Overcoming the Challenges to the Advancement of Transplantation Therapies

September 14, 2016
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Median years to kidney transplant for wait-listed adult patients
Kidney transplants

Transplants (in thousandths) vs. Year

Age Groups:
- <18
- 18-34
- 35-49
- 50-64
- 65+

Sex:
- Male
- Female

Year Range:
- 1998 to 2012

Graph showing the trend of kidney transplants over the years, categorized by age groups and sex.
What is the Problem?

1. We do not have enough organs to transplant.
2. Our overall graft survival is still limited
3. Limitation of graft function is largely a longer term problem
4. Short term PREDICTORS of long term graft survival are currently limited
5. Development of novel targets & therapeutics are needed:
   • Antibody medicated rejection
   • Recurrent Disease
   • Fibrosis
   • BK nephropathy
   • APOL1 risk variant related kidney failure
6. Changes to regulatory environment to facilitate above
Why the TTC?

The problems faced in developing new therapeutics can only be solved by a consortium that includes:

- Transplant professionals
- Academia
- Industry partners
- Regulatory agencies
- Research agencies
Where have we been?

• Theory is easier than practice
• Consensus takes time
• Structure is critical
The overall objective of the TTC will be to support collaborative development and regulatory endorsement of new drug development tools for transplantation which, in turn, may help to shorten the time needed to develop and deliver safe, effective therapies for transplantation patients.
Critical Path Initiative

Independent 501(c)3 founded in 2005 “… to foster development of new evaluation tools to inform medical product development”

Memorandum of Understanding created between the FDA and C-Path in 2005
C-Path: A Public Private Partnership

- Act as a trusted, neutral third party
- Convene scientific consortia of industry, academia, and government for sharing of data/expertise
  - The best science
  - The broadest experience
  - Active consensus building
  - Shared risk and costs
- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
- Official regulatory endorsement of novel methodologies and drug development tools
FDA and EMA Qualification:
A Formal Process of Review and Acceptance

Guidance for Industry and FDA Staff
Qualification Process for Drug Development Tools

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
January 2014
Procedural

Accelerating the Path to a Healthier World

The Critical Path Institute is a catalyst in the development of new approaches to advance medical innovation and regulatory science. We achieve this by leading teams that share data, knowledge and expertise resulting in sound, consensus based science.

As an independent and trusted partner we value integrity, innovation and teamwork.
## C-Path Consortia

**Twelve global consortia collaborating with 1,450+ scientists and 84 organizations**

<table>
<thead>
<tr>
<th>Consortia</th>
<th>Focus/Goal</th>
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<tbody>
<tr>
<td>Coalition Against Major Diseases</td>
<td>Focusing on diseases of the brain</td>
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<tr>
<td>Coalition For Accelerating Standards and Therapies</td>
<td>Data standards</td>
</tr>
<tr>
<td>Critical Path for Parkinson’s Consortium</td>
<td>Enabling clinical trials in Parkinson’s Disease</td>
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<tr>
<td>Critical Path to TB Drug Regimens</td>
<td>Accelerating the development of TB drug regimens and diagnostics</td>
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<tr>
<td>Duchenne Regulatory Science Consortium</td>
<td>Duchenne Muscular Dystrophy</td>
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<tr>
<td>International Neonatal Consortium</td>
<td>Neonatal clinical trials</td>
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<td>Multiple Sclerosis Outcome Assessments Consortium</td>
<td>Drug Effectiveness in MS</td>
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<td>Polycystic Kidney Disease Outcomes Consortium</td>
<td>New imaging biomarker for PKD</td>
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<td>Patient-Reported Outcome Consortium</td>
<td>Assessing treatment benefit</td>
</tr>
<tr>
<td>Electronic Patient-Reported Outcome Consortium</td>
<td>Electronic capture of treatment benefit</td>
</tr>
<tr>
<td>Predictive Safety Testing Consortium</td>
<td>Drug safety</td>
</tr>
<tr>
<td>Pediatric Trials Consortium</td>
<td>Developing effective therapies for children</td>
</tr>
</tbody>
</table>

- Biomarkers
- Clinical outcome assessment tools
- Clinical trial simulation tools
- Data standards
- In vitro tools
# C-Path Collaborators

## Industry
- AbbVie
- Acorda Therapeutics
- Actelion Pharmaceuticals
- Allergan
- Almac
- Amgen
- AstraZeneca
- Boehringer Ingelheim
- Bracket
- Bristol-Myers Squibb
- Celgene
- Cepheid
- CRF Health
- Daiichi Sanyo
- Edetek
- Eisai
- Eli Lilly and Company
- EMD Serono
- Ephibian
- ERT
- Exco InTouch
- Forest Laboratories, Inc.
- GE Healthcare
- Genentech
- Genzyme
- GlaxoSmithKline
- Hoffmann-La Roche, Inc.
- Horizon Pharma
- ICON
- Ironwood Pharmaceuticals
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Medidata Solutions
- Merck and Co., Inc.
- Meso Scale Discovery
- Millennium: The Takeda Oncology Company
- Mitsubishi Tanabe Pharma Corporation
- Novartis
- Novo Nordisk
- Oracle
- Otsuka Pharmaceutical
- Pfizer
- Pharsight/Certara
- PTC Therapeutics
- PHT
- Sanofi
- Santhera Pharmaceuticals
- Shire
- Sunovion Pharmaceuticals
- TAG
- Takeda
- Teva Pharmaceuticals
- UCB
- Vertex

