Welcome to Anna Ramsey-Ewing
Director, NCATS Office of Grants Management and Scientific Review

Started September 20, 2015
Organizational Update

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Penny Burgoon, Ph.D.
  Acting Director
  Starting January 18, 2016
Farewell, Dorit Zuk!

As of January 15, 2016
Outgoing CAN RB/Council Members

Thank you!

• Pamela B. Davis, Ph.D., M.D.
  Dean and Vice President for Medical Affairs
  Case Western Reserve University

• Mary L. Disis, M.D.
  Professor
  University of Washington School of Medicine

• Todd B. Sherer, Ph.D.
  CEO
  Michael J. Fox Foundation for Parkinson’s Research

• Lawrence A. Soler, J.D.
  President and CEO
  Partnership for a Healthier America

• Myrl Weinberg, M.A.
  Former President
  National Health Council, Inc.
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
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Matrix Drug Combination Screening Program

Clinical development of drug combinations typically achieved through trial-and-error

DPI scientists use unbiased small-molecule combination (matrix) screening to identify potential drugs to combine

In the example above, DPI and NCI scientists screened combinations with ibrutinib for activated B-cell like subtype (ABC) of diffuse large B-Cell lymphoma (DLBCL)
Drug Combination Dataset for Malaria

- **Collaborators**
  - Xin-zhuan Su (NIAID intramural) & Paul Roepe (Georgetown)
  - NCATS: Bryan Mott, Raj Guha, Paul Shinn, Sam Michael, Marc Ferrer, Craig Thomas (all DPI)

- **Background**
  - *P. falciparum* parasites with reduced sensitivity to Artemisinin combination therapies (ACTs) are being reported
  - New anti-malarial combinations from the existing pharmacopeia could be rapidly translated to clinical use

- **Project**
  - Tested large collection of approved and investigational drugs in combination in our Matrix Screening Platform. Tested 13,910 drug pairs, identified many promising antimalarial drug combinations, all data made public
  - Results highlighted new MOAs that have yielded new basic insights into overcoming potential ACTs resistance mechanisms
  - Several novel candidate drug combinations matched or exceeded therapeutic efficacy of the standard of care ACT
Snapshot of the Anti-Malaria Combination Dataset

Examples of response profiles for Artesunate (AS) + Mefloquine (MFQ)

Interaction plot of synergistic anti-malarial drug pairs

Mechanism-based interaction network of anti-malarial drug pairs, Hierarchical clustering and the statistical relevance of key MOA pairings

Mott et al., Scientific Reports 5, 13891 (2015)
New Mechanistic Insights and New Targets for Intervention

Acute disruption of digestive vacuole calcium stores disrupts mitochondrial polarity and results in strong drug synergy.

Combinations of anti-malarials and human PI3K inhibitors validate a role for parasite autophagy and the targeting of PfVPS34 as an effective treatment strategy.

No treatment

Artemisinin

Artemisinin + hPI3K inhibitor

autophagosomal complex imaging

Migration blocked

Autophagosome migration
"...the release of the entire dataset provides a public archive that we hope stimulates broader examination of drugs and drug combinations for the treatment of malaria."
Drug Combinations for Malaria: Summary

- 13,910 drug pairs tested
- Multiple classes of novel drug synergies discovered
- New mechanisms yielding conserved synergy found
- New targets identified for first in class discovery efforts
- Confirmation of efficacy in mouse model *in vivo*
- *Demonstrates translational efficiency and effectiveness of Matrix Technology*
Tox21 Issues New Challenge Competition

Transform Tox Testing Challenge: Innovating for Metabolism

Challenge Launched on Jan. 8, 2016

Key Development: Three federal agencies are offering toxicity test developers up to $1 million to modify high throughput screens to predict the toxicity of chemical metabolites.

Potential Impact: If successful, the Tox Testing Challenge will improve the relevance and predictive capacities of automated tests that can quickly and simultaneously evaluate hundreds, even thousands, of chemicals.

http://www.transformtoxtesting.com/
Pfizer’s Center for Therapeutic Innovation (CTI) for NIH Researchers

• **Background**
  » Pfizer CTI is an entrepreneurial research unit that pairs researchers with Pfizer resources
  » Jointly develop biologics against targets of NIH IC PI interest
  » Network includes 25 academic institutions, four patient foundations, and NIH
  
  Bridge the gap between early scientific biologics discovery and clinical application thru public-private resource sharing

• **Updates**
  » NIH joined the CTI network of Pfizer on Dec. 18, 2014
  » First NIH-wide biologics initiative with a pharmaceutical partner - NCATS coordinates program on behalf of all NIH intramural
Pfizer’s CTI program has 2-3 calls for proposals each year. All proposals are reviewed by the NIH Pfizer CTI Joint Steering Committee (JSC).

