Selected Translational Innovation Highlights

- **Early-stage translation**: chemical probe/lead development for target validation and therapeutic hypothesis testing

- **Mid-stage translation**: preclinical development to first-in-human studies

- **Late-stage translation**: large-scale studies in humans
Rapid Antidepressant Effect of Ketamine in Unmedicated Treatment Resistant Depression

Hamilton Depression Rating Scale (HAM-D)

Placebo
Ketamine

Day 1
Day 2
Day 3
Day 7

* * * *** *** ***

Drop in Depression Rating following a Single Ketamine Infusion (N=18)

-60 40 80 110 230

Placebo Ketamine

Zarate et al. Arch Gen Psychiatry 2006

- Rapid Effect in Major Depressive Disorder
- Rapid Decreases in Suicidal Ideation
- Rapid Effect in Treatment Resistant Bipolar (BP) Depression
Ketamine Metabolites for Depression

• Collaborators
   University of Maryland School of Medicine
   National Institute of Mental Health and National Institute on Aging

• Background
   Severe depression affects ~16% of the world population
   Current therapies require prolonged administration for clinical improvement and some patients are non-responsive

• Project
   Non-competitive, glutamatergic NMDAR antagonist (R,S)-ketamine exerts quick and prolonged antidepressant effects after a single dose, but also has side effects.
   Showed that ketamine metabolite ((2R,6R)-HNK) reversed depression-like behaviors in mice without triggering anesthetic, dissociative, or addictive side effects
   Data illustrate novel mechanism and have potential for the development of next-generation antidepressants
Extensive metabolism of ketamine
NMDAR inhibition–independent antidepressant actions of ketamine metabolites

Panos Zanos¹, Ruin Moaddel², Patrick J. Morris³, Polymnia Georgiou¹, Jonathan Fischell⁴, Greg I. Elmer¹,⁵,⁶, Manickavasagom Alkondon⁷, Peixiong Yuan⁸, Heather J. Pribut¹, Nagendra S. Singh², Katina S. S. Dossou², Yuhong Fang³, Xi–Ping Huang⁹, Cheryl L. Mayo⁶, Irving W. Wainer², Edson X. Albuquerque⁵,⁷,¹⁰, Scott M. Thompson¹,⁴, Craig J. Thomas³, Carlos A. Zarate Jr⁸ & Todd D. Gould¹,⁵,¹¹

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1Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. 2Biomedical Research Center, National Institute on Aging, National Institutes of Health, Bethesda, National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, Maryland 20850, USA. 3Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. 4Department of Pharmacology, University of Maryland School of Medicine, Baltimore, Maryland 21228, USA. 5Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. 6Department of Experimental Therapeutics and Pathophysiology Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20892, USA. 7Department of Medicine, University of North Carolina Chapel Hill Medical School, Chapel Hill, North Carolina 27516, USA. 8Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA.
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(a) (R,S)-KET (R,S)-norKET

MeHN

Cl

OH

MeHN

Cl

OH

(2S,6S;2R,6R)-HK (2S,6S;2R,6R)-HNK

(b) Escape failures

SAL (R,S)-KET (2S,6S)-HNK (2S,6R)-HNK

(10 mg kg⁻¹)

** ** **

NIH National Center for Advancing Translational Sciences
NMDAR inhibition-independent antidepressant actions of ketamine metabolites

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[Chemical structures and graphs showing changes in escape failures and percentage of responding on KET-paired lever]
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Lymphangioleiomyomatosis (LAM) is a rare, progressive lung disease that primarily affects women of childbearing age that is often fatal.
Sirolimus (aka rapamycin, Rapamune) is an mTOR inhibitor originally approved for prevention of transplant rejection.

LAM is associated with inappropriate activation of mTOR signaling, which regulates cellular growth and lymphangiogenesis.

