

Director's Report

NCATS Advisory Council and CAN Review Board

CHRISTOPHER P. AUSTIN, M.D.
DIRECTOR, NCATS
SEPTEMBER 15, 2016

NCATS



We would like to save trees, but please let us know in advance of next Council if you would like the Activity Summary document printed

Translational Innovation Highlights

- Early-stage translation
 - Drug repurposing for Zika
 - Chaperone therapeutics for rare and common disease
- Mid-stage translation
 - Gene therapy innovations
- Late-stage translation
 - Rare disease patient videos
 - Adherence research - AiCure SBIR
 - Community engagement research at CTSAs

Early-stage translational highlights

Zika drug repurposing

- **Background**

- Zika infection reported in 60 countries
- Associated with neurological disorders including microcephaly in babies of infected mothers, Guillain-Barré in adults
- No effective drug treatments or vaccines
- Zika virus (ZIKV) infects human embryonic cortical neural progenitor cells (hNPCs)
- ZIKV infection leads to increased cell death of hNPCs

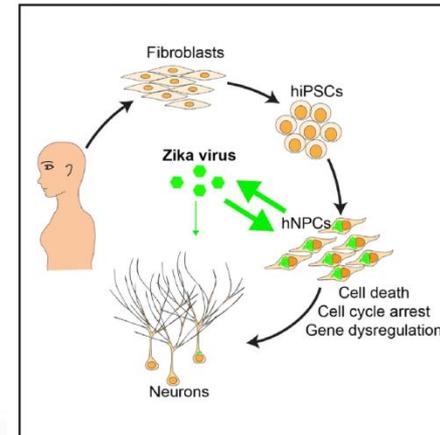
- **NCATS project**

- DPI rapidly established collaborative team, identified approved and investigational drugs as starting points for drug development to treat Zika infection
- Generalized paradigm applicable to public health emergencies, used previously in Ebola



Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth

Graphical Abstract



Authors

Hengli Tang, Christy Hammack, Sarah C. Ogden, ..., Peng Jin, Hongjun Song, Guo-li Ming

Correspondence

tang@bio.fsu.edu (H.T.), shongju1@jhmi.edu (H.S.), gming1@jhmi.edu (G.-l.M.)

In Brief

The suspected link between ZIKV infection and microcephaly is an urgent global health concern. Tang et al. report that ZIKV virus directly infects human cortical neural progenitor cells with high efficiency, resulting in stunted growth of this cell population and transcriptional dysregulation.

Tang et al., *Cell Stem Cell* 18: 1, 2016

Zika drug repurposing

ARTICLES

nature
medicine

published online 29 August 2016; doi:10.1038/nm.4184

Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen

Miao Xu^{1,2,16}, Emily M Lee^{3,16}, Zhexing Wen^{4-7,16}, Yichen Cheng³, Wei-Kai Huang^{7,8}, Xuyu Qian^{7,9}, Julia TCW¹⁰, Jennifer Kouznetsova¹, Sarah C Ogden³, Christy Hammack³, Fadi Jacob^{7,11}, Ha Nam Nguyen^{7,12}, Misha Itkin¹, Catherine Hanna³, Paul Shinn¹, Chase Allen³, Samuel G Michael¹, Anton Simeonov¹, Wenwei Huang¹, Kimberly M Christian^{7,12}, Alison Goate¹⁰, Kristen J Brennand¹³, Ruili Huang¹, Menghang Xia¹, Guo-li Ming^{7,9,11,12,14,15,17}, Wei Zheng^{1,17}, Hongjun Song^{7,9,11,12,15,17} & Hengli Tang^{3,17}

In response to the current global health emergency posed by the Zika virus (ZIKV) outbreak and its link to microcephaly and other neurological conditions, we performed a drug repurposing screen of ~6,000 compounds that included approved drugs, clinical trial drug candidates and pharmacologically active compounds; we identified compounds that either inhibit ZIKV infection or suppress infection-induced caspase-3 activity in different neural cells. A pan-caspase inhibitor, emricasan, inhibited ZIKV-induced increases in caspase-3 activity and protected human cortical neural progenitors in both monolayer and three-dimensional organoid cultures. Ten structurally unrelated inhibitors of cyclin-dependent kinases inhibited ZIKV replication. Niclosamide, a category B anthelmintic

Erica, Inc. All rights reserved.

All screening results have been deposited in Pubchem database for community use

Zika drug repurposing publicity



NIH DIRECTOR'S BLOG

Treating Zika Infection: Repurposed Drugs Show Promise



NEWS RELEASES

Monday, August 29, 2016

NIH collaboration helps advance potential Zika treatments

Zika drug repurposing publicity

Healio  Infectious Disease News



Various compounds may help advance Zika treatments

 **Homeland Preparedness News**
The Leading Source for Preparedness & Response News

NCATS research team identifies compounds for potential treatment against Zika virus

Zika drug repurposing publicity



NIH-LED TEAM IDENTIFIES 3 COMPOUNDS THAT WORK AGAINST ZIKA VIRUS-LINKED BRAIN CELL DEATH



Drugs Used to Fight Hepatitis, Worm Infections Might Stop Zika

Zika drug repurposing publicity

Miami Herald

FSU study: Drugs may stop Zika from replicating, damaging fetal brains

THE BALTIMORE SUN

Drug to treat parasites, liver disease shows promise for Zika



Zika treatable with existing drugs, says breakthrough study

Zika drug repurposing publicity

TECH TIMES

Scientists Identify Existing Drugs That Can Kill Zika

THE WALL STREET JOURNAL.

Potential Zika Virus Therapies Identified by Researchers

Several candidates found from among 6,000 drugs already commercially available or undergoing clinical trials

USA TODAY

Team of researchers inch closer to Zika treatment

Drug development for treatment of Zika virus infection

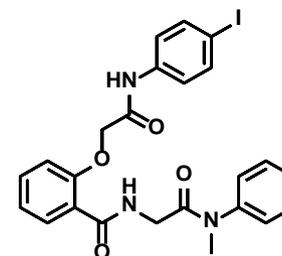
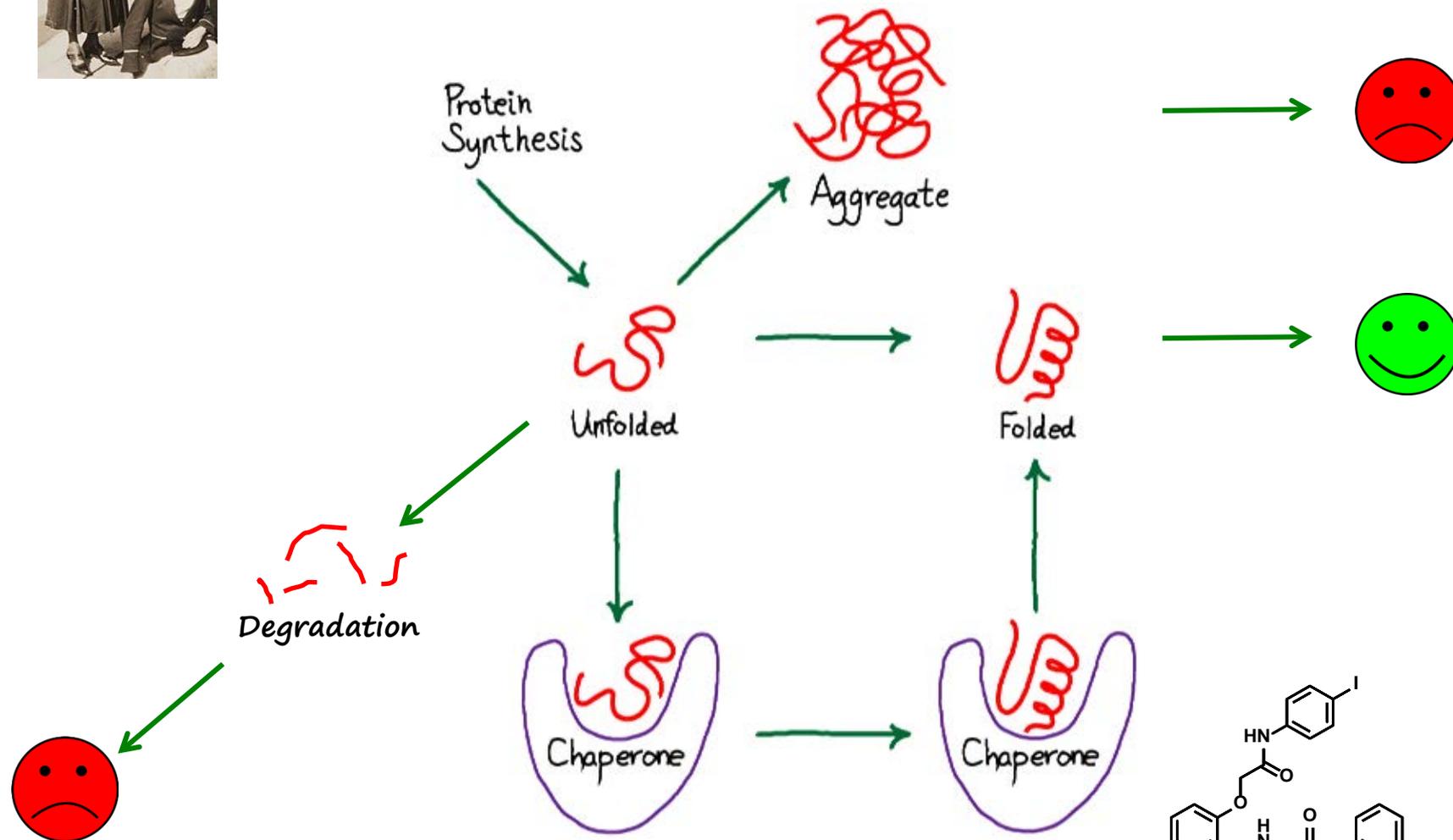
Next Steps