## Nonprofit Research Organizations
- Alzheimer’s Association
- Alzheimer’s Drug Discovery Foundation
- Alzheimer's Research UK
- Bill & Melinda Gates Foundation
- CDISC
- Cincinnati Children’s Hospital
- Engelberg Center for Health Care Reform
- EDCTP
- Flinn Foundation
- Foundation for National Institutes of Health
- National MS Society
- Parent Project Muscular Dystrophy
- Parkinson’s UK
- PKD Foundation
- Reagan-Udall Foundation
- Science Foundation Arizona
- SRI International
- Stop TB Partnership
- TB Alliance
- US Against Alzheimer’s

## Government and Regulatory Agencies
- Centers for Disease Control and Prevention
- European Medicines Agency
- Innovative Medicines Initiative
- International Genomics Consortium
- National Institute of Allergy and Infectious Diseases
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institutes of Health
- National Institute of Neurological Disorders and Stroke
- Pharmaceuticals and Medical Device Agency
- U.S. Food and Drug Administration
- World Health Organization

## Academic Institutions
- The University of Arizona
- Arizona State University
- Baylor University
- University of California San Francisco
- University of Colorado-Denver
- Emory University
- University of Florida
- Johns Hopkins
- Mayo Clinic
- University of Texas Southwestern Medical Center
- Tufts University
C-Path Core Competencies

• Regulatory qualification of preclinical and clinical biomarkers for safety, efficacy, and trial enrichment

• Outcome assessment instrument development

• Comprehensive modeling & simulation programs

• Novel *in vitro* tools to expedite proof-of-concept

• Clinical data standards development

• Secure data management, standardization, curation, database development

• Forming and managing large international consortia
C-Path Data Mapping and Integration Process

Data as contributed

Master Standardized Datasets

Analysis Datasets
C-Path Approach to Problem Solving:

**Problem**

- Uncertainty in design of clinical trials
- Highly variable subpopulations recruited into randomized clinical trials
- Inadequate outcome measures for assessing efficacy of drugs

**C-Path Approach**

- Regulatory endorsed clinical trial simulation tool
- Regulatory biomarker qualification for enrichment in randomized clinical trials
- Qualified innovative/sensitive clinical outcome assessment instrument for efficacy of novel drugs
C-Path Accomplishments

- First preclinical safety biomarkers (7) qualified by the FDA, EMA, and PMDA
- First imaging biomarker for trial enrichment qualified by the EMA (for Alzheimer’s disease)
- First imaging biomarker for trial enrichment qualified by the FDA and EMA (for Polycystic Kidney Disease)
- First Clinical Data Interchange Standards Consortium (CDISC) therapeutic area data standard (Alzheimer’s disease), and additional standards for TB, PD, PKD, MS, and Influenza
- First drug-disease-trial model for AD endorsed by the FDA & EMA
- First Drug Development Tool for TB Qualified by EMA and included in FDA Guidance for TB Drug Development
Overcoming the Challenges to the Advancement of Transplantation Therapies

September 14, 2016
Where do we want to go?

• Draft proposal designed to begin discussions

• Everything is still on the table
• The TTC’s initial goals will be determined by the members to address the greatest needs.

• The initial focus will be on kidney transplants, but it could be expanded over time.
• Establish a forum to identify and address *regulatory barriers* that impact the development and approval of new therapies in transplantation through advocacy and white papers for regulatory agency consideration in writing new guidance documents.

• Develop and compare composite endpoints in transplantation (*new endpoints*)

• Identify potential *biomarkers* for use in clinical trials and obtain regulatory endorsement for the use of these biomarkers based on a specific context of use.
• Other items could be considered over time depending on the needs and priorities of the consortium members such as new trial designs, master protocols, pharmacometric models, and simulation tools.
• What is needed?

• What do we already have and what do we need to create?

• What are industry priorities?
How can we translate these into specific activities that will “build the road” to new therapy?

- Identification of specific projects to address
  - Ex. antibody-mediated rejection

- Creation of workgroups to explore specific issues/specific charges
  - What data already exists?
  - What biomarkers might be useful and how can they be “validated” for use in clinical trials? etc.

- Consensus documents/white papers
  - Define the goals and frame discussion
  - Scientifically support new endpoints or biomarkers
How?

• Creation of a central database from existing data using one format (C-DISC)

• Develop new tools if they are needed (ex. combined endpoints, statistical assessments, modeling)
• Include people not here today. Learn from others who have built similar “roads”.

• Open, ongoing discussions and work. Not just one meeting and a white paper. Work as a TEAM
At the end of today...

• Would like to have a verbal commitment from potential members

• Would like you to be a champion to help with approval process

• Communicate what your priorities are

• Consider if there is anybody else that should be invited to participate
American Society of Transplant Surgeons
American Society of Transplantation
Critical Path Institute
Thank You!

www.c-path.org
## Agenda

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• What are industry priorities?

• What needs to be done (specific and general) to provide a pathway for new therapy for transplant recipients?
Focus of This Hour’s Discussion

• To review the survey and discuss:
  - What *types* of projects does the assembled group believe to be most impactful
  - What *types* of projects does the assembled group believe to be most feasible
Survey Summary – Short-term

• Most impactful projects in order (60% or greater highly impactful)
  - New efficiencies in clinical trial design
  - Registry to collect data leading to approval of new therapies for AMR
  - Study factors contributing to non-adherence
  - Seek orphan drug designation for transplant IS agents
  - Use SRTR data to support new indications of IS agents
  - Educate investigators about investigator initiated studies
  - Collect or use existing patient reported outcome data to support a label or design studies
  - Separate labeling for use of currently approved agents in transplantation

• Least impactful projects
  - Study of pharmacokinetics in patients with gastric bypass/sleeve

Green - >65% highly achievable, red <50% achievable
Survey Summary – Long-term

• Most impactful projects in order
  - Develop consensus position on new biomarkers to facilitate IS drug approval
  - Develop new technologies to predict subacute/chronic rejection without Bx
  - Develop novel trial designs applicable to rare disease conditions