RLDC conducted Multicenter International LAM Efficacy and Safety of Sirolimus (MILES) trial:

- PI: Frank McCormack, University of Cincinnati
- Collaborative effort among RDCRN-RLDC, Pfizer, LAM Foundation

FDA approved sirolimus for LAM in March 2015:

- First drug approved by FDA for the treatment of this rare disease.
New Therapeutic Uses Program

• First round of projects

<table>
<thead>
<tr>
<th>Disease</th>
<th>Academic Partner</th>
<th>Pharma Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>Yale</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>U Rhode Island/NIAAA</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Calcific Aortic Stenosis</td>
<td>Mayo Clinic</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>Kennedy Krieger/UWash</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>Baylor</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Peripheral Artery Disease</td>
<td>U Virginia</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td>VCU/Pittsburgh</td>
<td>Janssen</td>
</tr>
<tr>
<td>Schizophrenia (2)</td>
<td>Indiana U</td>
<td>Lilly</td>
</tr>
<tr>
<td></td>
<td>Yale</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>

• Translational Innovation Success Measures
  - Does use of template agreements speed negotiation time?
  - Does crowdsourcing of indications generate new ideas?
  - Do studies result in new indications/approvals?
NTU project: AZD0530 (saracatinib) for LAM

- Src family kinase inhibitor originally developed for cancer
  - Also being tested in NTU for Alzheimer’s Disease
- Src is activated in LAM cells
  - Contributes to oncogenic properties of LAM cells
- NTU LAM Phase 2a trial ongoing
  - PI: Tony Eissa (Baylor)
  - Frank McCormack (University of Cincinnati)
  - Stephen Rouss (Stanford University)
  - Daniel Dilling (Loyola University, Chicago)
  - Elizabeth Henske & Souheil El-Chemaly (Brigham and Women’s Hospital)
Selected Translational Innovation Highlights

• *Early-stage translation*: chemical probe/lead development for target validation and therapeutic hypothesis testing

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The NCATS Clinical and Translational Science Awards Program

**CTSA Hubs**
Clinical Trials
Opportunity for Operational Innovation

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

The State of Infectious Diseases Clinical Trials: A Systematic Review of ClinicalTrials.gov

Portfolio of Clinical Research in Adult Cardiovascular Disease as Reflected in ClinicalTrials.gov

Using ClinicalTrials.gov to Understand the State of Clinical Research in Pulmonary, Critical Care, and Sleep Medicine

The Landscape of Clinical Trials in Nephrology: A Systematic Review of ClinicalTrials.gov

Clinical Trials
Opportunity for Operational Innovation

Current Work Models
- Small, frequently single-center studies
- Inconsistent power, rigor
- Poor enrollment
- Suboptimal scientific impact

Operational Challenges
- Research: Clinical parallel universes
- Fragmented, duplicative infrastructure
- Lack of collaborative efforts
- Misaligned incentives

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

Robert M. Califf, MD
Deborah A. Zarina, MD
Judith M. Kramer, MD, MS
Rachel E. Sherman, MD, MPH
Laura H. Aberle, BS, MPH
Asha Tasneem, PhD

Need for a comprehensive and rapid analysis of ClinicalTrials.gov

The State of Infectious Diseases Clinical Trials: A Systematic Review of ClinicalTrials.gov

Asa D. Goswami, MD
Christopher D. Pfeiffer, MD
John R. Horton, MD
Karen Chiswell, PhD
Asha Tasneem, PhD

Using ClinicalTrials.gov to Understand the Nature of Clinical Research Activity, Critical Care, and Pulmonary Medicine

Pratik Doshi, MD, MPH

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National Center for Advancing Translational Sciences
Clinical Trials

Opportunity for Operational Innovation

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Poor enrollment
Suboptimal scientific impact

Operational Challenges
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Fragmented, duplicative infrastructure
Lack of collaborative efforts
Misaligned incentives

Opportunity for Operational Innovation
Invent and deploy new approaches to clinical studies

NIH Clinical Trials
Opportunity for Operational Excellence

NIH Budget – FY 2015

$3.2 B
~10%

$27.1 B

NIH tackles clinical trial shortcomings
The NIH is developing new tools, and overhauling its clinical trial funding system, to improve the stewardship of NIH-funded clinical trials

Additional Data Would Enhance the Stewardship of Clinical Trials across the Agency