- **Evaluation of *in vivo* efficacy of identified compounds**
 - Mouse models of Zika infection (collaborator at Florida State)
 - Mouse neuronal models for neuronal protections against Zika virus infection (collaborators at Johns Hopkins)
- **Chemistry optimization**
 - Niclosamide prodrug development to improve oral bioavailability and reduce toxicity
 - Analog development to improve potency, and increase blood-brain-barrier penetration
- **A new high-throughput ZIKV NS-1 assay developed**
 - To perform a new round of drug repurposing screen for identifying more compounds with different mechanism of action
 - To carry out genome-wide siRNA screen for identification of potential new drug targets



“Chaperone” drugs

A widely applicable therapeutic modality



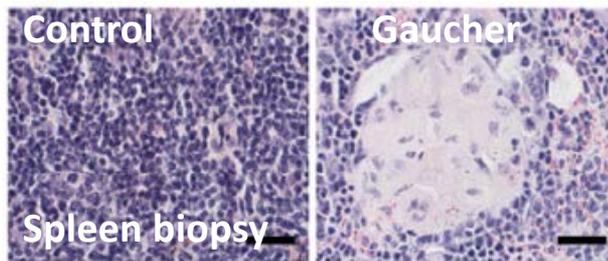
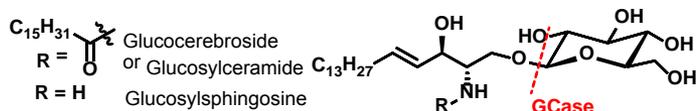
NCGC00241607

Glucocerebrosidase chaperones for Gaucher Disease (GD) and Parkinson's Diseases (PD)

Collaborators: Ellen Sidransky, NHGRI/NIH; Dimitri Krainc, Northwestern; Frank Schoenen and Steven Rogers, Univ Kansas

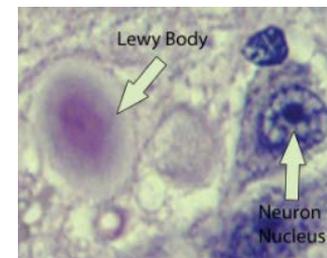
Gaucher Disease (GD)

Rare hematologic and neurologic disorder caused by mutations in gene encoding the enzyme glucocerebrosidase, characterized by **intracellular accumulation** of lipid in lysosomes of macrophages and/or neurons



Parkinson's Disease (PD)

Common neurologic progressive disorder characterized by dysfunction/death of brain dopamine-producing neurons, which show **intracellular accumulations** called Lewy bodies containing alpha-synuclein



Glucocerebrosidase chaperones for Gaucher Disease (GD) and Parkinson's Diseases (PD)

- **GD and PD are, remarkably, related**
 - Patients with **GD** have an increased risk of **PD**
 - Patients with **PD** have a high prevalence of **glucocerebrosidase** mutations



Multicenter Analysis of Glucocerebrosidase Mutations in Parkinson's Disease

E. Sidransky, M.A. Nalls, J.O. Aasly, J. Aharon-Peretz, G. Annesi, E.R. Barbosa, A. Bar-Shira, D. Berg, J. Bras, A. Brice, C.-M. Chen, L.N. Clark, C. Condroyer, E.V. De Marco, A. Dürr, M.J. Eblan, S. Fahn, M.J. Farrer, H.-C. Fung, Z. Gan-Or, T. Gasser, R. Gershoni-Baruch, N. Giladi, A. Griffith, T. Gurevich, C. Januario, P. Kropp, A.E. Lang, G.-J. Lee-Chen, S. Lesage, K. Marder, I.F. Mata, A. Mirelman, J. Mitsui, I. Mizuta, G. Nicoletti, C. Oliveira, R. Ottman, A. Orr-Urtreger, L.V. Pereira, A. Quattrone, E. Rogaeva, A. Rolfs, H. Rosenbaum, R. Rozenberg, A. Samii, T. Samaddar, C. Schulte, M. Sharma, A. Singleton, M. Spitz, E.-K. Tan, N. Tayebi, T. Toda, A.R. Troiano, S. Tsuji, M. Wittstock, T.G. Wolfsberg, Y.-R. Wu, C.P. Zabetian, Y. Zhao, and S.G. Ziegler

N ENGL J MED 361;17 NEJM.ORG OCTOBER 22, 2009

- **Therapeutic hypothesis**
 - Interventions that correct glucocerebrosidase defect will reduce intracellular accumulations in GD (lipids) and PD (alpha-synuclein) and reverse disease pathology and symptoms both diseases

Translational principle result #1

Disease-mimicking cellular models are critical

- Chaperones developed in non-disease relevant cell types (cell lines or patient fibroblasts) did not translate
- Macrophages created from Gaucher patient blood monocytes or iPSCs, and neurons created from Gaucher iPSCs show disease phenotype
 - Reduced GCase activity
 - Reduced lysosomal GCase
 - Pronounced lipid accumulation
- Aged iPSC-derived neurons from Gaucher patients with parkinsonism and Parkinson's patients without GCase mutations accumulate alpha-synuclein

Three classes of glucocerebrosidase inhibitors identified by quantitative high-throughput screening are chaperone leads for Gaucher disease

Wei Zheng*, Janak Padia*, Daniel J. Urban¹, Ajit Jadhav*, Ozlem Goker-Alpan[†], Anton Simeonov*, Ehud Goldin¹, Douglas Auld*, Mary E. LaMarca[†], James Inglese*, Christopher P. Austin^{*†}, and Ellen Sidransky^{1†}

^{*}NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, 9800 Medical Center Drive, MSC 3370, Bethesda, MD 20892-3370; and [†]Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Building 35 Rm1A213, 35 Convent Drive, Bethesda, MD 20892-3708

13192–13197 | PNAS | August 7, 2007 | vol. 104 | no. 32

Macrophage Models of Gaucher Disease for Evaluating Disease Pathogenesis and Candidate Drugs

Elma Aflaki,¹ Barbara K. Stubblefield,¹ Emerson Maniwang,¹ Grisel Lopez,¹ Nima Moaven,¹ Ehud Goldin,^{1*} Juan Marugan,² Samarjit Patnaik,² Amalia Dutra,³ Noel Southall,² Wei Zheng,² Nahid Tayebi,¹ Ellen Sidransky^{1†}

www.ScienceTranslationalMedicine.org 11 June 2014 Vol 6 Issue 240 240ra73

A new glucocerebrosidase-deficient neuronal cell model provides a tool to probe pathophysiology and therapeutics for Gaucher disease

Wendy Westbroek¹, Matthew Nguyen¹, Marina Siebert^{1,2}, Taylor Lindstrom¹, Robert A. Burnett¹, Elma Aflaki¹, Olive Jung¹, Rafael Tamargo¹, Jorge L. Rodriguez-Gil³, Walter Acosta⁴, An Hendrix⁵, Bahaftha Behre¹, Nahid Tayebi¹, Hideji Fujiwara⁶, Rohini Sidhu⁶, Benoit Renvoise⁷, Edward I. Ginns⁸, Amalia Dutra⁹, Evgenia Pak⁹, Carole Cramer⁴, Daniel S. Ory⁶, William J. Pavan³ and Ellen Sidransky^{1,*}

Disease Models & Mechanisms (2016) 9, 769-778

Translational principle result #2

Chaperones that don't inhibit are critical

- Chaperones bind to their target proteins and can inhibit, activate, or neither

➤ Most inhibit

- Chaperones that are noninhibitory or even activate can be found but require innovative testing systems to find them

Three classes of glucocerebrosidase inhibitors identified by quantitative high-throughput screening are chaperone leads for Gaucher disease

Wei Zheng*, Janak Padia*, Daniel J. Urban†, Ajit Jadhav*, Ozlem Goker-Alpan†, Anton Simeonov*, Ehud Goldin†, Douglas Auld*, Mary E. LaMarca†, James Inglese*, Christopher P. Austin*†, and Ellen Sidransky†‡

*NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, 9800 Medical Center Drive, MSC 3370, Bethesda, MD 20892-3370; and †Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Building 35 Rm1A213, 35 Convent Drive, Bethesda, MD 20892-3708

13192–13197 | PNAS | August 7, 2007 | vol. 104 | no. 32

Discovery, Structure–Activity Relationship, and Biological Evaluation of Noninhibitory Small Molecule Chaperones of Glucocerebrosidase

