assure core services are available in a coordinated & cooperative manner across funding mechanisms

Core Services Coordination

Implementation Concepts Under Discussion

- Inventory of existing cores to identify excess capacity & redundancy
- Publicly-accessible information system to track core facilities
- Incentive structures to reward consolidation & eliminate unnecessary duplication
- Core services that would benefit from regionalization through the creation of centers or networks
- Oversight & certification system that assures standardization & quality-assurance
- Mechanisms to ensure core services are multi-user, service-based entities
- Approaches to enhance GMP/GLP manufacturing capabilities

Project Management

Obstacle Addressed

Multidisciplinary nature of TR & need to integrate sequential steps in complex development pathways warrants dedicated project management resources

Draft Recommendation

Establish a formal management structure for early TR

Project Management

Goals of Draft Recommendation

- Speed the TR process
- Facilitate recognition of & access to internal & external resources
- Promote coordination & communication between the project scientific leads & the multi-disciplinary project team
- Facilitate progress across stages, disciplines & programs
- Assure progress (i.e., continued success or productive failure) through periodic review of project milestones

Project Management

Implementation Concepts Under Discussion

- Location of project managers – NCI, academic institutions or both
- Individual project managers versus a project management team with complementary areas of expertise
- Degree/scope of project management for investigator-initiated projects
- Roles of project management system for designated projects
  - Coordinate with PI to assure seamless progression of the development process
  - Identify, facilitate & coordinate access to resources & collaborators
  - Coordinate regulatory filings, interactions with industry, etc.
  - Monitor progress based on milestones; provide input on decisions
- Role of project management system during proposal development

Analysis & Evaluation

Draft Recommendations

- Develop coding & tracking system that allows real-time analysis of the nature & scope of the NCI's early TR enterprise
- As the proposed changes in the NCI's early TR enterprise are implemented, establish a formal evaluation system to assess their impact

TRWG Future Activities

- Continue Phase I subcommittee work
- Constitute Phase II subcommittees to develop draft recommendations on
  - External integration
  - Workforce/training
- Present interim progress to NCAB (Sept. ‘06)
- Invite public comment via web on draft recommendations (early fall ‘06)
- Convene 2nd public roundtable (fall ‘06)
  - Discuss Phase I & II draft recommendations
  - Solicit ideas regarding implementation
- Develop implementation plans
- Present final model, recommendations & implementation plan to NCAB (winter ‘07)