Director’s Report

NCATS Advisory Council and CAN Review Board

CHRISTOPHER P. AUSTIN, M.D.
DIRECTOR, NCATS
SEPTEMBER 3, 2015
Welcome to Keith Lamirande
Associate Director for Administration
NCATS Executive Office

Started August 9, 2015
Organizational Update

COUNCIL/CAN BOARD

OFFICE OF THE DIRECTOR
Christopher Austin, M.D.
Director
Pamela McInnes, D.D.S.,
M.Sc.(Dent.)
Deputy Director

EXECUTIVE OFFICE
Keith Lamirande, M.B.A.
Started Aug 9, 2015

OFFICE OF GRANTS MANAGEMENT & SCIENTIFIC REVIEW
Pamela McInnes, D.D.S.,
M.Sc.(Dent.)
Acting Director

OFFICE OF RARE DISEASES RESEARCH
Pamela McInnes, D.D.S.,
M.Sc.(Dent.)
Acting Director

OFFICE OF POLICY, COMMUNICATIONS & STRATEGIC ALLIANCES
Dorit Zuk, Ph.D.,
Director

DIVISION OF PRE-CLINICAL INNOVATION
Anton Simeonov, Ph.D.
Started Aug 9, 2015

DIVISION OF CLINICAL INNOVATION
Petra Kaufmann, M.D., M.Sc.
Director

NIH National Center for Advancing Translational Sciences
Welcome to Anton Simeonov
Scientific Director
NCATS Division of Pre-Clinical Innovation

Started August 9, 2015
Welcome to Petra Kaufmann
Director, NCATS Division of Clinical Innovation and Office of Rare Diseases Research

Starting September 3, 2015
Outgoing CAN RB/Council Members

Thank you!

• Frank Douglas, Ph.D., M.D.
  President and CEO
  Austen BioInnovation Institute in Akron

• Victoria Hale, Ph.D.
  CEO and Founder
  Medicines360
New NCATS Video Unveiled
August 11, 2015

• Released latest video:
  A virtual tour of our intramural laboratory facilities at 9800 Medical Center Drive

• Featured on our home page
  » www.ncats.nih.gov
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Full video will be playing on loop during lunch
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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“Drugging” Novel Targets

Target: Aldehyde dehydrogenase 1A1
Collaborator: Vasilis Vasililiou (Yale)
Therapeutic Scope: Cancer, Inflammation, Obesity, Development

Despite the success of some molecularly targeted drugs, the selection and validation of targets suitable for drug discovery programs remains challenging. Patel et al. now report a computational approach to assess biological and chemical space for the prioritization of potential therapeutic targets and apply this approach to cancer. The approach involves the annotation of biologically relevant genes (479, in their cancer example) based on homology to targets of approved drugs, the properties of existing active molecules, three-dimensional structures, druggability, functional class, subcellular localization and other publicly available disease information. The data are then combined to rank potential targets. The authors applied their approach to propose the repurposing of drugs approved for other indications to cancer and to identify new targets. On the basis of their analyses, the authors propose that PPARy, DNA methyltransferase 3A and aldehyde dehydrogenase 1A1 drug targets but not indicated for use in cancer—should be evaluated for cancer. In addition, they identify 46 druggable proteins via structure-based

Chemico-Biological Interactions 202 (2013) 2-10
“Drugging” Novel Targets
Aldehyde Dehydrogenase

- Developed two highly potent ALDH1A1 inhibitor series
- Excellent selectivity and ADME properties

<table>
<thead>
<tr>
<th></th>
<th>1A1</th>
<th>1B1</th>
<th>3A1</th>
<th>ALDH2</th>
<th>Permeability (PAMPA)</th>
<th>Aqueous Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 nM</td>
<td>&gt;57 µM</td>
<td>&gt;57 µM</td>
<td>&gt;57 µM</td>
<td>164 (10⁻⁶ cm/s)</td>
<td>&gt;60 µg/mL</td>
</tr>
<tr>
<td>RLM</td>
<td>&gt;84 min</td>
<td>&gt;2 h</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HLM</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Caco-2: $P_{(B-A)}/P_{(A-B)}$</td>
<td>Protein Binding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19.6/19.3 = 1.02</td>
<td>69%</td>
</tr>
</tbody>
</table>