Samarjit Patnaik,† Wei Zheng,† Jae H. Choi,‡ Omid Motabar,‡ Noel Southall,† Wendy Westbrook,‡ Wendy A. Lea,† Arash Velayati,‡ Ehud Goldin,‡ Ellen Sidransky,‡ William Leister,† and Juan J. Marugan*†

†NIH Chemical Genomic Center, National Center for Advancing Translation Sciences, National Institutes of Health, 9800 Medical Center Drive, Rockville, Maryland, United States

‡Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892, United States

J. Med. Chem. 2012, 55, 5734–5748

Progress and potential of non-inhibitory small molecule chaperones for the treatment of Gaucher disease and its implications for Parkinson disease

Olive Jung^a, Samarjit Patnaik^b, Juan Marugan^b, Ellen Sidransky^a and Wendy Westbrook^a

^aSection on Molecular Neurogenetics, Medical Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD, USA; ^bNational Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD, USA

EXPERT REVIEW OF PROTEOMICS, 2016
VOL. 13, NO. 5, 471–479

Translational principle result #3

Treatments for common diseases can come directly from rare diseases but requires a dedicated strategy

- Treatment with NCATS-developed GCase chaperones correct disease phenotype in Gaucher patient iPSC-derived macrophages and neurons
- GCase chaperones also cleared alpha-synuclein from neurons from both GD-Parkinsonism and PD patients
- Potential treatment for Gaucher Disease with Parkinsonism (enzyme replacement ineffective)
- Novel treatment modality for Parkinson's disease
- Approach generalizable to other lysosomal storage and neurodegenerative diseases

A New Glucocerebrosidase Chaperone Reduces α -Synuclein and Glycolipid Levels in iPSC-Derived Dopaminergic Neurons from Patients with Gaucher Disease and Parkinsonism

Elma Aflaki,¹ Daniel K. Berger,¹ Nima Moaven,¹ Barbara K. Stubblefield,¹ Steven A. Rogers,² Samarjit Patnaik,³ Frank J. Schoenen,² Wendy Westbrook,¹ Wei Zheng,³ Patricia Sullivan,⁴ Hideji Fujiwara,⁵ Rohini Sidhu,⁵ Zayd M Khaliq,⁶ Grisel J. Lopez,¹ David S. Goldstein,⁴ Daniel S. Ory,³ Juan Marugan,³ and Ellen Sidransky¹

¹Section of Molecular Neurogenetics, National Human Genome Research Institute, ²National Center for Advancing Translational Sciences, ³Clinical Neurocardiology Section, and ⁴Cellular Neurophysiology Unit, National Institute of Neurological Disease and Stroke, National Institutes of Health, Bethesda, Maryland 20892, ⁵University of Kansas Specialized Chemistry Center, University of Kansas, Lawrence, Kansas 66047, and ⁶Diabetic Cardiovascular Disease Center and Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110

The Journal of Neuroscience, July 13, 2016 • 36(28):7441–7452 • 7441

Activation of β -Glucocerebrosidase Reduces Pathological α -Synuclein and Restores Lysosomal Function in Parkinson's Patient Midbrain Neurons

Joseph R. Mazzulli,^{1,2} Friederike Zunke,² Taiji Tsunemi,^{1,2} Nicholas J. Toker,² Sohee Jeon,² Lena F. Burbulla,^{1,2} Samarjit Patnaik,³ Ellen Sidransky,⁴ Juan J. Marugan,³ Carolyn M. Sue,⁵ and Dimitri Krainc^{1,2}

¹Department of Neurology, Massachusetts General Hospital, Harvard Medical School, MassGeneral Institute for Neurodegeneration, Charlestown, Massachusetts 02129, ²The Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago IL 60611, ³Department of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, Maryland, 20850, ⁴Section of Molecular Neurogenetics, Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, 20892, and ⁵Department of Neurogenetics, Kolling Institute of Medical Research, Royal North Shore Hospital and the University of Sydney, St Leonards, New South Wales 2065, Australia

The Journal of Neuroscience, July 20, 2016 • 36(29):7693–7706 • 7693

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EDITORS' CHOICE | PARKINSON'S DISEASE



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A glucocerebrosidase chaperone to ward off Parkinson's disease



Ian Martin

+ Author Affiliations



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Science Translational Medicine 10 Aug 2016:
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DOI: 10.1126/scitranslmed.aah5492

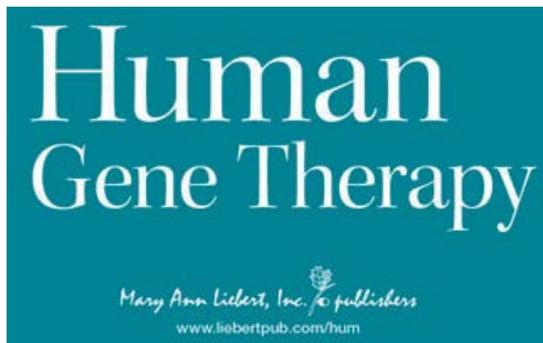
Gene Therapy at NCATS

- NCATS is interested in platform approaches that can be readily adapted to **multiple** diseases
- Gene therapy (GT) is such a platform approach and relevant to the treatment of rare genetic diseases
- NCATS supports GT development through several programs

Gene Therapy: The View from NCATS

Philip J. Brooks,^{1,*} N. Nora Yang,² and Christopher P. Austin³

¹Division of Clinical Innovation and Office of Rare Diseases Research, and ²Division of Preclinical Innovation, ³Office of the Director, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, Bethesda, Maryland.



Commentary published in January 2016



TRND Gene Therapy Learning Collaborative

- Platform focusing on building GT toolbox for treating rare genetic diseases
- Pilot projects addressing common GT translational issues:
 - Tissue-specific delivery
 - Vehicle and cargo design
 - New technology for large scale vector manufacturing and characterization
 - Long term safety and efficacy
- Uses hallmark NCATS collaborative model:
 - Partnerships between foundations, companies, academia, and NCATS

TRND Gene Therapy Portfolio

Disease	Collaborator	Target Tissue	Addressing GT Challenges
Pompe Disease	Duke University Medical Center	Liver	<ul style="list-style-type: none"> Immunomodulatory therapy Systemic delivery Liver expression
Aromatic L-amino acid decarboxylase (AADC) Deficiency	Agilis Biotherapeutics	CNS – putamen	<ul style="list-style-type: none"> CNS local delivery Delivery to newborns Global regulatory approval for ultra-rare diseases
Duchenne Muscular Dystrophy (DMD)	Solid GT, Solid Biosciences	Striated Muscles	<ul style="list-style-type: none"> Largest tissue by body mass; widely distributed throughout the body Lack of scalable manufacturing technology to support phase III testing and commercialization Re-dosing

GT for AADC Deficiency

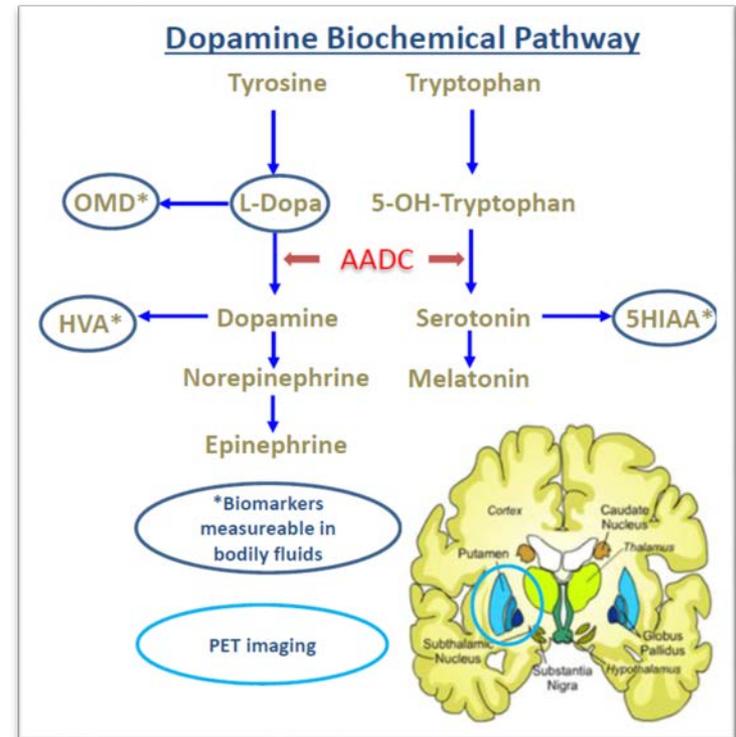
- Collaborators
 - Agilis Biotherapeutics, Taiwan Natl U

- Background

- Rare CNS disorder arising from a reduction in the enzyme, aromatic L-amino acid decarboxylase (AADC)
- Deficits in major neurotransmitters: dopamine, norepinephrine, epinephrine, serotonin, and melatonin

