Your host:
Ebony Boulware, MD, MPH
Contact PI, Duke CTSA
Welcome to the Duke CTSA Virtual Town Hall

Click here to see Participants and Chat Function

Click on the microphone by your name to mute or unmute your phone. (You are muted on entry.)

Use Chat Function to ask questions or add comments

Reminder: This WebEx conversation is being recorded. It will be posted on the CTSA website for future reference.
A quarterly WebEx conversation with the opportunity to...

• Learn about what the CTSA offers
• Meet the people who are providing services and resources
• Learn how to access these resources
• Ask questions of CTSA leadership
### Today’s Agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTSA Overview</td>
<td>Ebony Boulware, MD</td>
</tr>
<tr>
<td>CTSA Collaborations Overview</td>
<td>Ebony Boulware, MD</td>
</tr>
<tr>
<td>Collaborative Funding Efforts</td>
<td>Lynn Sutton, director of operations, DTRI</td>
</tr>
<tr>
<td>Collaboration Case Study #1</td>
<td>Christoph Hornik (Duke) and Danny Gonzalez (UNC)</td>
</tr>
<tr>
<td>Collaboration Case Study #2</td>
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</tr>
<tr>
<td>Q&amp;A</td>
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</tr>
</tbody>
</table>
Duke CTSA – Overview

• The CTSA is the NIH’s largest single investment in biomedical research. Over 60 CTSA programs now exist in the U.S.

• **Goal:** to develop and implement national standards and best practices for
  • *accelerating* the process of translating laboratory discoveries into treatments
  • *training* a new generation of clinical and translational researchers, and
  • *engaging communities* in clinical research efforts.

• In October **2013**, the NIH renewed Duke’s CTSA **grant**, committing to $47 million over five years. Duke will resubmit for another 5-year grant in 2017.
Programs/Areas Supported by the Duke CTSA

Today’s Focus

Collaborations in these areas that reach beyond Duke.
Collaborations take many forms, including:

- Work at the national level with the CTSA Consortium
- Providing Duke expertise to other institutions
- Sharing and using research tools created by institutions within the CTSA Consortium
- Providing direct funding for collaborative research efforts that cross institutional boundaries.
Who do we collaborate with?

As part of the **CTSA Consortium**, Duke is expected to work collaboratively with other institutions.

This includes collaborations in the areas of:

1. Workforce Development
2. Harmonizing research & administrative tools
3. Scientific collaborations
Since 2006, Duke has had intense representation on domain taskforces within the national CTSA consortium. Current Duke faculty and staff serving on task forces include:

Danny Benjamin  
– Education

Jennifer Li  
– Special Populations

Iain Lloyd Michener  
– Community Engagement

Becky Moen  
– Methods & Processes

Iain Sanderson  
– Informatics
Examples of Collaborations with other Institutions

**Workforce development**

Duke CTSA Regulatory Affairs (highlighted in a previous Virtual Town Hall)

- Offers free online training to people from any institutions
- Offers annual in-person trainings at Boston and UNC;
- Working with University of Arizona and Duke-NUS Medical School to create strong Regulatory Affairs teams modelled on Duke’s team
Examples of Informatics Collaborations

REDCap (Research Electronic Data Capture)

- Web-based, secure database for research data originally created by Vanderbilt CTSA.
- Duke heavily invested, with staff who participate in weekly programming meetings. (Duke sponsoring Sept. 2016 REDCapCon convention)

Carolinas Collaborative

- Project with CTSAs at Duke, UNC, Wake Forest, and MUSC
- Data resource that harmonizes the electronic health record data across local CTSA institutions to expedite clinical research and quality improvement activities.
Research & Administrative Tool Collaborations (example 1)

ACTA (Accelerated Clinical Trials Agreement)
- Standardized clinical trial agreement created by a CTSA Working Group.
- Adopted at Duke in 2015 for voluntary use
- As of March 2016, Duke signed 7 ACTAs without further negotiations, and the ACTA served as a starting point for 7 other studies which required minimum negotiation.
Research & Administrative Tool Collaborations (example 2)

IRBRe ly Pilot –

- CTSA initiative out of Dartmouth to create a national network in which institutions agree to rely on each others’ IRBs without reference to a specific trial.

- Once in the network, each site would choose to cede IRB approval on a case-by-case basis. Goal is to streamline IRB approval process and accelerate start up time.

- Duke’s Laura Schanberg is piloting this with the national CARRA pediatric rheumatology registry.