• Least impactful projects
  - Workshop to educate physicians about investigator initiated trials
  - Pharmacogenetic studies
  - Separate labeling for repurposing existing non-transplant agents
  - Examine the effects on safety of non-transplant drugs on IS drugs

Green - >65% highly achievable, red <50% achievable
Potential Project Areas

• Regulatory policies and procedures
• Design of new clinical trial strategies/efficiencies
• Surrogate endpoints
• Creation of databanks or data repositories to support drug applications
• Creation of biobanks – biomarker discovery
• Design and conduct novel clinical trials
• Other
Regulatory Projects

- Dual labeling/indications
  - Separate toxicities of agents used as monotherapy for a specific disease process from those observed with the agent used as part of a regimen in transplantation
  - Separate labeling for transplant uses of currently labeled medications.
  - Orphan drug approval pathways
  - Changes in patent life-span for “orphan” drugs?
  - Create pathway for approval of “standard of care” off label medications such as Work with Systematic Reviews, or Data Repositories
  - Create registries for safety & efficacy for new off label medications to support regulatory approval
Design of new clinical trial strategies/efficiencies

- **Special Designs for Small Clinical Trials**
  - $n$-of-1 design
  - Sequential design
  - Decision analysis-based design
  - Ranking and selection design
  - Adaptive design
  - Risk-based allocation design

- **Statistical Approaches to Analysis of Data from Small Clinical Trials**
  - Sequential analysis
  - Hierarchical models
  - Bayesian analysis
  - Decision analysis
  - Statistical prediction
  - Meta-analysis
  - Risk-based allocation design

Design of new clinical trial strategies/efficiencies

- Creation of a standardized control group that could be shared between studies
- Small study design and analysis
- Creating new composite endpoints or weighted composite endpoints to allow detection of difference in efficacy
Surrogate Endpoints

- Renal function
- Donor specific antibodies
- Composite endpoints
  - Renal function, DSA, histology, proteinuria
Creation of databanks or biobanks

• Creation of a large data repository
  - Similar to the C-FAST initiative?

• Creation of a biorepository to facilitate biomarker discovery
  - Competition with multiple ongoing projects
Design and conduct novel clinical trials

- Similar to Clinical Trials in Organ Transplantation
  - Opportunities to collaborate or conduct studies not currently underway
• What have we missed?
Thank You!

www.c-path.org
Lunch

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FDA Experience with Surrogate Endpoints and Drug Development in Other Therapeutic Areas

Renata Albrecht, MD
Director, Division of Transplant and Ophthalmology Products
Office of Antimicrobial Drugs
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Example from AIDS/HIV

Clinical Endpoints to Surrogate Endpoints

Courtesy Dr. Marc Cavaillé-Coll, M.D., Ph.D.
Division of Transplant and Ophthalmology Products
Clinical Endpoints

• In the 1980’s, Acquired Immune Deficiency Syndrome (AIDS)-defining opportunistic infections (OI) and other conditions were clinical endpoints
  – Infections
  – Wasting syndrome
  – Malignancies
• Standard definitions established by consensus groups, e.g., AIDS Clinical Trials Group.

• 1986 - Zidovudine or azidothymidine (AZT)
Clinical Endpoints
and Associated Peripheral Blood CD4+ Cell Count
(normal CD4+ count = 500-1500/µL )

- Tuberculosis
- Recurrent Pneumonia
- Kaposi Sarcoma
- Esophageal Candidiasis
- Pneumocystis
- Toxoplasmosis
- Cryptococcus
- Wasting
- CMV retinitis
- PML
- MAC
- Lymphoma

Clinical events were weighed equally, even though they may occur at different levels of immune function deficiency
Evolution of Surrogate Endpoints for HIV Drug Approval

1991
- CD4 cells
- p24 antigen
- ZDV
- ddI, ddC, d4T

1996
- CD4
- HIV-RNA
- 3TC, SQV

Current
- HIV-RNA
- CD4
- RTV, IDV, NFV, NVP
- Multiple drugs

Relationship between HIV-RNA and Clinical Benefit
1996 and HIV-RNA (viral load)

- HIV-RNA tests
  - Progress in standardization of methods and interpretation criteria.
  - Increase in HIV-RNA seen with disease progression
    - precedes CD4 cell decreases (CD4 better marker of net degree of immunosuppression and criteria for starting treatment).
  - Decrease seen in response to therapy
  - Rebound associated with drug resistance, need to change treatment regimen

- Good candidate for Surrogate Marker development
Collaboration

• 1996 Surrogate Marker Working Group
  – Industry, academia, and government

• To examine relationship between treatment-induced change in HIV-RNA and clinical endpoints
  – Correlations between viral load and clinical outcome
  – Correlations between short-term viral load suppression and durability of viral load response
## HIV RNA and Clinical Benefit

5 Analyses (1996), >5000 patients

<table>
<thead>
<tr>
<th>ANALYSES</th>
<th>N</th>
<th>REGIMENS</th>
<th>CD4</th>
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<tbody>
<tr>
<td>1) Abbott Single Study (subset)</td>
<td>159</td>
<td>PI + NRTIS</td>
<td>21</td>
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<tr>
<td>2) NIH AIDS Clinical Trial Group Multiple</td>
<td>1000</td>
<td>Many</td>
<td>218</td>
</tr>
<tr>
<td>Studies</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3) Glaxo-Wellcome Studies Multiple Studies</td>
<td>1581</td>
<td>ZDV + 3TC (others)</td>
<td>209</td>
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<tr>
<td>4) Pharmacia &amp; Upjohn Studies: Two Studies</td>
<td>1842</td>
<td>DLV+ZDV, DLV+DDI</td>
<td>230</td>
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<tr>
<td>5) Roche Study</td>
<td>940</td>
<td>SQV+DDC, SQV, DDC</td>
<td>170</td>
</tr>
</tbody>
</table>
Progression vs. HIV RNA levels