NIH Clinical Trials
Opportunity for Operational Excellence

Results of Current Work Models

Trials not finishing on time or within budget
Frequently large unobligated balances
Suboptimal return on research investments
Decreased public trust

Operational Challenge
Enhance stewardship and accountability of NIH clinical trials

NIH Budget – FY 2015

NIH Clinical Trials
Opportunity for Operational Excellence

Opportunity for Operational Excellence

Execute trials better, faster, & more cost-effectively

Results of Current Work Models

Trials not finishing on time or within budget

Frequently large unobligated balances

Suboptimal return on research investments

Decreased public trust

Operational Challenge

Enhance stewardship and accountability of NIH clinical trials

Imagine ... A Clinical Trials Superhighway

A Network that Accelerates the Translation of Novel Interventions to Evidence Based Treatments

- Single IRB Reliance Model
- Master Contracts
- Harmonized Data Collection
- Streamlined Protocols
- Poised Research Teams
- Patient Engagement
NCATS Trial Innovation Network

**Mission**

- Leverage the unmatched talent, expertise, and resources of the CTSA Program to transform clinical trials
  - Collaborative national network
  - Accelerate planning & implementation of high quality multi-center trials & studies
  - Provide more treatments to more patients
  - Improve public health

- Create a national laboratory to study, understand, and improve multi-center clinical trials
NCATS Trial Innovation Network

What Is It?

CTSA Hubs

Network Center

Collaborative Strategic Management

NCATS & Network Exec. Comm. & CTSA

Partners
NIH ICs
Federal
Non-federal

Partners
Patients

Trial Innovation Centers (TICs)

Recruitment Innovation Centers (RICs)

NIH ICs
Federal
Non-federal

Patients
NCATS Trial Innovation Network
How Will It Work?

- **Partnership**
  - Early Protocols
  - Operational Questions
    - NCATS
  - Scientific Questions
    - NIH Institutes
    - Industry
    - Other Partners

- **Operational Excellence**
  - Doing Trials Better, Faster, & More Cost- Efficiently

- **Trial Innovation Network**
  - CTSA Hubs
  - RICS
  - NCATS
  - TICS

- **Operational Innovation**
  - Testing New Approaches to Clinical Trials
    - Recruitment, Contracts, IRB, Other

- **Results**
  - New Science
  - Studies that Finish on Time & within Budget
  - Generate Evidence to Change Clinical Practice

- **Robust Clinical Trials**

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NIH National Center for Advancing Translational Sciences
NCATS Trial Innovation Network
Built on Operational Innovations from the CTSA Program

- Master Contracts
  - ACTA: Accelerated Clinical Trial Agreement
  - ACDA: Accelerated Confidential Disclosure Agreement

- SMART IRB Reliance Platform

- Standards for Competencies & Training in Clinical Trials

- EHR Based Recruitment

ACT Network
NCATS Trial Innovation Network

Value Proposition

• For Investigators
  ➢ One-stop shopping to implement clinical trials
  ➢ TICS & RICS - expertise in operational innovation & operational excellence
  ➢ CTSA Hubs - broad expertise; large, diverse patient populations
  ➢ More competitive clinical trials applications to NIH ICs, industry

• For NIH Institutes and Industry Partners
  ➢ Trials completed on time and within budget
  ➢ Shared NIH mission to innovate & transform clinical trials & optimize stewardship
NCATS Trial Innovation Network: Implementation Timeline

May
NCATS Council

June
Awards Released

First 6 Months
Develop Network Strategic Plan
Launch Demonstration studies

Year 1
Demonstrate & disseminate key elements of “superhighway”

Year 2
Launch large scale clinical trials

Operationalize SMART IRB Model, Master Contracts, Workflows, Other Strategic Priorities in Demonstration Studies
CAN Update
FY2016 Budget

