Utah Center for Clinical and Translational Science (CCTS)

Don McClain MD, PhD
Co-Director
The Best of Times, the Worst of Times

Fundamental science unprecedentedly advanced, but:

- Poor transition of basic or clinical observations into interventions that tangibly improve human health
- Drug/device/diagnostic development system in crisis
- Clinical trials system in crisis
- Poor adoption of demonstrably useful interventions

People unhealthier and funders of biomedical research enterprise (public and private) impatient
CLINICAL RESEARCH AT THE UNIVERSITY OF UTAH PRIOR TO THE CCTS

• GCRC – 1965-2008
  – Focus – Inherited Basis of Human Disease

  – Program Directors:
    • Frank Tyler, M.D. 1965-1985
    • J.P. Kushner, M.D. 1986-2006
    • D.A. McClain, M.D., Ph.D. 2006-2008
THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD ERA

- Elias Zerhouni, NIH Director, seeks an academic home for clinical investigators
- Wants to expand the narrow focus of the GCRC’s and create a much broader infrastructure
T1: Translation to Humans
T2: Translation to Patients
T3: Translation to Practice
T4: Translation to Population Health
THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD ERA

- 2006: CTSA awards begin (12/yr)
- 2008: Utah is awarded its CTSA
- 2013: CTSA program moves from NCRR to the new NIH Center for Advancing Translational Science (NCATS)
NCATS Mission:

- To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of interventions that tangibly improve human health across a wide range of human diseases and conditions.
Catalyzing Collaborations Within NIH
Catalyzing Collaborations Outside NIH

Diagram showing NCATS connected to Academia, Biotech, Pharma, Advocacy Groups, Non-Profits, and FDA.
NCATS History: A Synthesis
NCATS Programs and Initiatives

Clinical and Translational Science Activities
- Clinical and Translational Science Awards

Rare Diseases Research and Therapeutics
- Therapeutics for Rare and Neglected Diseases
- Bridging Interventional Development Gaps
- Office of Rare Diseases Research

Re-engineering Translational Sciences
- NIH Chemical Genomics Center
- Toxicology in the 21st Century
Why a national consortium?

Translation is a team sport

Requires top performers with a wide variety of different expertise to work together to a common goal
Examples of team/network-requiring translational problems

- Predictive toxicology
- Predictive efficacy
- Derisking undruggable targets/untreatable diseases
- Data interoperability
- Biomarker qualification process
- Clinical trial networks
- EHRs for research
- Harmonized IRBs
- Clinical diagnostic criteria
- Clinical outcome criteria (e.g., PROs)
Standard Model

- Basic Laboratory Research
- Clinical Research
- Translational Research
- Population Research

Improved Public Health
The Way It Should Work

- Basic Laboratory Research
- Population-based Clinical Research
- Improved Public Health
- Patient-oriented Clinical Research
- Clinical Trials
Clinical and Translational Science Awards

Led by NCATS Division of Clinical Innovation

CTSAs:

- Support a national consortium of medical research institutions
- Work together to improve the way clinical and translational research is conducted nationwide
- Accelerate the research translation process
- Provide innovative training for clinical and translation researchers
IOM Report on the CTSA Program

Current Status

• NIH commissioned study in July 2012
• IOM CTSA Report released June 2013
• Report includes 7 recommendations
  1. Strengthen leadership of the CTSA program by NCATS
  2. Reconfigure and streamline CTSA consortium
  3. Build on the strengths of the individual CTSAs across the spectrum of research
  4. Formalize and standardize clear, consistent, and novel metrics
  5. Advance innovative education and training models with a focus on team science, leadership, and entrepreneurship
  6. Ensure community engagement in all phases of research
  7. Strengthen translational research relevant to child health

• Working Group of NCATS Council commissioned to help implement, focusing on measurable deliverables
NCATS and the CTSA program should ensure that patients, family members, health care providers, clinical researchers, and other community stakeholders are involved across the continuum.

NCATS and the CTSA program should...