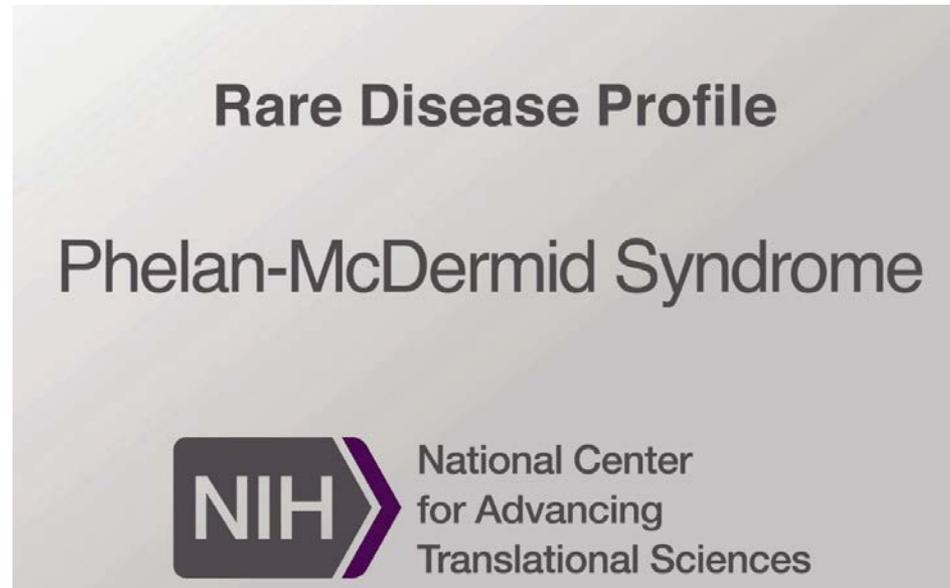
- Goals

- **First** CNS gene therapy approved worldwide
- Develop new devices for GT delivery in infants
- Global regulatory approval strategy for ultra rare diseases



Rare Disease Patient Profile

Megan O'Boyle tells the story of her daughter, who has Phelan-McDermid syndrome



<https://www.youtube.com/watch?v=VOMSq1D24Fc>



The cost of medication nonadherence and patient behavior is significant

\$40 billion

CLINICAL RESEARCH LOSSES
Over-recruitment, delayed launches,
and litigation.

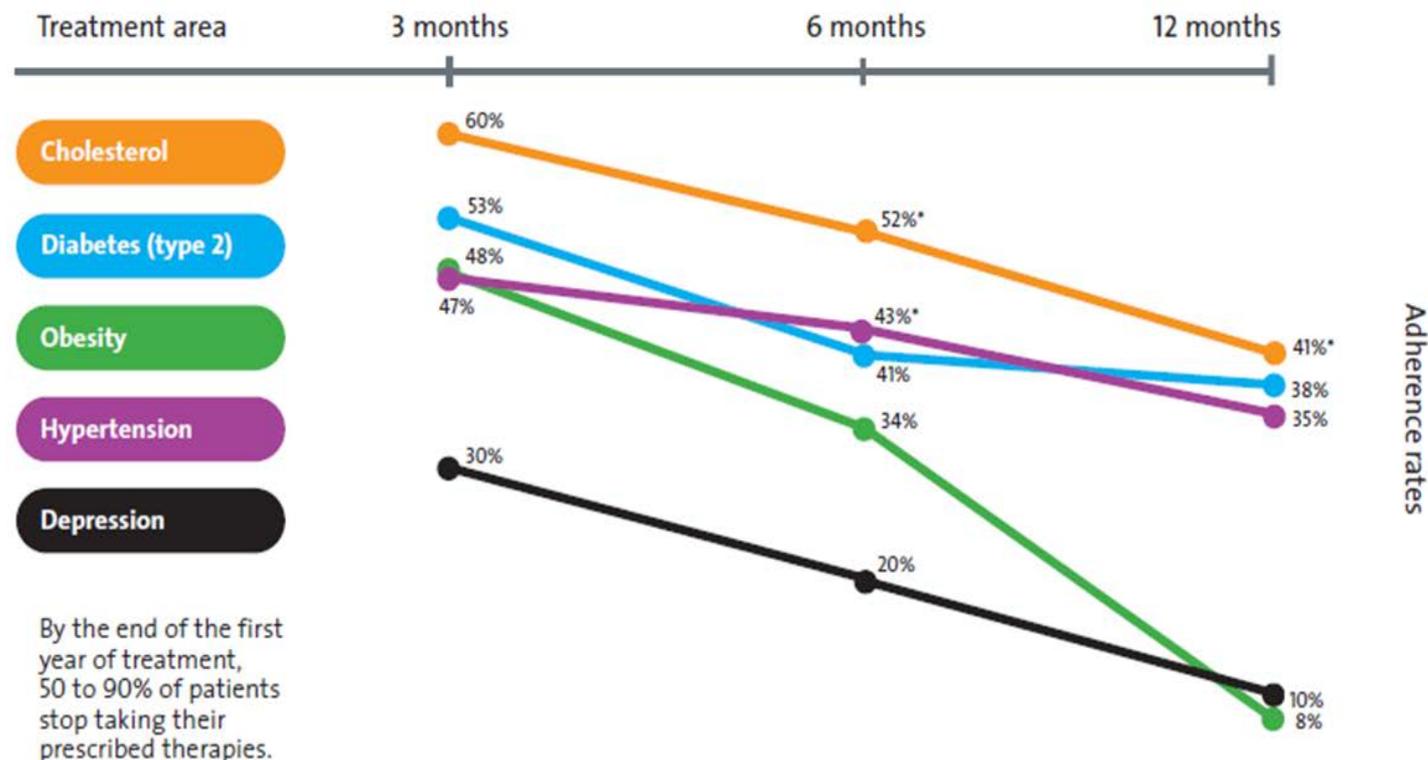
\$300 billion

NEGATIVE HEALTH OUTCOMES
Hospitalizations, adverse events,
and death.

**Goldman
Sachs**

“The economic impact of behavior modification in healthcare has been estimated to be “indefinitely large.”

Medication adherence drops across all therapeutic areas over time



* Adherence rate ranges were averaged. Source: Various sources; A.T. Kearney analysis

The Case for Smarter Medicine | 11

*Snow, David. The Case for Smarter Medicine: How Evidence-Based Protocols Can Revolutionize Healthcare. 2010, Medco Healthcare Solutions.

Largest economic costs derive from high-risk patients who are non-adherent

Scenario	Impact	Cost
 Patient misses one dose of Hepatitis C treatment	x2 course of therapy	\$50,000-\$90,000 additional cost
 Stroke patient stops Xarelto®	↑30% hospitalization risk	\$50,000 to \$100,000 inpatient services
 Schizophrenia discontinues treatment with Risperdal	↑25% hospitalization risk	Avg. \$60,000 inpatient stay
 30-50% of CNS trials fail because of subject nonadherence.	↓ statistical power	\$5,000 to \$20,000 cost per patient

5% of patients cause 50% of US healthcare costs. Current interventions such as text messages or electronic medication packaging have shown limited effect on both adherence and health outcomes