POOLED ACTG STUDIES

Stratifying factors
- study and treatment
- none
- study
- treatment

WEEK 24 HIV RNA Reduction:
- >1.0 log
- 0.5-1.0 log
- 0-0.5 log
- no reduction

ADJ. RR (natural log)
Progression vs. Viral Load Nadir

GSK Analyses

- Incidence
- Viral Load Nadir (copies/mL)

- Median
- >Median

Viral Load Nadir (copies/mL):
- <400
- <500
- <20,000
- >20,000

Incidence:
- 0
- 10
- 20
- 30
- 40
- 50
- 60
- 70
- 80
- 90
- 100
## Progression vs. Duration of Response

### Pharmacia-Upjohn Analyses

<table>
<thead>
<tr>
<th>Response Duration #DAYS</th>
<th>Hazard ratio</th>
<th>95% CI for HR</th>
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<tbody>
<tr>
<td>No response</td>
<td>1.000</td>
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<tr>
<td>1-29</td>
<td>0.68</td>
<td>(0.43, 1.04)</td>
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<tr>
<td>30-57</td>
<td>0.72</td>
<td>(0.41, 1.27)</td>
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<tr>
<td>58-113</td>
<td>0.55</td>
<td>(0.32, 0.95)</td>
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<tr>
<td>114-141</td>
<td>0.26</td>
<td>(0.128, 0.528)</td>
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<tr>
<td>&gt;142</td>
<td>0.29</td>
<td>(0.145, 0.564)</td>
</tr>
</tbody>
</table>
Analyses: Summary of Findings

• Lower risk of clinical disease progression when
  – HIV RNA decreases (> 0.5 log)
  – Greater Reductions in HIV RNA
  – More Sustained Reductions (> 8-12 weeks) in HIV RNA
July 1997 AC Meeting
Recommendations

• HIV RNA is a suitable endpoint for:
  – Accelerated Approval (24 weeks)
  – Traditional Approval (48 Weeks)

• Concordance with other markers (CD4)

• Precedents for “Lab” Endpoints:
  – Cholesterol and HbA1c
Relevance to Transplant

• Validated surrogate endpoints can substantially facilitate drug development.

• Multiple trials, large databases, and other types of supporting data are needed to "validate" a surrogate.

• 100% correlation of a surrogate and clinical endpoint is not likely. Clinical Endpoints are not perfect gold standards.
Selected References


Oncology Products

Courtesy of: Paul G Kluetz, MD
FDA Oncology
Two Approval Pathways

Regular Approval

- Regular approval requires
  - Substantial evidence of Safety and Efficacy
  - Well-controlled clinical trials (usually 2 or more)
  - Based on prolongation of life, a better life or an established surrogate for either of the above

- Efficacy endpoints for Regular Approval normally Direct Measures or Established Surrogates:
  - Overall Survival (“Prolongation of life”)
  - Patient Reported Outcomes (“A better life”)
  - SRE in Prostate Ca or DFS in Breast Ca (“Established Surrogates”)

- “Safe and Effective” — no comparative efficacy
  - Allows for non-inferiority designs

Accelerated Approval

- “Provide meaningful therapeutic benefit… over existing therapies”

- Can be based on a “Surrogate endpoint… reasonably likely… to predict clinical benefit”

- But are “Subject to the requirement that the applicant study the drug further”

- These Post-Marketing Clinical Trials are Required
  - Should usually be underway at the time of accelerated approval
  - Applicant should carry out studies with due diligence
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Risks/Benefits and Endpoints

Accelerated Approval

- Benefits and Risks to the Accelerated Approval Pathway
  - Benefits:
    - Use of an unestablished surrogate endpoint
    - Usually provides for earlier events and smaller, quicker trials
  - Risks:
    - Must demonstrate product is better than existing therapy (unlike regular approval, there is an implied comparative efficacy requirement here)
    - Must complete post-marketing trials and confirm meaningful clinical benefit

- 10% of Accelerated Approvals in oncology have been withdrawn for failure to confirm a benefit
  - NOT a failure of the accelerated approval program
  - We expect a small percentage of products to fail to verify this benefit
  - This is the anticipated tradeoff for earlier availability of promising anti-cancer agents.
Risks/Benefits and Endpoints

Accelerated Approval

- Benefits and Risks to the Accelerated Approval Pathway
  - Benefits:
    - Use of an unestablished surrogate endpoint
    - Usually provides for earlier events and smaller, quicker trials
  - Risks:
    - Data demonstrates benefit is higher than existing therapy
      - Regular approval: drug is effective but with substantial risk
    - Requires post-marketing trials to confirm meaningful clinical benefit

- 10% of Accelerated Approvals in oncology have been withdrawn for failure to confirm a benefit
  - NOT a failure of the accelerated approval program
  - We expect a small percentage of products to fail to verify the benefit
  - This is the anticipated risk of the earlier availability of promising anti-cancer agents

Refresher! Efficacy Endpoint Categories

- Direct Measure of Clinical Benefit, “Feels, Functions, Survives”
  - Overall Survival, Measures of symptoms or function

- Established Surrogates of Clinical Benefit
  - Substantial existing data and regulatory precedence
  - Higher certainty that the surrogate is predicting true clinical benefit (DFS in Breast Ca)

Unestablished Surrogate of Clinical Benefit

- Limited existing data, lack of regulatory precedence
- Lower certainty that the surrogate is predicting true clinical benefit (RR in Lung Cancer)
Efficacy Endpoints and Approval Pathways