1. Define community engagement broadly
2. Ensure active and substantive community stakeholder participation in priority setting and decision making across all phases
3. Define and clearly communicate goals and expectations and ensure the broad dissemination of best practices
4. Explore opportunities and incentives to engage a more diverse community
Examples of translational problems for next-gen CTSA focus

- Data interoperability/governance
- Clinical trial networks
- EHRs for research
- IRB federation
- Patient recruitment
- Clinical diagnostic criteria
- Clinical outcome criteria (e.g., PROs)
- Biomarker qualification process
- Adaptive clinical trial designs
- Shortening time of intervention adoption
- Methods to better measure impact on health (or lack of)
Most Recently Awarded CTSA Program Sites

September 2013

- Dartmouth College*
- Albert Einstein College of Medicine
- Duke University
- Harvard Medical School
- Indiana University
- Johns Hopkins University
- Ohio State University
- Scripps Research Institute

- Stanford University
- Tufts University
- University of Colorado
- University of North Carolina at Chapel Hill
- University of Texas Health Science Center, San Antonio
- University of Texas Southwestern Medical Center, Dallas
- University of Utah, Salt Lake City

*New member of consortium
Clinical and Translational Science Awards (CTSA) Program Sites
CTSA Budget: ~ $ 4.5 million/yr (Direct + Indirect)

Calculated as 3% of the total NIH funding of the participating partners at a given CTSA site

Sites can therefore have upwards of $20 m/yr
| Fig 2.4 | Vivian Lee MD PhD MBA  
Senior Vice President for Health Sciences |
|-------------------|------------------------------------------|
| Don McClain MD PhD  
Contact Program Director | Carrie Byington MD  
Co-Program Director |
| Matthew Samore MD  
Associate Director  
VAMC | Michael Varner MD  
Associate Program Director |
| Wu Xu MD  
Associate Director  
UDOH | |
| External Advisory Board | Executive Steering Cmte |
| | Internal Advisory Cmte |
| Tracking & Evaluation | |
| Education | Innovation | Services |
| Education KL2, TL1, MSCI | |
| Study Design & Biostatistics Center | |
| Clinical Services | |
| Biomedical Informatics | |
| Community Outreach and Collaboration | |
| Patient Centered Research Methods | |
| Research Participant Recruitment, Retention & Safety | |
| Translational Technologies | |
Critical elements of the competitive renewal process

• Focus on historical strengths and potentially unique contributions to the consortium
• Show that we have already been doing good work
• Emphasize partnerships: Intermountain, VAMC, Utah Department of Health, and (going forward) Utah State University
• Participating in the national consortium and in changing the way clinical research is performed
• Program income
Special strengths of the Utah CTSA site

• With our partners at Intermountain Healthcare, the VA Medical Center, and the State Department of Health, we are connected with > 85% of the state’s population, allowing unparalleled opportunities to capture study subjects.
  • As one example of the power of such an alliance, an ongoing study of teen suicides will capture data from 100% of those events in an effort to determine whether antidepressants in children actually cause suicides, or, as is more likely, the children who take their lives are the ones who stopped taking their antidepressants.
Fig. 1.2. Collaborative papers (IM = Intermountain)
Building on Historic Strengths

• Human Genetics
• Biomedical Informatics
• Biomedical Engineering
• Unique populations committed to participating in clinical research
• Strong basic science base now emerging as a force in translational science
Human Genetics

• Discovery of the genetic basis for ~40 human inherited disorders;
• Development of human genetic linkage maps;
• First WGS of a human family, allowing the first direct estimate of human mutation rates;
• Utah Population Database (14 million records supporting over 100 active research projects);
• New methods for analysis of genome sequence data.
Records Available in UPDB

Currently Available

- **Genealogy** (over 170,000 family group sheets) 1,599,292
- Utah **birth certificates** (1915-21, 1947-2005) 2,088,389
- Utah **marriage and divorce** (1978-2004) 783,993
- Utah **death certificates** (1904-2005) 707,971
- **Social security death** index 479,311
- Utah **Cancer Registry** (in situ and invasive) 216,266
- **Cancer Data Registry** of Idaho 124,079
- **Driver License** 2,773,562
- **Total** 8.9 million