- 14 of the 63 CARRA sites using Duke as the IRB of record. Thus far, the 14 pilot sites’ start-up times are, on average, **4 times faster than other sites**.
More collaborations in the pipeline

- **WORKFORCE DEVELOPMENT:** Working with UNC to have some shared writing classes for faculty and staff

- **RESEARCH TOOLS:** VitalCrowd (an application to invite electronic collaboration from patients in the development of study protocols)

- **TEAM SCIENCE:** Working on a collaboration with 20 other CTSA's looking at institutional readiness to support team science
Scientific Research Collaborations

The Duke CTSA also provides funding for a variety of scientific collaborations between researchers from different institutions.

Lynn Sutton, operations director for the Duke Translational Research Institute, will walk us through these funding programs.
CTSA Pilot Funding
Inter-Institutional Collaborations

Lynn C. Sutton
Director of Operations, DTRI Central
April 28, 2016
Inter-Institutional Collaborations

• Duke/UNC-Chapel Hill
• Duke/NC State University
• Carolinas Collaborative
Duke/UNC Chapel Hill Pilots

• Launched 2014
• 57 applications received
• 8 projects funded at $50k each
Duke/NC State University Pilots

• Launched 2016
• 7 applications received
• Awards expected to be $50k each
• Evaluation process underway

Howard Levinson, MD
Associate Professor of Surgery
Duke University

Jon P. Rust, PhD
Professor of Textile Engineering
NC State University

Jonathan M. Horowitz, PhD
Assistant Vice Chancellor for Research Infrastructure
NC State University
Carolinas Collaborative Pilots

The Carolinas Collaborative is a data resource that harmonizes the electronic health record data across local CTSA institutions to expedite clinical research and quality improvement activities.

- Launched 2016
- 10 applications received
- Awards expected to be $50k-$100k each
- Evaluation process underway

CTSAs
Duke University
Medical University of SC
UNC Chapel Hill
Wake Forest University
# Next on the Agenda – Case Studies

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker Details</th>
</tr>
</thead>
<tbody>
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Sildenafil Exposure and Safety in Premature Infants

Daniel Gonzalez, PharmD, PhD
Assistant Professor
UNC Eshelman School of Pharmacy

Christoph Hornik, MD, MPH
Assistant Professor of Pediatrics
Duke University School of Medicine

April 28, 2016
Investigators

Daniel Gonzalez, PharmD, PhD
Assistant Professor
UNC Eshelman School of Pharmacy

Christoph Hornik, MD, MPH
Assistant Professor of Pediatrics
Duke University School of Medicine
Problem

• Infants are at high risk of catastrophic drug adverse events due to unpredicted high exposures

• Traditional drug safety studies in infants are challenging due to sample size limitations and cost

• Electronic Health Records provide access to large sample sizes at low cost, but lack drug exposure

Andersen DH et al, Pediatrics 1956;18(4); Burns LE et al, NEJM 1959;261; Laughon MM and Benjamin DK Jr, Pediatrics 2014;134(2); Spitzer AR et al, Clin Perinatol 2010;37(1).
## Specific Aims and Approach

### Aim:
1. Leverage EMR data to evaluate sildenafil use and dosing in premature infants
2. Apply population pharmacokinetic (PPK) modeling to predict sildenafil exposures in premature infants
3. Evaluate the association between predicted sildenafil exposure and safety in premature infants

### Approach:
1. Query the Pediatrix™ database for premature infants exposed to sildenafil and record relevant demographic, laboratory, and clinical parameters
2. Develop a PPK model to perform dosing simulations for prediction of sildenafil exposure (\(\text{AUC}_{0-24,ss}\))
3. Perform multivariable logistic regression modeling adjusted for clinical characteristics to describe association between predicted sildenafil exposure and hypotension.
AUC$_{24}$ Simulations

<table>
<thead>
<tr>
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<th>Mean (Range)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulated AUC$_{24}$, ng·h/mL</td>
<td>Simulated AUC$_{24}$, ng·h/mL</td>
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<tr>
<td>Gonzalez Parameter Estimates</td>
<td>3386 (128 – 12640)</td>
<td>2243 (1193 – 4870)</td>
</tr>
<tr>
<td>Ahsman Parameter Estimates</td>
<td>3468 (68 – 16460)</td>
<td>2174 (947 – 4260)</td>
</tr>
</tbody>
</table>