- Demonstrated efficacy in cancer stem cell (3D-spheroid and organoid) models of glioblastoma multiforme brain cancer
- Animal efficacy studies ongoing

*J. Med. Chem., 2015, 58: 5967–5978*
NCATS - Lilly Open Innovation Drug Discovery (OIDD) Partnership

• 2,500 approved drugs from NCATS Pharmaceutical Collection tested in Lilly OIDD assays relevant to
  » Cardiovascular diseases, diabetes, cancer, endocrine disorders

• All data made public

PLOS ONE 2015, 10: e0130796. doi:10.1371
NCATS - Lilly OIDD Partnership

Unprecedented systems pharmacology data enabling therapeutic discovery

Collaborative phenotypic assays for screening drugs in NPC

Phenotypic assays have a proven track record for generating leads that become first-in-class therapies. Whole cell assays that inform on a phenotype or mechanism also possess great potential in drug repositioning studies by illuminating new activities for the existing pharmacopeia. The National Center for Advancing Translational Sciences (NCATS) pharmaceutical collection (NPC) is the largest...
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Prescription Drug Abuse is an urgent national priority
Abuse-resistant narcotic formulations face scientific and business hurdles
NIDA partnered with NCATS BrIDGs program and Signature Therapeutics (Palo Alto, CA) to develop oral prodrug formulation of oxycodone

**Novel Project Model**
- MOU between NIDA and NCATS
- 3-way CRADA

IND cleared June 2015
Clinical trial expected to begin August 2015
New NTU Projects Awarded  
July 2015

<table>
<thead>
<tr>
<th>Original Indication</th>
<th>Pharma Partner</th>
<th>Academic Partner</th>
<th>New Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary COPD, cystic fibrosis, bronchiectasis</td>
<td>AstraZeneca</td>
<td>Allegheny Health Network Research Institute</td>
<td>Type 2 Diabetes</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>AstraZeneca</td>
<td>Duke University</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>Sanofi</td>
<td>UC San Diego</td>
<td>Chagas disease</td>
</tr>
<tr>
<td>Solid tumors, e.g., ovarian</td>
<td>AstraZeneca</td>
<td>Massey Cancer Center, VCU</td>
<td>Acute Myeloid Leukemia (AML)</td>
</tr>
</tbody>
</table>
You will be hearing more on this shortly
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Evolving the CTSA Program to Transform Clinical Translational Science

CTSA Hubs

TIC: Trial Innovation Centers
- Central IRB
- Contracting
- Budgeting
- Other support PRN

RIC: Recruitment Innovation Centers
- Feasibility Assessment
- Recruitment Plan and Implementation

Multi-site Study funded by NIH IC or others
- Clinical Lead
- Stats/Data Management

No need to rebuild trial components each time
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Innovation Corps (I-Corps) Program

- I-Corps training program aims to accelerate commercialization of biomedical technologies
- NIH-NSF pilot program
  - Developed with SBIR/STTR funding
  - NCATS made 3 supplemental awards to Phase 1 SBIR/STTR awards
- Now creating NSF/CTSA I-Corps Program
  - Applying the I-Corps teaching methodology to the CTSA program via “train-the-trainer” approach
  - Pilot: NCATS will provide funding and access to this program for up to 10 institutions
  - Featured at White House “Demo Day” August 4
Petra Kaufmann, DCI Director
White House Demo Day showcasing NIH I-Corps Program
CTSA Common Metrics Initiative

• “Advancing” translational science
  - From Latin ab ‘from’ + ante ‘before.’
• “The CTSA Program...should use clear, consistent, and innovative metrics...that go beyond publications and number of grant awards”
  - IOM, The CTSA Program at NIH, 2013
• “If you can’t measure it, you can’t manage it.”
• “Not everything that can be counted counts, and not everything that counts can be counted.”