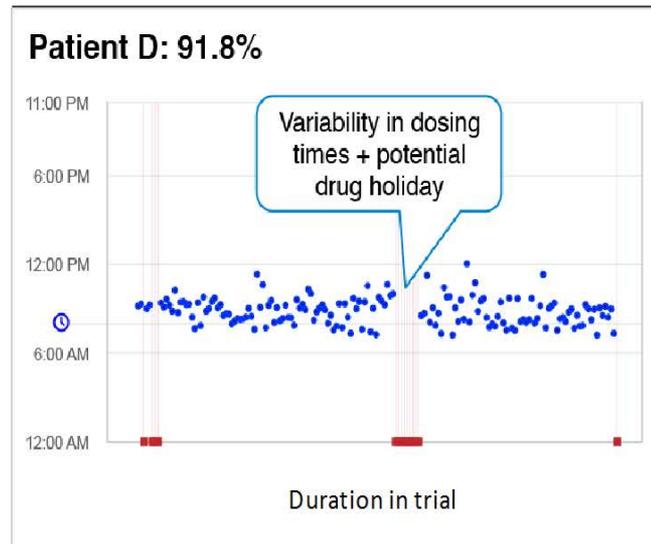
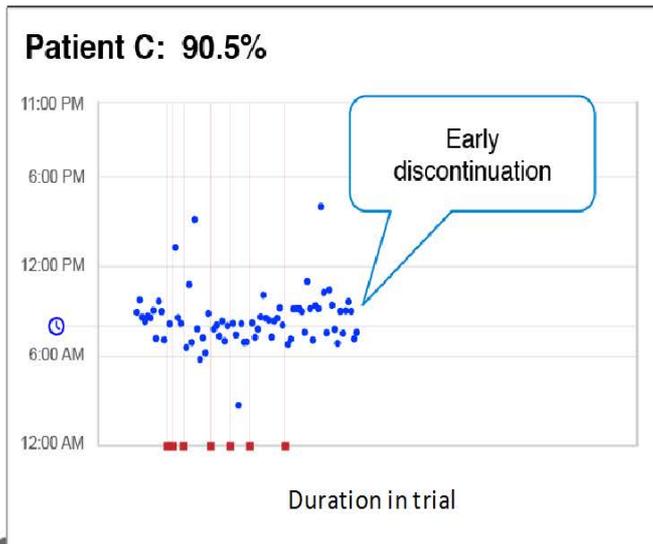
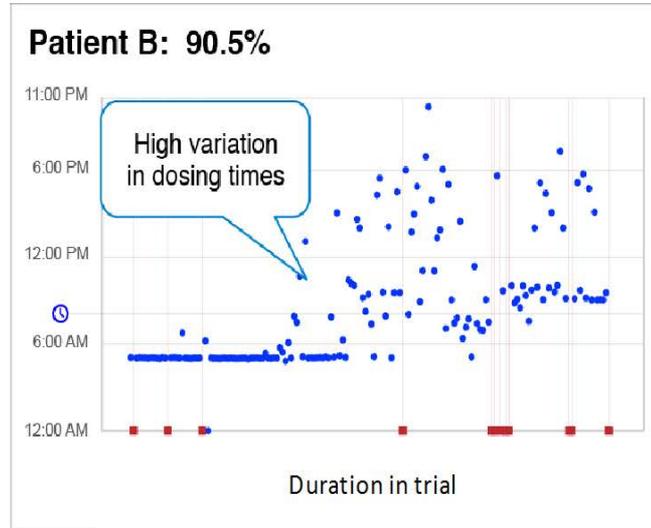
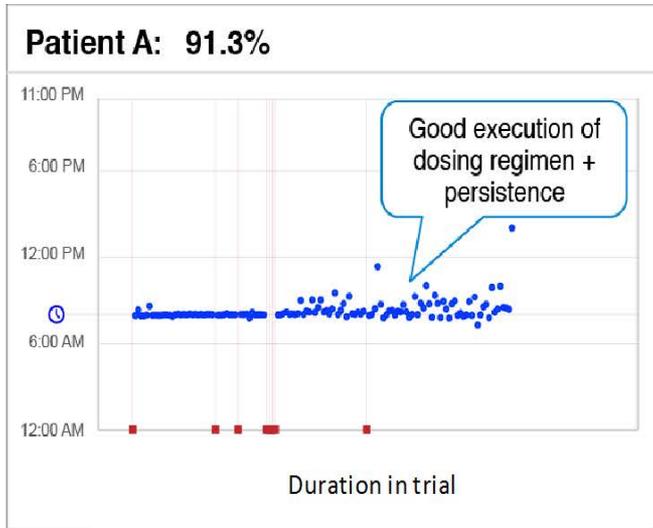
(Checchi et al, JAMA, 2014; de Jongh et al, Cochrane Database Systemic Review, 2012).

SBIR support of a technology solution

- AiCure is a small company based in NYC
 - Focused on medication adherence solutions based on artificial intelligence
- SBIR Phase I and Phase II awards
 - Supported development and initial testing of app
 - Supported validation of technology against blood levels of medications and showed that the app improves adherence rates in schizophrenia and stroke clinical trials (study publication expected late 2016)
- SBIR support from NCATS, NIMH, and NHLBI have now allowed company to attract VC financing

Watch a short video about AiCure at <https://www.aicure.com>

Importance of capturing accurate dosing patterns

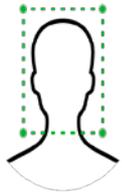


Clinical trials: *“Need for measures of adherence that do not solely rely on self-reporting and that are not easily manipulated by participants.”* (Marazzo et al, NEJM, 2015)

Population health: *“providers usually have had to rely on the patient for information about his/her use of the medication, even though such information is subject to problems of recall and various barriers to candor.”* (Blaschke et al, 2012)

AiCure uses Artificial Intelligence (AI) to visually confirm medication ingestion

The platform has been clinically validated against blood levels.



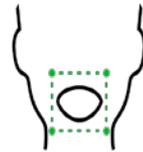
FACIAL RECOGNITION

HIPAA-compliant identification of the patient.



IDENTIFY MEDICATION

Verify that the medication and/or the blister pack is correct.



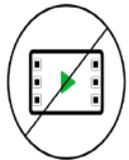
CONFIRM INGESTION

Ensure ingestion for oral medications in real-time.



ANTI-FRAUD

Identify duplicate enrollment and other types of fraudulent activity.



NO VIDEO REVIEW

The software replaces the need to perform manual review of video.



BYOD OR PROVISIONED

Downloadable onto any iOS or Android device or provision devices.



REAL-TIME ANALYTICS

Access accurate data in real-time allowing for pre-emptive intervention.

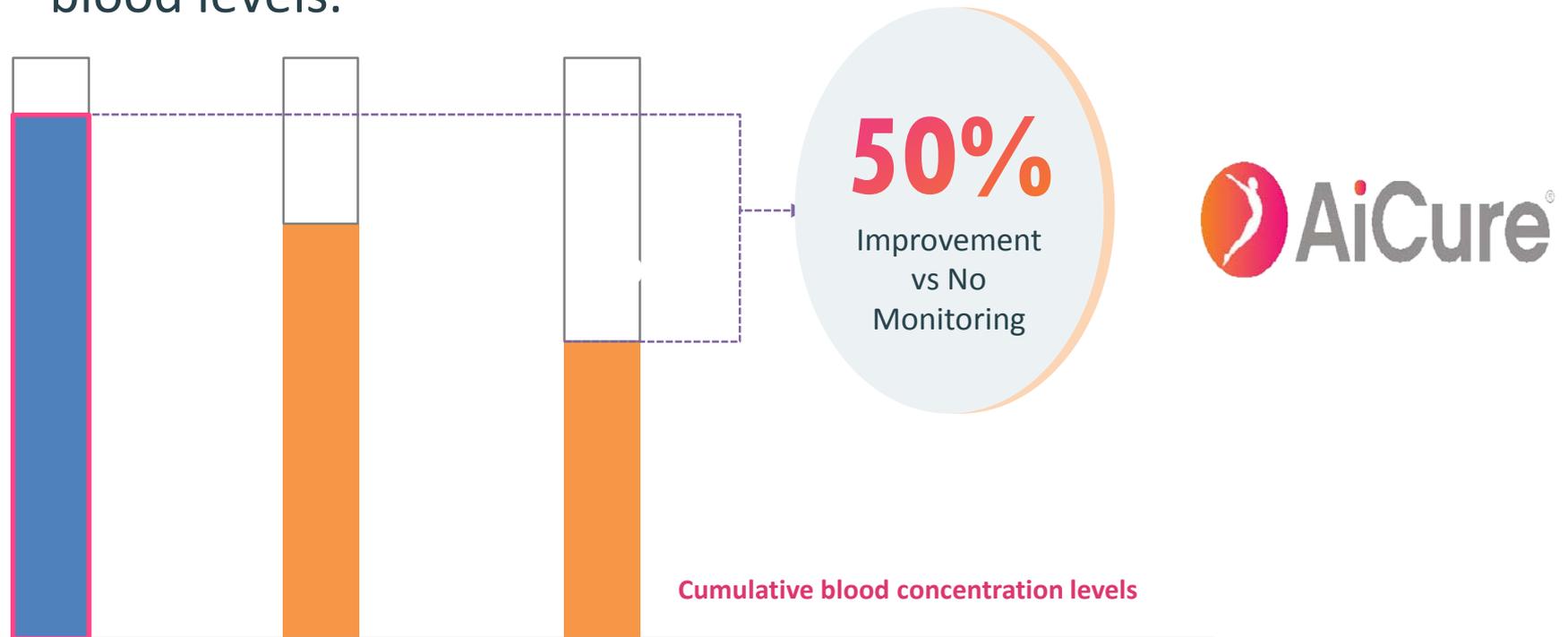


PATIENT ENGAGEMENT

An assistive technology that provides reminders, instructions and site contact.

Quantifiable impact: reducing drug development time and preventing hospitalizations

The platform has been clinically validated against blood levels.



AiCure



Observed Dosing



No
monitoring
(est.)

Peer-reviewed publications:

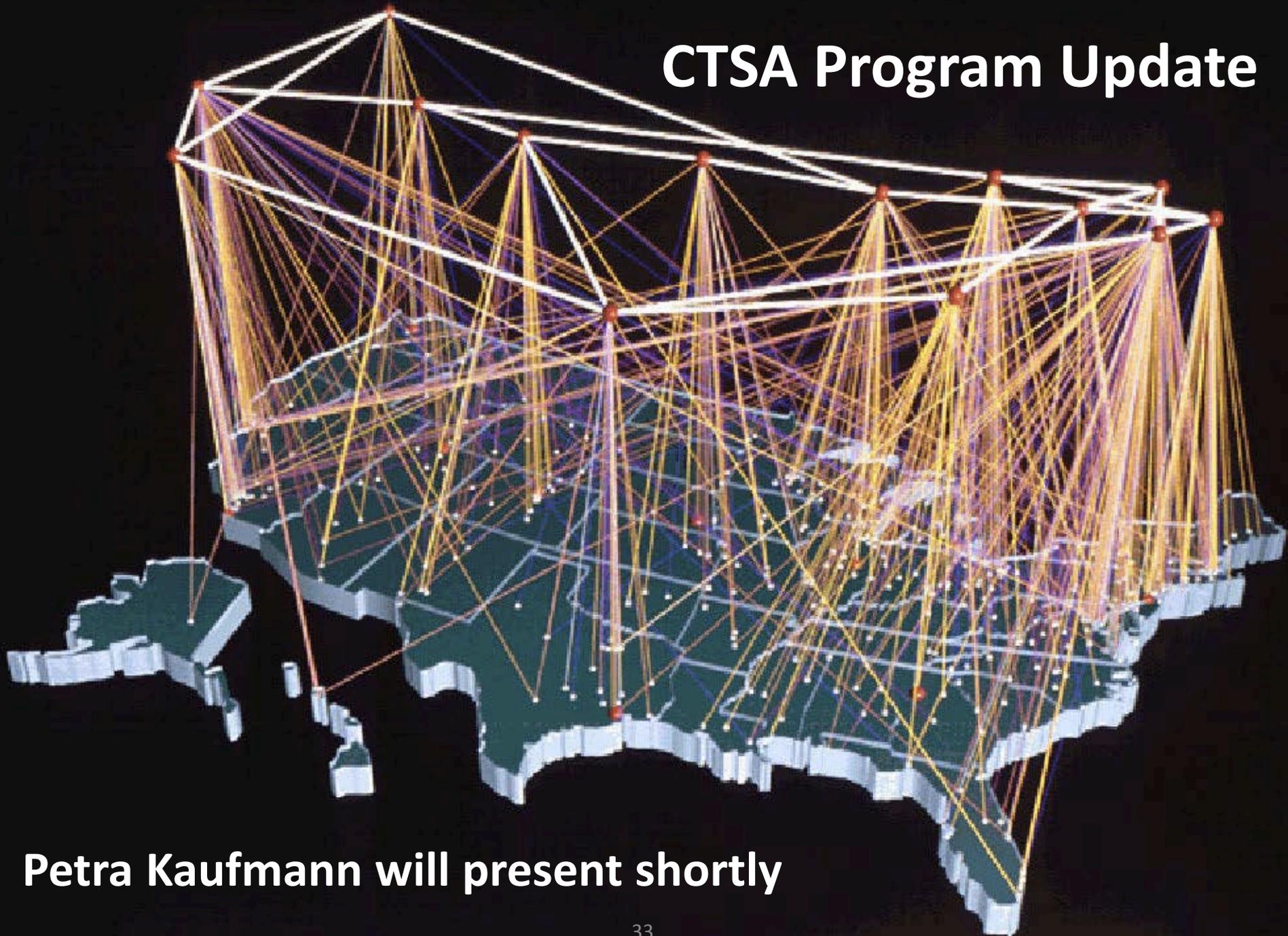
Shiovitz TM, Bain EE, McCann DJ, et al: Mitigating the effects of nonadherence in clinical trials. *J Clin Pharmacol* 2015; Dec 4

Hanina A, Shafner L. Using Artificial Intelligence (AI) to monitor adherence on mobile devices. SIRS (Schizophrenia International Research Society), poster presentation

Bain EE, et al. Use of an Artificial Intelligence Platform on Mobile Devices to Assess Dosing Compliance in a Phase 2 Schizophrenia Study. ISCTM (The International Society for CNS Clinical Trials and Methodology), poster to be presented

Labovitz D, et al. Using Artificial Intelligence to measure and optimize adherence on anticoagulation therapy. Connected Health Symposium, poster to be presented

CTSA Program Update



Petra Kaufmann will present shortly

Community Engagement is a critical component of the CTSA Program

- Community Engagement (CE) section in most recent CTSA Program Funding Opportunity Announcement (PAR-15-304)
 - Defines communities broadly
 - Addresses CE as a scientific problem
 - Integrates CE into leadership, research and communication at hubs
 - Integrates CE across translational spectrum
 - Acknowledges CE in academic policy and culturally competent training for staff fosters innovation, disseminate best practices

Rockefeller CTSA

Community-Engaged Research Navigation (CEnR-Nav) Program

Background

Rockefeller University Center for Clinical and Translational Science (RU-CCTS) has partnered with Clinical Directors Network (a PBRN) to create a community-engaged research navigation (CEnR-Nav) Program

Community-Engaged Research Navigation (CEnR-Nav) Program

- Provides model for basic scientists to engage communities, community clinicians, patients and other stakeholders
- Develops and conducts collaborative study protocols
- Incorporates principles of CE, team science and community-engaged participatory research
- Involves clinical scholar trainees, early-career physician-scientists, faculty, students, postdocs
- Led by an academic navigator and a practice-based research network (PBRN) navigator

Community-Engaged Research Navigation (CEnR-Nav) Program

- 23 approved protocols and 2 substudies
 - 19 identified community partners
 - Nine named community partners as coinvestigators
 - 2/3 focused on T1-T2 translational aims
 - Seven secured external funding
 - 11 disseminated results through presentations or publications
 - Five included a community partner as a coauthor

http://journals.lww.com/academicmedicine/Abstract/publishahead/Helping_Basic_Scientists_Engage_With_Community.98512.aspx

Helping Basic Scientists Engage With Community Partners to Enrich and Accelerate Translational Research

Rhonda G. Kost, MD, Andrea Leinberger-Jabari, MPH, Teresa H. Evering, MD, MS, Peter R. Holt, MD, Maija Neville-Williams, MPH, Kimberly S. Vasquez, MPH, Barry S. Collier, MD, and Jonathan N. Tobin, PhD

Abstract

Problem

Engaging basic scientists in community-based translational research is challenging but has great potential for improving health.

Approach

In 2009, The Rockefeller University Center for Clinical and Translational Science partnered with Clinical Directors Network, a practice-based research network (PBRN), to create a community-engaged research navigation (CEnR-Nav) program to foster research pairing basic science and community-driven scientific aims. The program is led by an academic navigator and a PBRN navigator. Through meetings and joint activities, the program

facilitates basic science–community partnerships and the development and conduct of joint research protocols.

Outcomes

From 2009–2014, 39 investigators pursued 44 preliminary projects through the CEnR-Nav program; 25 of those became 23 approved protocols and 2 substudies. They involved clinical scholar trainees, early-career physician–scientists, faculty, students, postdoctoral fellows, and others. Nineteen (of 25; 76%) identified community partners, of which 9 (47%) named them as coinvestigators. Nine (of 25; 36%) included T3–T4 translational aims. Seven (of 25; 28%) secured external funding, 11 (of 25; 44%) disseminated

results through presentations or publications, and 5 (71%) of 7 projects publishing results included a community partner as a coauthor. Of projects with long-term navigator participation, 9 (of 19; 47%) incorporated T3–T4 aims and 7 (of 19; 37%) secured external funding.

Next Steps

The CEnR-Nav program provides a model for successfully engaging basic scientists with communities to advance and accelerate translational science. This model's durability and generalizability have not been determined, but it achieves valuable short-term goals and facilitates scientifically meaningful community–academic partnerships.

Characteristics of Investigators and Research Protocols in the Community-Engaged Research Navigation (CErNav) Program at The Rockefeller University Center for Clinical and Translational Science and Clinical Directors Network, 2009 to 2014, With Outcomes Through 2015

Year of initial CErNav (PI career stage ^a)	Status	Area of inquiry	Subject group	Origin ^b	Extent ^c	Location of protocol-specific aims on translational continuum ^d					Community partner identified in protocol (as coinvestigator)	External funding since CErNav (directly related)	No. of presentations, no. of publications (no. with community coauthors) ^e
						T0	T1	T2	T3	T4			
2013 (H)	Ongoing	Surveillance network to compare HA-MRSA and CA-MRSA	MRSA patients	Bottom-up team	Brief	✓					Community hospital (yes)	No	No
2014 (F)	Completed	Increase diversity of polycystic kidney disease registry	Minority patients	Middle-out	Brief	✓					No	No	No
2009 (C)	Completed	Development of bleeding phenotyping instrument	FQHC patients	Middle-out	Brief		✓				FQHCs (no)	No	1 (1), 3 (1)
2013 (C)	Ongoing	Engaging patients with obesity or diabetes ^f	FQHC patients	Top-down ACCER	Brief	✓	✓				No	No	No
2013 (N)	Ongoing	Engaging patients' families to upload data to registry	Fanconi anemia registry	Bottom-up team	Brief	✓	✓				Registry patients (no)	No	No
2014 (C)	Completed	Mechanistic study of psoriasis in Asians; engage stakeholders	Asians with psoriasis	Bottom-up team	Brief	✓	✓				Community clinician (yes)	No	No data, 1 (1) ^g
2013 (C)	Completed	Engagement of Down syndrome patients for mechanistic study ^f	Patients with Down syndrome	Middle-out	Moderate	✓					Down syndrome advocates (no)	Yes (yes)	No
2014 (C)	Ongoing	Immunologic defects in chronic hepatitis B virus infection; mechanistic study	Patients with chronic hepatitis B virus	Middle-out	Moderate	✓					PBRN (no)	No	No
2013 (C)	Completed	Quality of life and metabolic alterations in statin therapy	Patients taking statins	Middle-out	Moderate	✓					No	No	No
2013 (P)	Completed	Biology of stress related to shifted circadian rhythm (shift work) ^f	Shift workers	Top-down ACCER	Moderate	✓					Transit union (no)	Yes (yes)	No
2012 (N)	Completed	CA-MRSA surveillance at ambulatory surgery centers	Patients utilizing ambulatory surgery centers	Bottom-up team	Moderate				✓		No	No	No
2013 (N)	Completed	Hepatitis C virus education in barbershops	FQHC patients	Top-down ACCER	Moderate				✓		Local educator, barbers (no)	No	1 (0), 1 (1)**
2013 (C)	Ongoing	Study of virulence factors and MRSA recurrence	FQHC patients	Middle-out	Extended	✓					FQHC clinicians (no)	No	No
2011 (H)	Ongoing	Mechanism and pathobiology of keloid formation	Minority patients with keloid	Bottom-up team	Extended	✓	✓				Community clinician (yes)	No	No
2011 (C)	Ongoing	Recruitment to Alzheimer disease study	Patients with Alzheimer disease	Middle-out	Extended	✓	✓	✓			Alzheimer foundation (no)	No	No
2013 (F)	Ongoing	Critical thinking outcomes for science outreach participants	Science Outreach students	Bottom-up team	Extended				✓		Educator evaluators (no)	No	1, 0
2011 (N)	Completed	Assessing the community research participant's experience	FQHC patients	Bottom-up team	Extended				✓		PBRN FQHC clinicians (yes)	No	2 (2), 0