- November 2, 2015: President signed Bipartisan Budget Act of 2015 (P.L. 114-74)
  - Raises Sequester caps for FY16 and FY17
- Continuing Resolutions: thru Dec. 11, Dec. 16, and Dec. 22
- December 18, 2015: President signed Consolidated Appropriations Act, 2016 (P.L. 114-113)
  - NIH: $32 B ($2 B increase over FY 15)
  - NCATS: $685.4 M ($52.7 M increase over FY 15)
  - CTSA: $500 M
    - Includes $22.7M increase to implement IOM recommendations, such as building network capacity (i.e. TICs, RICs, CCIAs)
  - CAN: $25.8 M ($16M increase over FY 15)
New CAN Program:  
**Biomedical Data Translator Program**

- New signature initiative, utilizing OTA
- Informatics platform enabling interrogation of relationships across full spectrum of data types:
  - Disease names
  - Clinical signs & symptoms
  - Organ and cell pathology
  - Genomics
  - Drug effects
  - ...

- First stage: Team-based proposals to address architecture needs to build Translator and assess technical feasibility

- Timeline
  - Call for projects posted: April 29
  - Proposals received: June 1
  - In person presentations: June 29-30
  - Negotiations begin: July
  - Awards announced: September
Policy and Legislative Updates
FY 2017 Budget

• February 9, 2016: President releases FY 2017 budget
  • NCATS’ request is $685.417 million (same as FY16)

• Congressional Hearings
  • House: March 16, 2016
    • Witnesses: Drs. Collins, Fauci (NIAID), Hodes (NIA), Lowy (NCI), Volkow (NIDA)
  • Senate: April 7, 2016
    • Witnesses: Drs. Collins, Austin, Hodes (NIA), Koroshetz (NINDS), Lowy (NCI), and Volkow (NIDA)
Congressional Visit to NIH

• April 12, 2016 - Five Representatives visited NIH to learn more about NIH’s mission and programs
  ➢ David Valadao (R-CA)
  ➢ Susan Brooks (R-IN)
  ➢ Robert Dold (R-IL)
  ➢ Katherine Clark (D-MA)
  ➢ Joseph Kennedy (D-MA)

• Met with Drs. Collins, Austin, Gibbons (NHLBI), and Volkow (NIDA)
Organized by NCATS and CC

Featured speakers included

- Rare Disease Congressional Caucus - 4 co-chairs
  - Senator Orrin Hatch (R-UT) - via video
  - Senator Amy Klobuchar (D-MN)
  - Rep. Leonard Lance (R-NJ)
  - Rep. Joseph Crowley (D-NY)
- Sharon Terry, President & CEO, Genetic Alliance
- Mike Porath, Founder & CEO, The Mighty
- Martha Rinker, Vice President of Public Policy, National Organization of Rare Disorders (NORD)

Reached >900 people

View the videocast at http://1.usa.gov/1Q8Exi9
NCATS Strategic Plan

Updated Timeline

https://ncats.nih.gov/strategicplan

Fall 2015
- Launch Strategic Plan Website
- Publish Request for Information (RFI)
- Hold Town Hall Webinars

Winter 2016
- Update NCATS Advisory Council & CAN Review Board
- Analyze Stakeholder Comments & Suggestions

Spring - Summer 2016
- Update NCATS Advisory Council & CAN Review Board
- Draft and Publish NCATS Strategic Plan
NCATS Office of Policy, Communications and Strategic Alliances

Proposed Changes

• Remove the Office of Strategic Alliances from the Policy and Communications Office
  - Better reflection of NCATS alignment and priorities

• Establish an Education Office
  - Ensure NCATS remains a leader in public education and community involvement related to translational science

• Both changes are budget neutral and will utilize existing resources within the Center
Existing OPCS A Structure

Office of the Director

Executive Office
Office of Grants Management and Scientific Review
Division of Pre-Clinical Innovation
Division of Clinical Innovation
Office of Rare Disease Research

Office of Policy, Communications, and Strategic Alliances
Office of Science Policy
Office of Communications
Office of Strategic Alliances
Questions or Comments

• Please email NCATSReOrgComments@mail.nih.gov by Thursday, June 30
  ➢ Include your name, and when applicable, your professional affiliation

• NCATS will respond to your email by Friday, July 15
Discussion