Surrogate Endpoints → Direct Clinical Benefit Endpoints:
- RESPONSE RATE → PFS → DFS → SRE → PRO → OVERALL SURVIVAL

Lower Certainty
- ACCELERATED APPROVAL
- Certainty of Measuring / Predicting Direct Clinical Benefit

Higher Certainty
- REGULAR APPROVAL

The greater uncertainty that exists that the endpoint measures direct clinical benefit, the more data that will be required to support approval:
- Large magnitude of effect
- Internal consistency via key secondary endpoints
- Randomized Data
- Supporting Clinical Trials
- Confirmatory Post-Marketing Trials (Accelerated Approval)
Antimicrobial Products

• Courtesy of: John H. Rex, MD Keynote Speaker ICAAC 2014

• Enabling drug discovery & development to address the crisis of antimicrobial resistance:
  • New tools, new pathways, & remaining challenges

ICAAC = International Conference on Antimicrobial Agents and Chemotherapy
The Challenge: Declining Antimicrobial Development
IDSA: “Bad Bugs No Drugs”

In the face of this, few new drugs!

Rate of new antibacterials over 30 years

Why so few new drugs?
For today, let’s break it down to four things

Three big problems
1. It’s hard to discover new antibiotics
2. It’s hard to develop new antibiotics
3. The economic value of a new antibiotic to a developer can be close to zero

And the idea that
1. Fixing this requires us to see it as an ecosystem
2. This lecture will explore these themes in detail
3. But first, one more introductory comment...
Challenge with Clinical Trials

Development is hard
*A series of linked challenges*

- The superiority-based approaches that work for other areas do not offer a long-term path to a diverse, vibrant antibiotic pipeline
- We have to make non-inferiority (NI) work. How?
  - The tiered framework
- The necessity for pathogen-focused labeling
- The role of (rapid) diagnostics
- Other issues

The problem with superiority

For superiority in a prospective, randomized study to be a reliable path for antibiotics, we have to be in a situation in which randomization to potentially ineffective or toxic therapy is acceptable\(^1,2\)

- Remember: Untreated infections are lethal
- Unless we have no other choice, we must not enroll if the patient’s pathogen is resistant and the comparator thus likely ineffective
- For comparator-susceptible pathogens, modern comparators at full dose are very effective

---

Framework for – “diverse, vibrant pipeline”

That’s a problem we must solve

- To restore vitality to the pipeline and ensure we have the life-saving drugs we will need in the future,
- We have to move these models back into positive territory

Global Leadership: A partial list

- 2003 et seq: IDSA: “Bad Bugs, No Drugs”
- 17 Sep 2009: (EU) Swedish presidency
  - “Innovative Incentives for Effective Antibacterials”
- 7 April 2011: WHO World Health day on AMR
  - “No action today, no cure tomorrow”
- 17 Nov 2011: (EU) ND4BB program
  - PPP for Discovery & Development
- 2011 forward: (US & EU) FDA & EMA
  - A steady stream of new guidances
- 2012: (US) GAIN Act (see subsequent slide)
- 3-4 Oct 2013: (EU) Chatham House Conference
  - “Antimicrobial resistance: Incentivizing Change Towards a Global Solution”
- 2014: (US) PCAST Report
  - Hopefully out soon
Collaboration

Public-Private Partnerships

_in the US: NIAID & BARDA_

- NIAID: Antibacterial Resistance Program
  - Extensive array of preclinical services
  - Phase 1 clinical units
  - ARLG (Antibacterial Resistance Leadership Group)
  - Modeled on ideas such as I-SPY, master protocols are being considered as a way to provide infrastructure that would support development efforts
- BARDA (Biomedical Advanced Research & Development Authority)
  - Several public-private partnerships established to date

In the EU: IMI’s ND4BB program (New Drugs For Bad Bugs)

ND4BB cross topic collaboration and dissemination

IMI = Innovative Medicines Initiative

IDSA - 10 by ‘20 initiative
Net Present Value (NPV)
Tackling the NPV model

Two intriguing economic ideas

(Push) Refundable tax credits
- For some percentage (e.g., 50%) of qualified expenses, the company either gets a tax credit (if the company has income) or receives a payment of that amount
- Has immediate impact on NPV while also ensuring the company has "skin in the game" that ensures delivery

(Pull) Insurance-based approaches
- National acquisition at a fixed, predictable rate (e.g., US buys $100m/year of a new antibiotic for 5 years)
- Annual fee guarantees availability of a certain number of courses of therapy, whether used or not
- We should be pleased to buy but not use the drug, just as we are pleased when our life insurance does not pay off

We're now tackling the entire model!

• With support from NIAID, BARDA, ND4BB, & others plus the tiered approach, we are truly taking a systems approach to this problem
• The Discovery and Development support + the tiered approach is already having an impact
• Last step: Rethinking value and business models

GENERATING ANTIBIOTIC INCENTIVES NOW (GAIN)
FDASIA created Section 505E for Qualified Infectious Disease Products (QIDPs). A QIDP is defined as "an antibacterial or antifungal drug for human use intended to treat serious or life threatening infections" including those caused by antibiotic or antifungal resistant pathogens, novel or emerging infectious pathogens, or "qualifying pathogens."
Parallels in Transplantation

- Effective therapy is available for many patients
  - analogous to “susceptible pathogens”
- New therapies needed
- Superiority vs. Non-inferiority trials challenging
  - Ineffective comparator regimen (no treatment) unethical
  - Additional primary endpoint(s) (beyond AR)
    - Measure direct clinical benefit
    - Measure (unestablished) surrogate endpoint
Parallels in Transplantation

• Regular approval vs. Accelerated Approval
  – For the latter need to identify (unestablished) surrogate endpoints
  – Risks and benefits of surrogates (experience in oncology)

• Orphan indication(s) and patient enrollment challenge

• Role of rapid diagnostics
  – Incorporate in clinical studies

• Stalled/stopped innovation & drug development
Thank You!