Linked into 6.5 million “person records” and across generations

New Data Sources

- **Hospital Discharges** 2,726,004

Slide created by Geraldine Mineau, PhD (modified)
<table>
<thead>
<tr>
<th>Inherited Disorder</th>
<th>Gene(s)</th>
<th>Inherited Disorder</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td>APC</td>
<td>Neonatal epilepsy</td>
<td>KCNQ2</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>NF1</td>
<td>Hyperkalemic periodic paralysis</td>
<td>SCN4A</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>BRCA1</td>
<td>Hyperkalemic periodic paralysis</td>
<td>SCN4A</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>Paramyotonia congenita</td>
<td>SCN4A</td>
</tr>
<tr>
<td>Melanoma</td>
<td>p16</td>
<td>Hypokalemic periodic paralysis</td>
<td>CACNA1S</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>KVLQT1</td>
<td>Periodic paralysis 3</td>
<td>KCNE3</td>
</tr>
<tr>
<td></td>
<td>mink</td>
<td>Andersen syndrome</td>
<td>KCNJ2</td>
</tr>
<tr>
<td></td>
<td>HERG</td>
<td>Frings audiogenic epilepsy</td>
<td>Mass1</td>
</tr>
<tr>
<td></td>
<td>SCN5A</td>
<td>Spinocerebellar ataxia type 7</td>
<td>SCA7</td>
</tr>
<tr>
<td></td>
<td>MiRP1</td>
<td>Familial advanced sleep phase</td>
<td>hPer2</td>
</tr>
<tr>
<td>Supravalvular aortic stenosis</td>
<td>ELN</td>
<td>Freeman-Sheldon syndrome</td>
<td>MYH3</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>COL4A5</td>
<td>Miller syndrome</td>
<td>DHODH</td>
</tr>
<tr>
<td>Hypertension</td>
<td>XIB</td>
<td>Ogden syndrome</td>
<td>NAA10</td>
</tr>
<tr>
<td></td>
<td>AGT</td>
<td>Distal arthrogryposis 1a</td>
<td>TPM2</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>ABCR</td>
<td>Paraganglioma</td>
<td>SDH5</td>
</tr>
<tr>
<td>Ulnar-mammary syndrome</td>
<td>TBX3</td>
<td>Lactic acidosis hyperpyruvatemia</td>
<td>MPC1</td>
</tr>
<tr>
<td>Williams syndrome</td>
<td>LMK1</td>
<td>Childhood alternating hemiplegia</td>
<td>ATP1A3</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>URO-D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chediak-Higashi syndrome</td>
<td>CHS-1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Vignette 1.1. Using VAASS to Identify an X-Linked Disorder Due to N-Terminal Acetyltransferase Deficiency. Discovering genes responsible for rare syndromes has traditionally required analysis of large pedigrees or combining unrelated individuals into one cohort after clinical evaluation to ensure that the syndromes are indeed identical. In a recent study from the CCTS (3), however, investigators used exon capture and sequencing, combined with a statistical method developed by Mark Yandell of the UU (4), to identify the basis of an X-linked disorder by studying only two affected individuals from unrelated families. The huge potential of this technology for common diseases was highlighted in commentary in Nature News.

This study acknowledged significant support by the CCTS, including a Pilot Project Award, the Clinical Services Core for subject phenotyping, the Clinical Genetics Research Program of the Novel Methodologies Core for subject recruitment, and the Translational Technologies Core for DNA purification. One of the authors (Lyon) was trained in the MSCI program of the Research Education Core and another (Jorde) is Director of the proposed T program.
Biomedical Informatics

• Early leadership in the development of the EHR (the HELP system of the LDS Hospital developed by Homer Warner).

• VA (CPRS development, IDEAS investigators)

• UDOH (All Payer Claims Database, one of nine in the nation; IBIS for tracking of health indicators)
Engineering and Computing

• UU luminaries include the principal architect of digital recording, developer of the notion of a graphical user interface, founders or co-founders of Adobe, WordPerfect, Pixar, and WebMD.