Community-Acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA) Project (CAMP1) Surveillance Network

Goals

1. Define incidence of CA-MRSA in New York area Community Health Centers (CHCs)
2. Insure that CHCs clinicians have the training to provide optimal care to patients with CA-MRSA
3. Identify substrains of MRSA responsible for infections
4. Assess relationship between the MRSA colonizing a patient's nose and the MRSA causing the clinical infection
5. Build a respectful, enduring, bidirectional partnership and network infrastructure for conducting and disseminating future studies

Policy and Legislative Updates



FY 2017 Budget

- February 9, 2016: President's budget request
 - NCATS' request is \$685.417 million (same as FY 16)
- Appropriation bills
 - Each House and Senate Appropriation committee passed a Labor, HHS, and Education bill
 - Neither bill was voted on by the full chamber
- Continuing Resolution likely - *stay tuned!*
 - Senate vote possible next week
 - If passed, it would:
 - Extend government funding through Dec. 9 at FY16 levels
 - Include funding for Zika

Congressional Authorizing Activity

- House - 21st Century Cures (H.R. 6, 7/10/15)
 - NIH “Innovation Fund” - \$8.75 billion over five years
- Senate - Innovations for Healthier Americans
 - Held hearings to discuss potential bills for inclusion, but no complete bill released yet
 - Mandatory funding for NIH is main sticking point
- Status
 - Rep. Fred Upton (Chair, House E&C) and Senator Lamar Alexander (Chair, Senate HELP) have indicated that President will have bill on desk by end of September

Presidential Transition

- **At Administration level**
 - Obama administration has convened:
 - White House Transition Coordinating Council (WHTCC)
 - Agency Transition Directors Council (ATDC)
- **At NIH level**
 - NIH has begun developing briefing materials for the new Administration



- **Designation of “Acting”**
- **Preparation of materials**

- **Agency Review Teams arrive**
- **Selection of incoming Presidential Appointees begins**

- **Inauguration and onboarding of new Political Appointees begins**

NCATS Annual Report



Director's Corner



Christopher P. Austin, M.D.

- Director's Message
- NCATS Strategic Plan
- NCATS E-Newsletter
- **NEW NCATS Annual Report** (PDF - 3MB)
- Director's Biography
- Election to National Academy of Medicine



National Center
for Advancing
Translational Sciences

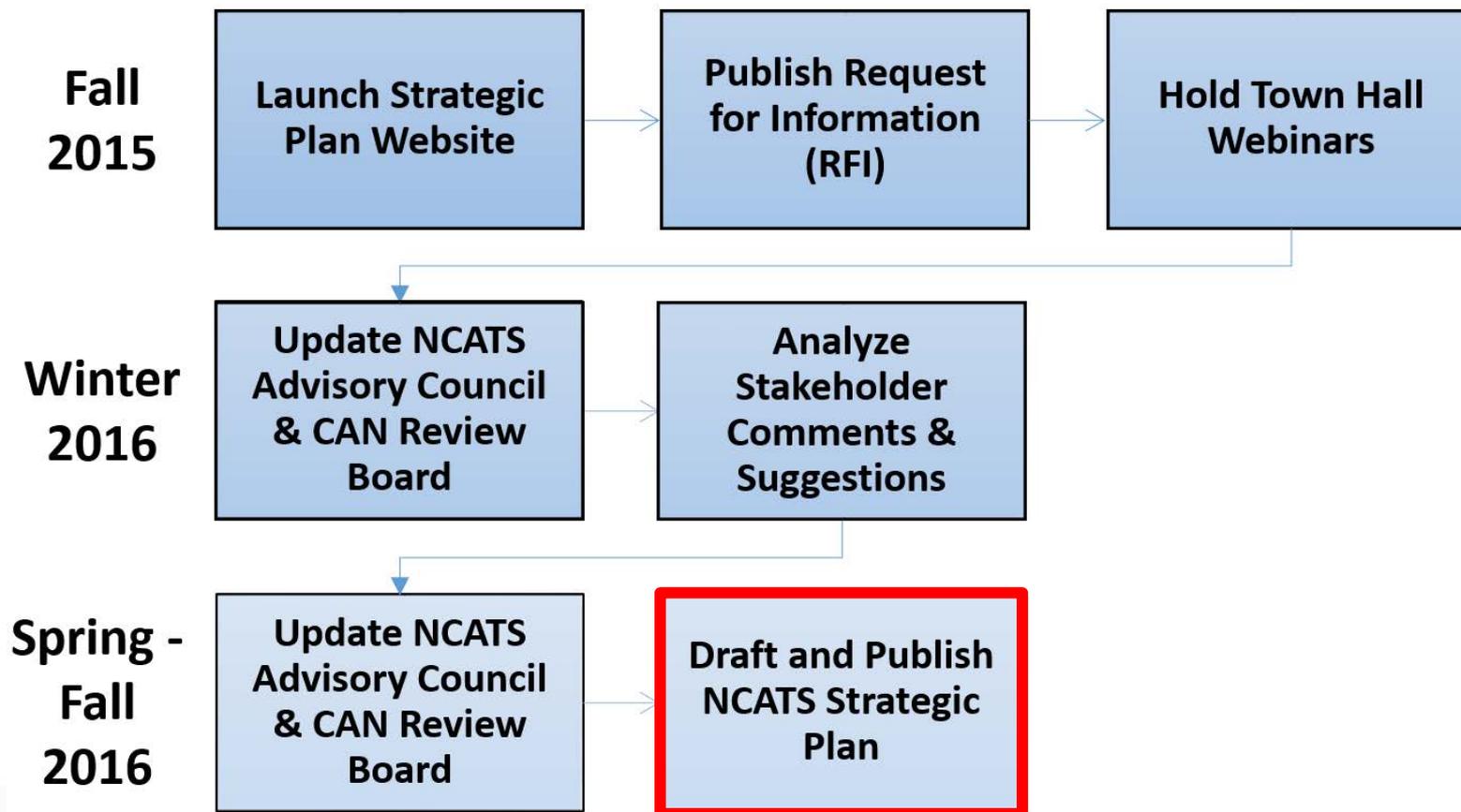


National Center
for Advancing
Translational Sciences

NCATS Strategic Plan

Timeline

<https://ncats.nih.gov/strategicplan>



NCATS Strategic Plan

Stakeholder Engagement

- **Internal**

- NCATS employees engaged to provide perspectives and develop strategic principles

- **External**

- **Council/CAN RB**

- Series of focus groups were created including internal staff and Council/CAN RB members
 - Identified priorities and challenges in overarching translational areas
- Provided additional input at Open Session of Sept. 2015 Council

- **Request for Information (RFI) & Webinars**

- Public RFI was published and a series of four “town hall”-style webinars were held in late Fall-Winter 2015
- Identified areas of opportunity and research needs in translational science space

NCATS Strategic Plan

Strategic Goals

1. Conduct and support innovative research that uncovers fundamental scientific and operational principles of translational science to catalyze the development and dissemination of novel medical interventions
2. Advance translational team science by fostering innovative partnerships and collaborations with a strategic array of stakeholders
3. Develop and foster innovative translational training and a highly skilled, creative and diverse translational science workforce
4. Enhance good stewardship of public funds by promoting and employing efficient and effective management practices

Enhancing NIH Stewardship of Clinical Trials

New initiatives progressed by the NIH Clinical Trial Stewardship Reforms Task Force