Median Ahsman et al. value (3935 ng·h/mL)
## Adjusted Odds of Hypotension

<table>
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<tr>
<th>Measure</th>
<th>Odds Ratio* (95% confidence interval)</th>
</tr>
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<tbody>
<tr>
<td>Total daily dose (mg/kg/day)</td>
<td>0.85 (0.63, 1.15)</td>
</tr>
<tr>
<td>Cmax$_{ss,p}$ (ng/mL)</td>
<td>0.99 (0.99, 1.01)</td>
</tr>
<tr>
<td>Cmax$_{ss,m}$ (ng/mL)</td>
<td>0.99 (0.99, 1.01)</td>
</tr>
<tr>
<td>AUC$_{24,ss}$ (ng*hr/mL)</td>
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</tr>
</tbody>
</table>

*adjusted for postnatal age, weight, gestational age, small for gestational age status, exposure to inotropes, pulmonary hypertension therapy, or mechanical ventilation, exposure to CYP3A4 inducers or inhibitors.
Future Directions

• Apply simulated exposures to evaluate drug efficacy or safety in infants
  • Ampicillin: seizure risk
  • Piperacillin-Tazobactam: seizure risk and laboratory abnormalities
  • Methylprednisolone: inflammatory biomarker alterations, hyperglycemia, and infections after cardiac surgery

• Continued collaboration in the area of early phase pediatric trials
  • Duke: clinical trials, electronic health records
  • UNC: clinical pharmacology/pharmacometrics
Process

- Complementary investigator skillset
- Joint grant writing
- Weekly meetings
- Delegation of tasks
  - EHR extraction and analysis: Hornik research group
  - PK modeling: Gonzalez research group
Recommendations for Cross-Institution Collaboration

• Identify the resources available at each respective institution

• Outline roles and responsibilities for the project

• Communicate often
  • Regular face-to-face meetings

• Outline future projects for collaboration
  • Identify research ideas that require unique expertise across both institutions
In Vivo Genome Editing to Correct a Mouse Model of Duchenne Muscular Dystrophy

Charles A. Gersbach, Ph.D.
Department of Biomedical Engineering
Department of Orthopaedic Surgery
Center for Genomic and Computational Biology
Duke University

Aravind Asokan, Ph.D.
Department of Genetics
Department of Biochemistry & Biophysics
The University of North Carolina at Chapel Hill

April 28, 2016
Duke-UNC CTSA Consortium
Collaborative Translational Research Grant
Gene Therapy for Human Genetic Disease?

Proposals for genetic manipulation in humans raise difficult scientific and ethical problems.

Theodore Friedmann and Richard Roblin

SCIENCE

3 March 1972, Volume 175, Number 4025

These advances have led to proposals (7) that exogenous “good” DNA be used to replace the defective DNA in those who suffer from genetic defects. In fact, a first attempt to treat patients suffering from a human genetic disease with foreign DNA has already been made (8).
Genetic Engineering vs. Gene Editing

Adding genes to cells
vs.
Precise modification of genome sequences
Genetic Engineering vs. Gene Editing

Gene Editing Offers Hope for Treating Duchenne Muscular Dystrophy Studies Find

By NICHOLAS WADE

A Powerful New Way to Edit DNA

A 30-year-old, Feng Zhang is the youngest member of the core faculty at the Broad Institutes of Harvard and M.I.T. He is also among the most accomplished. In 1999, while still a

Genetic engineering
Even CRISPR

A new way to edit DNA may open avenue to new therapies for old diseases

The age of the red pen

It is now easy to edit the genomes of plants, animals and humans

by Gene-Editing Technology Has Scientists Excited

A new tool for "cutting" defective genes has raised hopes for a future generation of
Genome Editing

Opportunity for precise and reproducible genetic engineering
Programmable Nucleases

RNA-Guided CRISPR/Cas9 Nucleases

Nishimasu et al., *Cell* 2014
Therapeutic Gene Editing

Duchenne Muscular Dystrophy

Extracellular Matrix

Dystrophin Glycoprotein Complex

Cell membrane

Dystrophin

Actin

Gene Editing for Muscular Dystrophy

- Exon 51 skipping can correct 13% of DMD mutations
  - Requires lifelong treatment once a week
- Goal: Restoration by genome editing
Gene Editing for Muscular Dystrophy

Precise deletion of exon 51 from the genome

Gene Editing for Muscular Dystrophy

Deletion of exon 51 from the genome results in restored dystrophin expression.