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<td>• Determining workgroups</td>
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<td>Wrap Up and Summary</td>
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CDER’S BIOMARKER QUALIFICATION PROGRAM AND THE ROLE OF CONSORTIA

Shashi Amur, Ph.D.
Scientific Lead, Biomarker Qualification Program, Office of Translational Sciences, Center for Drug Evaluation and Research, FDA
OVERVIEW

• DDT Qualification
• Biomarkers
• Biomarkers in Drug Development
• Biomarker Development and Qualification
• Role of Consortia in Biomarker Development
• Summary
DRUG DEVELOPMENT TOOLS (DDT) QUALIFICATION AT CDER

Clinical Outcome Assessments
Animal Models (Animal Rule)
Biomarkers

DDTs are methods, materials, or measures that aid drug development
DDT QUALIFICATION AT CDER, FDA

Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools

Drug Development Tools (DDT) Qualification Programs Webpage on FDA.gov
“Biomarker,” or “biological marker,” generally refers to a measurable indicator of some biological state or condition.

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

**Types:** Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers.

**Examples:**
- Blood glucose (molecular)
- Biopsy-proven acute rejection (histologic)
- Tumor size (radiographic)
- Blood pressure (physiologic)
BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care

- Created by the NIH-FDA Biomarker Working Group

BIOMARKER CATEGORIES

- Safety
- Diagnostic
- Susceptibility/Risk
- Predictive
- Prognostic
- Monitoring
- Response
EXAMPLES OF HOW BIOMARKERS ARE USED IN DRUG DEVELOPMENT

- Basic Research
  - Molecular Pathways Leading to Disease

- Prototype Design or Discovery
  - Preclinical Safety Assessment
  - Mechanism of Action
  - Dose Selection

- Preclinical Development
  - Stratification
  - Patient Selection
  - Enrichment
  - Dose Selection
  - Safety Assessment
  - Efficacy Assessment

- Clinical Development
  - Phase 1
  - Phase 2
  - Phase 3

- FDA Filing/Approval and Launch

- Clinical Development
  - Molecular Pathways Leading to Disease
  - Preclinical Safety Assessment
  - Mechanism of Action
  - Dose Selection
BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT

Drug Approval Process

- Drug Labels
- Reviews
- Guidances, as needed

Scientific Community Consensus

- Published Articles
- Guidances, as needed, upon regulatory acceptance

Biomarker Qualification Program

- Biomarker Qualification Guidances
- Reviews
- Workshops, as needed
SOME ENABLERS FOR BIOMARKER DEVELOPMENT

• Data standards
• Data quality
• Data reproducibility
• Statistical considerations
• Assay/imaging considerations/validation
• Assay/imaging protocols
• Establishing cut points
STAKEHOLDERS IN BIOMARKER DEVELOPMENT

- Academia
- Industry
- Regulatory Agencies
- Consortiums
- Biomarker Evaluation/Qualification/Utilization
- Patient Groups, Foundations, and Professional Societies
- Federal Partners
OPPORTUNITIES FOR CDER ENGAGEMENT IN BIOMARKER DEVELOPMENT

- Biomarker Discovery
  - Beyond
  - The biomarker may be integrated in a new drug application at CDER

- Letter of Support
  - Issued for a promising biomarker with potential application in drug development, based on research findings

- Qualification For Limited Context of Use
  - The qualified biomarker undergoes clinical and statistical validation and a qualification guidance is issued for the limited COU

- Qualification For Expanded Context of Use
  - The qualified biomarker undergoes clinical and statistical validation and a qualification guidance is issued for the expanded COU

- Beyond
  - Issued for a promising biomarker with potential application in drug development, based on research findings
**BIOMARKER QUALIFICATION (BQ)**

**Definition:** A conclusion that, within a carefully and specifically stated “context of use,” the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development.

**Context of Use (COU):** A comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development.
BIOMARKER QUALIFICATION: SUBMITTER ROADMAP

Stage 1: Initiation
- Submit Letter of Intent (LOI)
- FDA determines acceptability of LOI

Stage 2: Consultation and Advice
- Submit briefing package
- Collaborative discussion with FDA regarding the biomarker development plan

Stage 3: Review
- Submit full qualification package
- FDA reviews package and makes yes/no decision to qualify
- FDA drafts guidance document

Publication of Guidance
- Draft guidance document posted to Federal Register for public comment
- FDA publishes final guidance document