Conclusions
- Measurement is difficult to get right but essential to knowing if advancement is occurring
- Measurement is a science that must be approached experimentally
- Measurement must be reiterative, collaborative, and tied to hypotheses and a variety of data types
The Problem

If we fear (the misuse of) data/metrics

we end up flying blind
The Challenge

Building a culture that encourages the use of data/metrics in the strategic management of the CTSA Program
The Vision

The strategic management of the CTSA Program by the PIs and NCATS is

- data-driven
  
  and

- collaborative...

...to maximize the impact of the CTSA Program.
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RDCRN-Rare Lung Diseases Consortium (RLDC)

Sirolimus Trial for LAM

• Lymphangioleiomyomatosis (LAM) is a rare, progressive lung disease that primarily affects women of childbearing age that is often fatal

• RLDC conducted Multicenter International LAM Efficacy and Safety of Sirolimus (MILES) trial
  – PI: Dr. Francis McCormack
  – Collaborative effort between RDCRN-RLDC, Pfizer, and LAM Foundation

• In early 2015 FDA accepted sNDA via priority review

• In March 2015 FDA approved sirolimus for LAM
  – First drug approved by FDA for the treatment of LAM
Policy and Legislative Updates
FY 2016 Budget Request

• On February 2, 2015, President Obama released the FY 2016 budget
   NIH: request for $31.3B, increase of $1B over FY15
   NCATS: request for $660.1M, increase of $27.4M over FY 2015
   NCATS’ Congressional Justification (CJ) and appropriation status is available at: https://ncats.nih.gov/about/center/budget

• House and Senate appropriation bills approved by committees, but never voted on by full chambers

• Continuing Resolution (CR) may be needed to keep government running after September 30
Congressional Authorizing Activities

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

• **Senate: “Innovation for Healthier Americans”**
  - Hearings held in Spring
    - NCATS participated in April hearing
  - Draft bill may be released in Fall
FOR IMMEDIATE RELEASE
September 2, 2015

HHS announces proposal to update rules governing research on study participants

Proposed changes enhance protections for individuals involved in research, while modernizing rules and improving efficiency

The U.S. Department of Health and Human Services today announced proposed revisions to the regulations that govern research on individuals who participate in research.

The current regulations that protect individuals who participate in research, which have been in place since 1991, are followed by 18 federal agencies and are often referred to as the Common Rule. They were developed at a time when research was predominantly conducted at universities, colleges and medical institutions, and each study generally took place at a single site. The expansion of research into new scientific disciplines, such as genomics, along with an increase in multisite studies and significant advances in technology, has highlighted the need to update the regulatory framework. Notably, a more participatory model of research has also emerged, with individuals looking for more active engagement with the research enterprise.

In July 2011, HHS issued an Advance Notice of Proposed Rulemaking to seek the public’s input on updating the Common Rule. The Notice of Proposed Rulemaking (NPRM) issued today reflects that input and requests comments for HHS to consider as it drafts the final rule.

The protection of research participants is of paramount importance. Medical advances would not be possible without individuals who volunteer to participate in research. This NPRM proposes to modernize the current regulations by enhancing the ability of individuals to make informed decisions about participating in research, while reducing unnecessary burdens by streamlining the regulatory requirements for low-risk research.

Changes proposed in the NPRM issued today include:

- Strengthened informed consent provisions to ensure that individuals have a clearer understanding of the study’s scope, including its risks and benefits, as well as alternatives to participating in the study.
- Requirements for administrative or IRB review that would align better with the risks of the proposed research, thus increasing efficiency.
- New data security and information protection standards that would reduce the potential for violations of privacy and confidentiality.
- Requirements for written consent for use of an individual’s biological samples, for example, blood or urine, for research with the option to consent to their future use for unspecified studies.
- Requirement, in most cases, to use a single institutional review board for multisite research studies.
- The proposed rule would apply to all clinical trials, regardless of funding source, if they are conducted in a U.S. institution that receives funding for research involving human participants from a Common Rule agency.

To view the NPRM, click here. HHS will take public comment on this NPRM for 90 days, beginning Sept. 8.
Strategic Planning underway

• NIH Strategic Plan
  ➢ Dr. Lawrence Tabak will update Council on the process to date

• NCATS Strategic Plan
  ➢ Dr. Dorit Zuk will update Council on NCATS planning activities
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Discussion