**Stage I**
- April 14, 2015: Call for pre-proposals
  - 1st call: *9 Submitted
  - 2nd call: October 2015: Call for pre-proposals
    - *3 Submitted
  - 3rd call: February 2016: Call for pre-proposals

**Stage II**
- November 2015: Out of the 9 proposals submitted, the JSC asked 1 PI to submit a full proposal.
- November 2015: Out of the 3 proposals submitted, the JSC asked 1 PI to submit a full proposal.

**Stage III**
- December 2015: The JSC approved the full proposal from NIAID. NIAID and Pfizer are currently working on SOW.
- TBD: 1st call
- TBD: 2nd call
- TBD: 3rd call

**Proposal Stages**
- **Stage I**: Pre-proposal submission and non-confidential review
- **Stage II**: Full proposal submission and confidential review
- **Stage III**: Work plan and budget
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Gene Therapy: Background

- Gene therapy (GT) refers to the transfer of nucleic acids into a patient cells to treat disease.
- Can involve viral vectors or non-viral delivery systems.
- Past concerns about GT have been revisited.

  - Patient safety will not be compromised if the RAC does not review all individual GT protocols.
  - RAC should review only those protocols that are considered to raise exceptional or unknown risk.

- NIH Director Accepts IOM Recommendations (May 2014)
  - “Given the progress in the field, I am confident that the existing regulatory authorities can effectively review most gene transfer protocols and that a streamlined process will reduce duplication and delays in getting gene transfer trials initiated.”

- Proposed changes to RAC review process published in Federal Register (Oct. 2015) with request for public comment - changes to be implemented in 2016.
Gene Therapy: Scientific Progress

- **Delivery**
  - Emergence of adeno-associated virus (AAV) as a clinical gene therapy platform
    - Evidence of clinical efficacy for AAV vectors in the treatment of monogenic disorders has emerged
    - Discovery of a specific serotype of AAV that can cross the blood brain barrier
  - Lentivirus for clinical *ex vivo* gene therapy
  - Non-viral nucleic acid delivery

- **Gene editing nucleases** (CRISPR-Cas9, others)

- **Limitations**
  - Toxicity testing
Gene Therapy: NCATS

• NCATS is interested in “platform” approaches that can be readily adapted to multiple diseases

• Gene therapy is such a platform approach and relevant to the treatment of rare genetic diseases

• NCATS supports GT development through several programs
Gene Therapy at NCATS

- **RDCRN**
  - Ongoing GT development projects in Urea Cycle Disorders and Primary Immune Deficiency Treatment consortia; others starting

- **SBIR/STTR**
  - Program announcement: “Platform Delivery Technologies for Nucleic Acid Therapeutics” (PA-14-307 and PA-14-308)

- **Other**
  - Commentary in-press: “Gene Therapy: The View from NCATS”
  - Planning to ramp up GT work via TRND/BrIDGs
    - Will update at future Council meeting
BrIDGs Program:  
**AAV Gene Therapy for Osteoarthritis**

- **Collaborator**
  - Christopher Evans, Mayo Clinic

- **Background**
  - Osteoarthritis is most common form of arthritis, affecting >25M Americans
  - Non-surgical treatments limited; surgical treatments invasive and expensive

- **Project**
  - Interleukin-1 (IL-1) plays an important role in the pathophysiology of osteoarthritis
  - Intra-articular recombinant Interleukin-1 Receptor Agonist (IL-1RA) rapidly cleared from affected joints (X. Chevalier et al 2009)
  - AAV carrying human IL-1RA cDNA holds promise for sustained efficacy
BrIDGs Program: AAV Gene Therapy for Osteoarthritis

- Previously demonstrated that sc-rAAV2.5IL-1RA was efficacious in two large animal models
- BrIDGs supported safety and biodistribution assessment of sc-rAAV2.5IL-1RA
- Contract resources provided by NHLBI’s Gene Therapy Resource Program
- IL-1RA expression was observed with no local or systemic toxicity
- Published in Molecular Therapy — Methods & Clinical Development

Gensheng Wang et al (In press)
ExRNA Communication Program: Exosome-based Therapeutics in Huntington’s Disease

exRNA Investigators: Aronin and Khvorova (UH3)

- Autosomal dominant neurodegenerative disorder: motor, cognitive, and emotional symptoms.
- Lack of simple and efficient methods to deliver of oligonucleotides to primary neurons in culture or to the brain.
- Exosomes can serve as delivery system for drug delivery:
  - Natural exosome-mediated transfer of miRNA from cell to cell
  - Efficient exosome-mediated transfer of siRNA in vitro and in vivo

exRNA Project:

- Use of hydrophobically modified siRNAs (hsiRNAs) targeting mutation in huntingtin mRNA (Htt).

![Chemically modified siRNA diagram]

- Stability
- Efficient cellular uptake
  -> No delivery vehicle
NPC Project Update: *Breakthrough therapy designation granted by FDA, Jan. 6, 2016*

- NCATS-NICHD-Vtesse (Gaithersburg, MD) CRADA signed January 7, 2015...
  - **Just 1 year later...**

**Fledgling Vtesse grabs a 'breakthrough' title at FDA for rare disease drug**

January 6, 2016 | By John Carroll

The biotech startup Vtesse is celebrating its first anniversary with a breakthrough therapy designation from the FDA.