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FDA publishes final guidance document
<table>
<thead>
<tr>
<th>General Area</th>
<th>Submitter(s)</th>
<th>Biomarker(s) Qualified for Specific Contexts of Use</th>
<th>Issuance Date with Link to Specific Guidance</th>
<th>Supporting Information</th>
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<tr>
<td>Nonclinical</td>
<td>Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)</td>
<td>Urinary biomarkers: Albumin, β2-Microglobulin, Clusterin, Cystatin C, KIM-1, Total Protein, and Trefoil Factor-3</td>
<td>4/14/2008: Drug-Induced Nephrotoxicity Biomarkers</td>
<td>Reviews</td>
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<td>Urinary biomarkers: Clusterin, Renal Papillary Antigen (RPA-1)</td>
<td>9/22/2010: Drug-Induced Nephrotoxicity Biomarkers</td>
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<td>Nonclinical</td>
<td>PJ O'Brien, WJ Reagan, MJ York, and MC Jacobsen</td>
<td>Serum/plasma biomarkers: Cardiac Troponins T (cTnT) and I (cTnI)</td>
<td>2/23/2012: Drug-Induced Cardiotoxicity Biomarkers</td>
<td>Reviews</td>
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<tr>
<td>Clinical</td>
<td>Mycoses Study Group</td>
<td>Serum/bronchoalveolar lavage fluid biomarker: Galactomannan</td>
<td>10/24/2014: Patient Selection Biomarker for Enrollment in Invasive Aspergillosis (IA) Clinical Trials</td>
<td>Reviews</td>
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<td>Chronic Obstructive Pulmonary Disease (COPD) Biomarker Qualification Consortium (CBQC)</td>
<td>Plasma biomarker: Fibrinogen</td>
<td>7/6/2015: Prognostic Biomarker for Enrichment of Clinical Trials in Chronic Obstruction Pulmonary Disease (COPD)</td>
<td>Reviews</td>
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<td>Clinical</td>
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<td>Imaging biomarker: Total Kidney Volume (TKV)</td>
<td>8/17/2015: Prognostic Biomarker for Enrichment of Clinical Trials in Autosomal Dominant Polycystic Kidney Disease</td>
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[www.fda.gov/biomarkerqualificationprogram]
### Biomarker Qualification Program Metrics

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<td>Number in Initiation Stage</td>
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<td>Number in Consultation and Advice Stage</td>
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<td>Number in Review Stage</td>
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<td>Total Number of Active Projects</td>
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<tr>
<td>Number Qualified</td>
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From the Drug Development Tool (DDT) Qualification Projects at CDER, FDA:  
# Biomarker Qualification Submitters

<table>
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<tr>
<th>Organization</th>
<th>Number (N=28)</th>
<th>Percentage of Total BQ Submission</th>
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<tbody>
<tr>
<td>Consortia</td>
<td>19</td>
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<tr>
<td>Diagnostics and Biotechnology</td>
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<td>14%</td>
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<tr>
<td>Academia</td>
<td>3</td>
<td>11%</td>
</tr>
<tr>
<td>Contract research organizations</td>
<td>2</td>
<td>7%</td>
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**Consortium**: A group that is “formed to undertake an enterprise beyond the resources of any one member” (includes disease foundations)

**Contract research organization (CRO)**: is an organization that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.
Consortia products

http://consortiapedia.fastercures.org/
Consortia-pedia

Consortia-pedia is:

- a qualitative and quantitative analysis of the emerging model of collaboration-by-consortium,
- a framework for understanding the breadth and scope of approaches to a wide range of consortia
  how they are getting organized,
- identifying and categorizing consortia with a similar goal, and
- designing observation tools (podcasts, KBAI) that are part of a consortium interested in participating in or creating a consortium.

http://consortiapedia.fastercures.org/about/
Biomarkers as Intended Products of Consortia

Fig. 3. Initiators and outputs. (A) Intended products of consortia, by initiating sector. (B) Sectors that initiate consortia, by intended product.
Consortia By Disease Focus

Research objectives

Biomarker
Basic science
Tool
Product

Continent (by number)

Oncology
Rare diseases
Alzheimer's disease
Diabetes

Asia
Europe
North America
International

(n = 46)
(n = 41)
(n = 22)
(n = 20)

1
27
17
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11
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2

Why are Consortia the Main Sources of BQ Submissions?

Consortia Provide

• A neutral environment to use collective expertise
• Opportunities to pool resources and share costs
• A governance structure for coordination of scientific research to develop biomarkers, leveraging resources and expertise
• Opportunities to bring in outside experts from industry/academia
• Opportunities to have a scientific liaison from government agencies such as FDA and NIH
Summary

- **BEST (Biomarkers, Endpoints, and other Tools Resource)** provides biomarker-relevant definitions, in an effort at harmonization of biomarker terminology.

- **Biomarker Qualification**
  - Submitter can be a person, a group, organization (including the federal government), or consortium that takes responsibility for and initiates a BQ proposal using the procedures described in the DDT guidance.
  - No fees for submissions to the BQ program.
  - Biomarker qualification is voluntary.
  - Once qualified for a specific context of use, a biomarker can be used by drug developers for other applications.

- **New FDA initiatives**, such as LOS and limited COU qualification, can be utilized as early goal posts in biomarker development.

- **Consortia** contribute the majority of submissions for biomarker qualification through coordination of collective expertise and shared resources.
ACKNOWLEDGEMENTS

Janet Woodcock
ShaAvhrée Buckman-Garner
Suzie McCune
Chris Leptak
Marianne Noone
Sarmistha Sanyal
Kylie Haskins
Ru Chen
Thank You!

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Why Form a Consortium?

- Bring together industry, regulators, academic experts, and key societies/foundations to collaborate in areas of common interest
- Solve challenging problems difficult for one organization to tackle
- Engage FDA and EMA for advice to facilitate regulatory approval of new tools and methods
- Spread costs and risks to advance research in areas of unmet need
- Defined governance structure; scientific and project management leadership support, data acquisition and data platform support
- All leading to meaningful regulatory science deliverables
Membership Legal Agreement

• Initial Scope
• Responsibilities and Expectations of Members
• Governance
• Confidentiality
• Intellectual Property
• Publications and Publicity
• Fees
• Anti-Trust
• Anti-Corruption, Anti-Bribery
• Termination, Liability, Indemnification, etc.
Governance Model

• Executive Team consisting of C-Path executive director and co-director(s) from founding societies
• Coordinating committee with representation for all members makes all significant decisions
• Separate Working Groups created to focus on each deliverable – led by a chair or co-chairs
Typical Governance Structure

Executive Leadership Team

Coordinating Committee

Co-Chairs
- Working Group
- Working Group
- Working Group
- Working Group

Cross WG Teams

Project Manager
Project Management

- Written Goals and Deliverables
- Project Plan with Schedules
- Clear Tasks with Owners
- Tracking and Communicating
- Budgets and Finance
- Meetings and Workshops
Typical Project Schedule