Western blot

Gene Editing *In Vivo* with rAAV

Adeno-associated virus:
- Intramuscular injection of AAV1 approved in Europe (Glybera)
- In preclinical development for delivery of ZFNs to liver for hemophilia by Shire/Sangamo (Li et al., *Nature* 2011, Anguela et al., *Blood* 2013)
Gene Editing *In Vivo* with rAAV

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Deletion of exon 23 in the *mdx* mouse

Gene Editing *In Vivo* with rAAV

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![Diagram of AAV and SaCas9](image)

**SaCas9:** Feng Zhang, Broad/MIT  
**AAV:** Aravind Asokan, UNC-CH

Gene Editing *In Vivo* with rAAV

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i.m. injection of AAV8 (1E12 vg) into tibialis anterior muscle

gDNA and mRNA PCR
Western blot and IHC

Chris Nelson

Multiplexed Cas9 Deletes Exon 23 from the Genome

Genomic Deletion Removes Exon 23 from the Transcript
Exon 23 Removal Salvages Protein Expression

Wild-type
mdx
Mdx + CRISPR/Cas9
Percent Dystrophin Positive Fibers

![Graph showing comparison between Sham and Cas9/gRNA treatments. The Cas9/gRNA treatment shows a significantly higher percentage of dystrophin-positive fibers compared to the Sham group.](image)
Recovered Dystrophin Recruits the DGC to the Sarcolemma

Recovered Dystrophin Recruits nNOS to the Sarcolemma

Scale bars = 600 μm in full-view images and 100 μm in high-power images.

Gene Editing Improves Muscle Function

Heart Disease is Major Source of Mortality in Duchenne Muscular Dystrophy

- Heart disease is second leading cause of death in DMD
- Latent cardiomyopathy can often be detected at 6 years of age
- Almost all patients have heart disease by age 18
- DMD heart disease usually results in a dilated cardiomyopathy
Gene Editing in the Heart

Intravenous AAV delivery

Acknowledgements

In vivo genome editing improves muscle function in a mouse model of Duchenne muscular dystrophy

Christopher E. Nelson,1,2 Chady H. Hakim,1,3 David G. Ousterout,1,2 Pratiksha I. Thakore,1,2 Eirik A. Moreb,1,2 Ruth M. Castellanos Rivera,3 Sarina Madhavan,1,3 Xiufang Pan,3 F. Ann Ran,5,7,8 Winston X. Yan,5,7,8 Aravind Asokan,1,3 Feng Zhang,5,9,10,11 Dongsheng Duan,3,12 Charles A. Gersbach1,2,13,8

The New York Times | http://nyti.ms/1NXrTiF

SCIENCE

Gene Editing Offers Hope for Treating Duchenne Muscular Dystrophy, Studies Find

By NICHOLAS WADE DEC. 31, 2015

After decades of disappointingly slow progress, researchers have taken a substantial step toward a possible treatment for Duchenne muscular dystrophy with the help of a powerful new gene-editing technique.

Kristi Viles
Duke-UNC CTSA Consortium Collaborative Translational Research Grant
Follow on funding: R01AR069085

Moving Forward

- Better efficiency
- Increased targeting to muscle
- Decreased targeting to liver and other tissues
- Manage immune response

Engineering Liver-detargeted AAV9 Vectors for Cardiac and Musculoskeletal Gene Transfer
Nagesh Pulcherla1, Shen Shen1,2, Swati Yadav1, Karl Debbink1, Lakshmanan Govindean1, Mavis Agbandje-McKenna1 and Aravind Asokan1,2,3

Reengineering a receptor footprint of adeno-associated virus enables selective and systemic gene transfer to muscle
Aravind Asokan1,2, Julia C Conway1, Jana L Phillips1, Chengwen Li1, Julia Hegge1, Rebecca Sinnott1, Swati Yadav1, Nina DiPrimio1, Hyun-Joo Nam1, Mavis Agbandje-McKenna1, Scott McPhee1, Jon Wolff5 & R Jude Samulski1

Systemic Gene Transfer to Skeletal Muscle Using Reengineered AAV Vectors
Jana L. Phillips, Julia Hegge, Jon A. Wolff, R. Jude Samulski, and Aravind Asokan

Development of Patient-specific AAV Vectors After Neutralizing Antibody Selection for Enhanced Muscle Gene Transfer
Chengwen Li1,2, Shuqing Wu1,2, Blake Albright1, Matthew Hinchliffe, Waping Li1, Yu-Shan Tseng1, Mavis Agbandje-McKenna1, Scott McPhee1, Aravind Asokan1 and R Jude Samulski1

The AAV Vector Toolkit: Poised at the Clinical Crossroads
Aravind Asokan1,2, David V Schaffer3,4 and R Jude Samulski1,5
Thank You