The move—a rare win for a fledgling biotech—puts a spotlight on VTS-270, a treatment of Niemann-Pick Type C1 Disease that was hustled along by a virtual team and investigators at the NIH right into an ongoing Phase II/III pivotal study. And now it can proceed with assurances of an open-door policy from the agency as it helps accelerate the rare disease drug.

"This designation is supported by strong preclinical and early clinical data with VTS-270, including that from the Phase I study conducted by the National Institutes of Health," noted CEO Ben Machielse in a statement. "It is our hope that this designation will help expedite the development and regulatory review process, getting the drug to patients who can benefit sooner."
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Streamlined CTSA Program Communications Structure: Domain Task Forces

- Outcomes-driven
- NIH, FDA, and patient/community members
CTSA Common Metrics Initiative

• Data for the strategic management of the CTSA Program
  - Local and nationally
  - Focus on impact
  - Not evaluation but management tool
• Process is bottom-up with active engagement of PIs, evaluators, administrators, coordinators and others
• First set of templates adopted at December PI meeting
• Now in process of developing SOPs and launching pilot study
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**Summary and Next Steps**

- 14 total proposed metrics in first wave
- Operational guidelines and procedures in development for each proposed metric
- 3 metrics will be ready for pilot study
Policy and Legislative Updates
FY 2016 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 Obama signed the Consolidated Appropriations Act, 2016 (P.L. 114-113)
  - NIH: $32 B ($2 B increase over FY 15)
    - Includes $130 M for PMI Cohort Program
  - NCATS: $685.4 M ($52.7 M increase over FY 15)
    - CTSA: $500 M
      - Includes $22.7 M increase to implement IOM recommendations, such as building network capacity (i.e. TICs, RICs, CCIAs)
    - CAN: $25.8 M ($16 M increase over FY 15)
Congressional Briefing

- November 5, 2015 - Congressional Rare Disease Caucus briefing on “Precision Medicine: New Frontiers for Rare Diseases”
  - Hosted by Rare Disease Legislative Advocates (RDLA)

Participants (L-R): Chris Austin (NCATS), Erynn Gordon (23andMe), John Crowley (Amicus Therapeutics), Matt Might (Univ. of Utah), Sean Sigmon (Oracle Health Sciences)
Congressional Authorizing Activities

- **House - 21st Century Cures (H.R. 6)**
  - July 10, 2015 - passed by large majority (344-77)
  - NIH “Innovation Fund” - $8.75 billion over five years

- **Senate - Innovations for Healthier Americans**
  - Draft bill not yet released
  - Senator Lamar Alexander (R-TN), Chairman, Senate Health Committee, said that this is their first priority for 2016
Precision Medicine Initiative - Cohort Program

- Launched by President Obama in January 2015
- NIH Cohort Program will build a national, large-scale research group of one million or more U.S. participants
  - Longitudinal effort to identify molecular, environmental and behavioral factors that impact health
- Multiple funding opportunities announced in November 2015
- NCATS is administering Common Fund’s Other Transaction Awards (OTA)

Common Rule

- Sept. 8, 2015: Notice of Proposed Rulemaking (NPRM) published in Federal Register
  - Sought comment on proposals to better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators
  - Extended comment period closed Jan. 6, 2016

- CTSA Program collaborated to host several national one-day meetings about the NPRM and the proposed changes

- For more information on the NPRM and to browse comments that have been submitted, please see:
  http://www.hhs.gov/ohrp/humansubjects/regulations/nprmhome.html
NIH-Wide Strategic Plan

- Published December 16, 2015
- Mandated by Congress in FY 2015 Appropriations Bill
- Main objectives:
  - Advance opportunities in biomedical research
  - Foster innovation by setting priorities
  - Enhance scientific stewardship
  - Excel as a federal science agency by managing for results
- Highlights NCATS Programs: Tissue Chip for Drug Screening, Tox21, CTSA, NTU-Alzheimer’s

NIH Big Data to Knowledge (BD2K) Initiative

• Mission
  To use data science to foster an open digital ecosystem that will accelerate efficient, cost-effective biomedical research to enhance health, lengthen life, and reduce illness and disability

• Implementation
  ✓ Data science research programs (Centers, Software, Standards…)
  ✓ NIH Data Commons (Findable, Accessible, Interoperable, Reusable)
  ✓ Data science training and education programs
  ✓ Sustainability of data science resources, technology, and tools

• Future Direction
  ✓ NCATS represented via participation of program staff and Geoff Ginsburg is on the BD2K Multi-Council Working Group
  ✓ Program transition to National Library of Medicine

https://datascience.nih.gov/bd2k
Discussion