Data Mapping

Modeling

Regulatory
Proposal Scope and Timeline

- Development of a data sharing platform for clinical data
- Complete/Update CDISC therapeutic area standard where gaps exist
- Use data to inform the development of regulatory documents and publications
Data Capability & Safeguards

Establish a pooled, standardized, secure database of clinical trial data

- Data access is determined by owners/contributors of the data
- Full data de-identification that meets HIPAA “Safe Harbor” specifications
- C-Path CODR database platform
  - Extensive security measures for online data access & database management
  - Proven database technology
- Leverage existing data standards partnerships
  - C-Path consortia expertise
  - CFAST data standards project with CDISC
C-Path Online Data Repository

C-Path Data Project Examples
CAMD – AD Clinical Trial Simulation Tool
CPTR – CDC Clinical Trial Data Sharing
PKD - Biomarker Qualification Project
MSOAC – New Outcome Assessment Instrument for MS
Clinical data contributed to C-Path

Clinical data: 86 studies, 50,147 subjects

Nonclinical data: 116 studies, 6296 subjects.

ReSeqTB: 3558 Individual Isolates

- Duchenne Muscular Dystrophy
- Kidney healthy volunteer study
- Polycystic kidney disease
- Multiple sclerosis
- Tuberculosis
- Parkinson’s disease
- Alzheimer’s disease
C-Path Policies for Handling of Clinical Data

Key guiding principles:

• We operate as a responsible steward for the clinical data contributed to, used by C-Path, and shared by C-Path

• Data are shared as allowed by contributor

• We will abide by all applicable regulations that govern the use of clinical data
Funding potentially provided through multiple sources:

- Philanthropic foundations
- Member organizations
- Other grants
- Combination of one or more of the above

C-Path funding model examples:
Next Steps

• Update and review draft proposal with initial goals
• Finalize consortium membership agreement
• Announce and formal launch
• Staff working groups and select leadership
• Ramp up to full scope once sufficient organizations have agreed to join consortium and required funding level is achieved
Thank You!

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Break

2:30 pm – 2:40 pm
## Agenda

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<thead>
<tr>
<th>Time</th>
<th>Topic</th>
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Please rate the following statements on the degree you agree with them. A cross-industry/academia/government consortium would be helpful to transform the way clinical and translational research is conducted in the US.
The government should be involved in this consortium and at a minimum, play an advisory role.
Please rate the following potential short team projects that Transplant Therapeutics Consortium (TTC) could develop. Funding to support the TTC and its projects should come from the "private" sector versus the public sector.
Look at separate labeling for transplant uses of currently labeled medications. Develop pros and cons and create an opinion paper for publication.
Look at off label usage of medications in transplantation that are considered the "standard of care". Assess the SRDR as a mechanism for summarizing transplant immunosuppressant literature for use in creating a Transplant Immunosuppressant Drug Compendia.
Look at bringing novel and needed therapies to the forefront for treating antibody mediated rejection, both acute and chronic. This would include a need for central recording of all data, including pathology (with central over-read), HLA data (with central review). This could be in the format of a registry to include studies using eculizumab, bortezomib, IVIg. Define the data that would be collected and then put it out to the community to help facilitate bringing trials quickly to patients.
Create an independent working group to advise and coalesce the numerous single center/single PI small studies with single INDs: create a review mechanism internally and encourage collaboration in these small studies to provide more hard hitting data. This could bring up questions that the FDA cannot ask. Can also create a symposia or seminar/webinar series on this issue.
Characterize the pharmacokinetics for immunosuppressants in recipients with gastric “sleeve” and other GI bypass procedures.
Explore Orphan drug designation for transplant immunosuppression. List pros and cons and create an opinion paper.
Study the behavioral and financial factors that contribute to non-adherence in transplantation for the purposes of understanding the extent of non-adherence in transplantation. Develop new ways to deter non-adherence.
Current clinical trials lack patient reported outcomes. Some data has been collected by industry sponsored studies but not shared in the public domain. Sharing this data could provide significant impetus for either new trials or considerations of current treatments.
Identify major barriers to new drug development according to the transplant community, industry, and the FDA.
Identify new efficiencies in clinical trial development and execution.
Create a workshop(s) to assist and educate investigators in devising and improving opportunities for investigator initiated projects with industry. The cost and time for the investigator has deterred many attempts. Improving the process of investigator initiated projects in terms of cooperation amongst centers IND and cost and regulatory paperwork.
Please rate these potential long term projects. Identification, evaluation, and validation of new predictive technologies (complementary to biopsy) which could identify sub-acute/acute/chronic rejection earlier and facilitate Rx changes to improve graft survival (improving existing immunosuppressive therapy).
Pharmaco-genetics of transplant immunosuppressive therapies (ISM) (i.e. both safety and efficacy studies) associated with the major ISM drugs used today (segmented by key transplant phenotypes); 50-100 patient cohorts across these key sub-phenotypes, along with matched/population controls would yield critical insights to better tailor personalized ISM therapies (improving existing ISM therapies and reducing the risk of developing new ISM therapies).
Develop a consensus position on existing transplant and/or potential new transplant biomarkers that could be validated and approved for use in new ISM clinical trials. Start with the kidney (reducing the risk of developing new ISM therapies). This may entail collaboration with other consortia efforts in the US (e.g. The Biomarkers Consortia) or Europe (e.g. IMI).
Assess the safety of new non-immunosuppression medications and their impact in transplant recipients, specifically, any unique toxicities, and concerns about use with focus on impact on immunosuppressive drug metabolism and levels.