- **Single IRB for Multi-site Studies**
 - Policy regarding domestic sites of NIH-funded multi-site studies will use a single IRB
 - Policy was released in June 2016, effective May 2017
- **Clinical Trials Registration and Results Submission**
 - Developing the requirements for clinical trial registration and results submission to CT.gov and the final NIH policy
 - Will be published in Sept
- **Clinical Trial Specific FOAs**
 - NIH policy requiring all clinical trials to be submitted to specific FOAs (i.e., clinical trial-specific FOA template)
 - Will be published in NIH Guide in Sept; tentatively effective ~Sept 2017
- **Good Clinical Practice Training for Investigators**
 - Policy establishing expectation that NIH-funded investigators will be trained in GCP
 - Will be published in NIH Guide in Sept; effective Jan 2017
- **Clinical Trial Protocol Template**
 - NIH-FDA joint initiative; electronic format of template will be available early 2017 and electronic tool in late 2017



NIH-FDA Joint Leadership Council

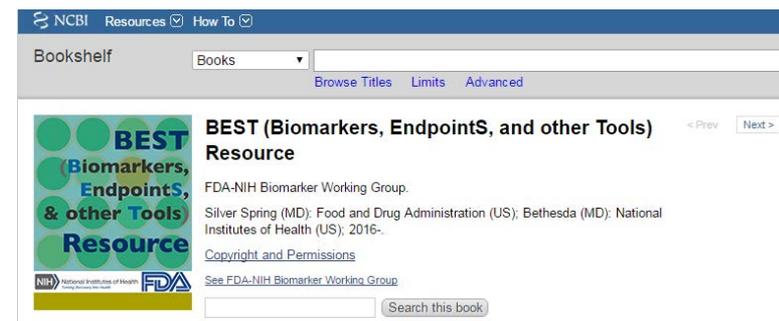
Biomarkers Taxonomy

- **Co-Chairs:** Rob Califf (FDA) & Pamela McInnes (NIH) & Mike Pacanowski (FDA)
- **Goal:** Ensure consistent use of terminology and further explore opportunities for biomarker infrastructure development
- **Updates:**
 - Biomarkers, EndpointS, and other Tools (BEST) resource published as NCBI eBook
 - Published JAMA article

JAMA The Journal of the
American Medical Association

Biomarkers and Surrogate Endpoints Developing Common Terminology and Definitions

Melissa A. Robb, BSN, MS (RegSci)¹; Pamela M. McInnes, DDS, MSc (Dent)²; Robert M. Califf, MD³



The screenshot shows the NCBI Bookshelf interface. At the top, there are navigation links for 'NCBI Resources' and 'How To'. Below that, a search bar is visible with the text 'Books' and a dropdown menu. To the right of the search bar are links for 'Browse Titles', 'Limits', and 'Advanced'. The main content area displays the cover of the 'BEST (Biomarkers, EndpointS, and other Tools) Resource' eBook. The cover features a green and blue design with the text 'BEST (Biomarkers, EndpointS, and other Tools) Resource'. To the right of the cover, the title 'BEST (Biomarkers, EndpointS, and other Tools) Resource' is displayed, along with the author 'FDA-NIH Biomarker Working Group' and the publication information 'Silver Spring (MD); Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US); 2016-'. There are also links for 'Copyright and Permissions' and 'See FDA-NIH Biomarker Working Group'. At the bottom of the page, there is a search bar with the text 'Search this book'.



NIH-FDA Joint Leadership Council

Clinical Trial Protocol Template

- **Co-Chairs:** Petra Kaufmann (NIH) & Peter Marks (FDA)
- **Goal:** Develop a clinical trial protocol template to be used by NIH investigators submitting protocols to FDA
- **Updates:**
 - Published NIH Guide notice and gathered public comments via a request for information (RFI) on draft protocol template
 - Analyzed RFI responses
 - Incorporating suggested changes with trans-NIH-FDA group
 - Working with TransCelerate to make templates consistent

International Rare Diseases Research Consortium (IRDiRC)



- Global coordination and cooperation to stimulate and maximize output of rare disease research efforts
 - Members from Europe, North America, Asia, Australia, Middle East
 - Each funder supports its own research
- Initial focus on developing common scientific and policy frameworks
- 2011-2016 objectives: 200 new therapies for rare diseases & means to diagnose most rare diseases by 2020

IRDiRC

Background

- **2009** - Idea for IRDiRC precipitated from meeting between Dr. Ruxandra Draghia-Akli (EC) and Dr. Francis Collins (NIH)
- **October 2010** - European Commission and NIH announced IRDiRC at workshop in Reykjavik
- **April 2011** - IRDiRC established with Dr. Draghia-Akli elected as Chair at workshop in Bethesda
- **October 2011** - Gathered for workshop with private and public organizations in Montreal
- **January 2013** - Dr. Paul Lasko (Canadian Inst. of Health Research) elected as new Chair
- **April 2013** - First IRDiRC Conference for researchers, clinicians, patient groups and representatives of public and private organizations in Dublin
- **November 2014** - Second IRDiRC Conference in China
- **March 2015** - Task Forces established to tackle specific areas of importance
- **February 2016** - Dr. Chris Austin (NIH/NCATS) elected as new Chair



IRDiRC

NCATS Representation

- **Chris Austin** - Chair of Consortium Assembly
- **Steve Groft** - Member of Interdisciplinary Scientific Committee
- **Petra Kaufmann** - Member of Interdisciplinary Scientific Committee; member of Automatable Discovery and Access, Patient-Centered Outcome Measures, and Participant Unique Identifiers for Research Data Sharing Task Forces
- **Noel Southall** - Member of Steering Committee of Data Mining/Repurposing Task Force



3rd IRDiRC Conference

February 8-9, 2017, Paris, France



- Five year celebration
- All stakeholders – investigators, policy makers, opinion leaders, critical thinkers, young investigators, patient advocates – active in the area of RD are invited to join
- Celebrate achievements in the field, identify future milestones and goals, and work toward bringing diagnoses and therapies to all RD patients
- Registration will open shortly: www.irdirc.org/conference-2017

New Global Preclinical Collaborative

- Global collaborative effort among national/regional organizations to accelerate preclinical translational science:
 - European Infrastructure for Translational Medicine (EATRIS)
 - Canadian Centre for Drug Research and Development (CDRD)
 - Therapeutic Innovation Australia (TIA)
 - UK Medical Research Council Technology (MRCT)
 - US National Center for Advancing Translational Sciences (NCATS)
- Emphases on
 - Communicating common messages on importance of TS
 - Training platforms and resources
 - Sharing best practices
 - Sharing complementary capacities on projects

COMMENT

Putting translational science on to a global stage

C. Taylor Gilliland, David Zuk, Petr Kovacs, Mike Johnson, Stewart Hay, Martin Hojchak, Florence Biatrix, Gregorio Aviera, Christopher P. Austin and Anton E. Ussi

Global collaboration in translational science promises to accelerate the discovery, development and dissemination of new medical interventions. Here, we introduce a new international collaboration of translational science organizations and highlight our initial strategy to reduce or remove bottlenecks in translation.

There is broad consensus that the development of new medical interventions takes too long, costs too much and too often ends in failure. Furthermore, the 'translation gap' between fundamental discoveries related to human disease and the delivery of new therapeutic options to patients has remained stubbornly persistent. However, the field of translational science is growing to provide solutions to bridge this gap and thereby help to bring more medicines to more patients more quickly. This article aims to increase the awareness of the burgeoning field of translational science as a discipline, and introduce a nascent international collaborative effort in this arena.

Defining translational science
Translation is defined as the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public — ranging from therapeutic and diagnostic to medical prevention and behavioral changes. However, this process is poorly understood, scientifically and often divorced within and between organizations. This contributes substantially to the high failure rate of translation, indicating the need for systematic study. Here, we define translational science as the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process.

A new player arrives
There has been a rapid growth of opportunities for translation of biomedical research over the past decade and a half, aided by the development of ever-higher-throughput technologies, such as next-generation sequencing platforms, to probe biological systems. Building on this growth of basic research knowledge, however, has been a reduction of internal financing by large pharmaceutical companies.

Realization that a new type of organization was needed to serve as an 'adapter' and 'leveler' between basic research and commercial organizations led to the creation of dedicated translational science organizations by governments, non-profit organizations and researchers in multiple countries. Between 2000 and 2011, MRC Technology (MCRCT) in the UK, the European Infrastructure for Translational Medicine (EATRIS) in the European Union, the Centre for Drug Research and Development (CDRD) in Canada, Therapeutic Innovation Australia (TIA), and the National Center for Advancing Translational Sciences (NCATS) in the United States (Supplementary Information S1, Table 1) were established to optimize the translational process and accelerate therapeutic innovation.

Despite their geographic diversity and somewhat country-specific mandates, our organizations approach translational science with a shared mindset and our common language to describe the nature of the opportunities and challenges in the field. There is also consensus among our organizations concerning the need to raise the level of awareness and understanding of translation and translational science among basic scientists, funders, policy makers and patients, and their associated communities. The organizations therefore agreed to establish a collaborative effort to leverage the experience, expertise and credibility of each and promote translational science with a unified voice globally.

Increasing awareness
Scientists engaged in basic biomedical research provide the foundation for translational development. However, such researchers are often not aware of the nature and complexity of the steps required for sponsoring discovery or technology to advance to the clinic. Only a small percentage of projects from traditional academic and non-profit research laboratories have progressed to a point sufficient to receive an FDA or EMA registration, a prerequisite necessary to progress into preclinical and clinical testing.



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Discussion