• Scientific Computing Institute, now supporting >40 projects on the Health Sciences campus.
Vignette 2.4. Utah Electrode Array Technologies. Utah Slanted Electrode Arrays (USEAs) consist of 100 microelectrodes implanted into the cerebral cortex and/or the fascicles of the peripheral nervous system. The active tips of the electrodes provide unprecedented selective access to large numbers of individual neurons. Ongoing work is directed at the development of wireless versions of the arrays that can be fully implanted in the nervous systems. Arrays have succeeded in animal models in: Stimulation of visual cortex, production of unilateral stance in paralysis, and restoration of bladder function in paraplegia.

In a project supported by CCTS pilot funds, USEAs are being transplanted into the severed nerve stumps of human amputees in order to record neural activity that is volitionally evoked by desired movements of the phantom limb. In the same amputee, currents are passed into the nerve via the electrodes and subjective sensations recorded. The goal is to use the USEA as an interface for the control of future generation multiple degrees-of-freedom prosthetic arms/hands that will also be able to ‘feel’ what is being grasped.

The first array was implanted in a human on November 2, 2012. Investigators were able to record good action potentials on a number of electrodes. ‘On line’ decoding of volitional desires to move the index finger and the middle finger were successful. Investigators displayed a simulacrum of the prosthetic arm and the subject was able to flex its fingers separately and volitionally. This CCTS Pilot Award was used to leverage a $750,000 grant from DARPA. More exciting, however, was the look of pure joy and wonder on the participant’s face as he flexed those virtual fingers.
Pilot Projects: Partnering with the Scientific Computing Institute.

Vignette 2.3. Full Torso Finite Element Modeling of Cardiac Defibrillation. Implantable cardioverter defibrillators (ICD) are the standard of care for treatment of patients with potentially lethal arrhythmias. Unfortunately, many children receiving ICDs have congenital heart disease or anatomic considerations such that ICD placement must be personalized. A project between Pediatric Cardiology and the Department of Bioengineering uses a patient's MRI and software developed by the SCI to create computer models of defibrillation and test ICD placement scenarios. Two projects from this collaboration were presented at national meetings in 2011.

This group receives substantial support from the CCTS including an early career development award for the PI (Pilcher) and statistical data processing support.
Basic Science Base with a Strong Translational Track Record

Vignette. 1.3. Case Study in Translational Investigation by Basic Scientists at UU: Jared Rutter, PhD.

This young scientist provides proof of the effective integration of bench-to-bedside science at our Center. A molecular biologist primarily working with yeast, Rutter partnered with clinicians and a Drosophila lab to systematically investigate mitochondrial proteins of unknown function. Two papers in Science (2009 and 2012) each identify the function of a unique mitochondrial protein, both of which were also determined to be encoded by human disease genes (23,24). These studies made use of the CCTS Technology and Metabolomics Cores.
Unique aspects of the Utah CTSA site

• A majority of Utah is not even “rural” but rather “frontier” as classified by the US Census Bureau.
  • The frontier designation is given to areas with < 6 persons per square mile, with 14 entire counties (of 29 total in the state) qualifying for this designation.
  • In the map to the left, dark green represents < 1 person/sq. mi., and the next lighter shade 1-10.
Fig. 1.1. Federal awards (non-VA, annual total $) to UU, 2007-present. A. Total Federal awards and awards for studies involving human subjects ("Translational"); B. Fraction of total awards that are Translational.

- VA funding increased by 5-fold,
- Intermountain by 2.2-fold
New grants dependent upon the CCTS:

- NeuroNEXT: One of 25 NINDS Centers of Excellence in Neuroscience clinical trials;
- VA-NODES: One of 10 national sites for the VA Cooperative Studies Program;
- Two contracts to the Eccles HS Library, including the NLM Training Center;
- Several awards in the Comparative Effectiveness/Care Delivery realm;
- Five new training grants based on the MSCI template;
- $16 million NIH-funded Translational Research Center, many of whose leaders were formerly trained in CCTS programs;
- PHIS+ ($9 million) for pediatric CER.
New Centers and initiatives dependent upon the CCTS:
• UU Center for Molecular Medicine;
• UU/Intermountain Woman and Child Institute;
• Center for Excellence in Women’s Health (DHHS);
• Program in Personalized Health Care;
• Center for Health System Innovation and Research, to reside in a new Department of Population Science;
• Utah Genome Project
Research Education:

MSCI (Master of Science in Clinical Investigation);

KL2 (mentored junior faculty development award);

TL1 (postdoctoral training grant in human genetics)
Fig. 2.2. Numbers of K applicants unfunded (white) or funded (gray), before (59%) and after (93%) the Utah CCTS (p=0.004)
Study Design and Biostatistics

Figure 3.2 Growth of the SDBC
Study Design and Biostatistics

<table>
<thead>
<tr>
<th>Table 3.1: Statistical/Epidemiologic Collaboration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Sharpen research questions and formulate testable hypotheses</td>
</tr>
<tr>
<td>2) Development of optimal feasible study design</td>
</tr>
<tr>
<td>3) Determine valid measurement methods and questionnaires</td>
</tr>
<tr>
<td>4) Develop appropriate methods for data extraction and storage</td>
</tr>
<tr>
<td>5) Formulate and document pre-specified analysis plan</td>
</tr>
<tr>
<td>6) Conduct pre-specified data analyses</td>
</tr>
<tr>
<td>7) Initial presentation and interpretation of results</td>
</tr>
<tr>
<td>8) Formulate and conduct of post-hoc analyses (sensitivity analyses)</td>
</tr>
<tr>
<td>9) Final presentation and interpretation of results</td>
</tr>
</tbody>
</table>
Clinical Services Core (aka GCRC)

Fig. 3.3. CSC Utilization 2007-2011

- Total visits
- Scatter, Industry, NIH/PI
Translational Technologies

• Infrastructure for CCTS-wide biorepository

Table 3.5. Utilization of Core

<table>
<thead>
<tr>
<th>Service</th>
<th>Number (2011)</th>
<th>Protocols supported</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA extraction</td>
<td>4396</td>
<td>51</td>
</tr>
<tr>
<td>DNA archiving</td>
<td>4396</td>
<td>51</td>
</tr>
<tr>
<td>Transformed cell lines</td>
<td>906</td>
<td>21</td>
</tr>
<tr>
<td>RIA/ELISA (studies)</td>
<td>85</td>
<td>16</td>
</tr>
</tbody>
</table>
Community-Oriented Cores

- Patient Centered Research Methods (Pcrm) Core
- Research Participant Recruitment, Retention, and Safety
- Community Collaboration Group
Community-Oriented Cores

Vignette 3.4. Engaging women in becoming their family’s wellness coach. The CFU community leaders identified obesity and diabetes as health issues affecting all of their communities and on which they wanted to focus. The UU Center of Excellence in Women’s Health was interested in developing a community-engaged research project focused on improving women’s health. Discussions between the 2 groups led to their collaboration on the 6-year Utah Women and Girls research study, which is designed to answer the question “Is a community wellness coach enough to change behavior or is a more intensive program needed and is it worth the cost?” Using the principles of community engagement and bi-directional learning, the partnership has collaborated in developing the study design, research instruments and a 60-hour training for Community Wellness Coaches that also will be available online. At least 2 coaches from each of the 5 CFU communities have been trained; all coaches are HIPAA and CITI certified and trained in using the RedCap database. The project collaborated with the CCTS Biomedical Informatics Core to incorporate counseling messages for the Coaches to share with their clients during data collection interviews. This is the first time “decision support” has been incorporated into a RedCap database.
MAJOR NEW INITIATIVES

• SHARED LEADERSHIP (Co-PI, plus new Associate Directors)
• T32-HUMAN GENETICS
• RESEARCH SUBJECT RECRUITMENT
• OUTREACH TO REMOTE PARTS OF THE STATE
• CENTRALIZATION OF FACULTY DEVELOPMENT PROGRAMS
• EXPANSION OF CSC AND COST RECOVERY TO FUND EXPANSION
• INFORMATICS: Biospecimen tracking, expand FURTHeR, improve REDCap (standard terminology services)
• TECHNOLOGIES: DNA Repository.
• EDUCATION: Expand MSCI (personalized HealthCare, CER, etc.)
• EXPAND KL2 (doubling)