Collaboration for Innovation in Healthcare

Chairs: Lori Dickes, Larry Fredendall and Modi Wetzler
Future Biometrics

Dr. Jillian Weise
Associate Professor
Department of English
College of Architecture, Arts & Humanities
First 3D-Printed Poetry Broadside in the USA

transcribed into Braille by Sean Tikkun
designed and printed by Tom Burtonwood
at the School of the Art Institute Chicago

sponsored by Poetry Magazine and Makerbot
Methodology / Research Methods

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The body that used to contain your daughter we found it behind the fence.

It was in a red coat. It was collected.

Is she saved? Is she in the system?
Future Biometrics

You’re lucky
we have other bodies
to put your daughter in
Come on down
to the station

from *Cyborg Detective* (BOA Editions, 2019)
Revealing the mechanistic effects of genetic variants associated with postsurgery drug addiction

Emil Alexov
Professor
Department of Physics and Astronomy
College of Sciences
Dr. William Hand, anesthesiologist in Greenville, South Carolina and is affiliated with Prisma Health Greenville Memorial Hospital.

Overview

• Importance of research question: The outcome of the study will be used to develop a protocol that given a patient variant in these opioid-addiction-linked genes, one can predict the addiction risk with respect to specific opioid medications and to possibly select the drug with lowest risk for addiction.

• This is along the NIDA PA-18-076 which “encourages applicants to develop innovative research applications on prescription drug abuse” and emphasizes on proposals that “identify and/or characterize the mechanistic roles and/or clinical application of genetic variants that have previously been demonstrated to contribute to addiction.”

Title (R21 to NIODA): “Genetic variants associated with post-surgery drug addiction: revealing their mechanistic roles and paving the way for development of standard testing kit for precision administration of analgesics”. We will select addicted individuals of similar background (age, gender, race, ethnics) and surgical procedure. This will allow us to reduce the noise and to better identify genetic component of addiction. In addition, the finding will be used to develop a test kit that will be offered to interested patients to take prior opioid medication is prescribed.
Overview

**Research Question:** Opioid medications are useful for treating acute pain, however over the past two decades their use has been liberalized and addictive potential underestimated; this has resulted in approximately 116 million people with opioid-prescription dependency. This project focuses on revealing the mechanistic effects of known genetic variants that are associated with elevated risk of opioid addiction, while our ultimate goal is to identify new opioid-linked variants. Such an analysis will identify what is the major mechanistic effect for given gene/variants that likely influence vulnerability to addiction.

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- **SAAFEC**
- **SAAMBE**
- **SAMPDI**

Identify the common mechanistic effect of a given pain-killer within several (targeted) genes

Opioid addicted individuals
Research Question: Opioid medications are useful for treating acute pain, however over the past two decades their use has been liberalized and addictive potential underestimated; this has resulted in approximately 116 million people with opioid-prescription dependency. This project focuses on revealing the mechanistic effects of known genetic variants that are associated with elevated risk of opioid addiction, while our ultimate goal is to identify new opioid-linked variants. Such an analysis will identify what is the major mechanistic effect for given gene/variants that likely influence vulnerability to addiction.
Methodology / Research Methods

- Overview of Methodology
  - Synthesis

(a) Use computational approaches developed in the lab to model the effects

(b) Use Online resources to filter-down false predictions and to infer about the phenotype
Delta-type opioid receptor: A G-protein coupled receptor that functions as a receptor for endogenous opioids and a subset of other opioids. Ligand binding causes a conformation change that triggers signaling via guanine nucleotide-binding proteins (G proteins) and modulates the activity of downstream effectors, such as adenylate cyclase. Signaling leads to the inhibition of adenylate cyclase activity and the inhibition of neurotransmitter release by reducing calcium ion currents and increasing potassium ion conductance. Plays a role in the perception of pain and in opioid mediated analgesia. Plays a role in developing analgesic tolerance to opioids.

Mu-receptor: Receptor for endogenous opioids such as beta-endorphin and endomorphin. Receptor for natural and synthetic opioids including morphine, fentanyl, DAMGO, heroin, etorphine, buprenorphine, and methadone. Agonist binding induces coupling to an inactive GDP-bound heterotrimeric G-protein complex and subsequent exchange of GDP for GTP in the G-protein alpha subunit leading to dissociation of the G-protein complex with the free GTP-bound alpha subunit and the G-protein beta-gamma dimer activating downstream cellular effectors.

Dopamine receptor: A G-protein coupled receptor whose activity is modulated by second messengers which inhibit adenylyl cyclase. A missense mutation in this gene causes myoclonus dystonia; other mutations have been associated with schizophrenia. Alternative splicing of this gene results in two transcript variants encoding different isoforms. A third variant has been described, but it has not been determined whether this form is normal or due to aberrant splicing.
Conclusions

- Important findings to date:
  (a) Collected data from literature, however, the data is very scarce and in many cases the reports contradict to each other.
  (b) Built 3D structures of the corresponding proteins, initiated computational modeling of mechanistic effects of mutations.

- Limitations of current research
  (a) Deals with VERY limited number of cases. Only about 10 genes with a few mutations
  (b) There is no data for co-occurrence of more than one variant per patient
  (c) There is no data about gender/age/social conditions etc.
  (d) No studies of phenotype

- Next steps
  (a) Sequence DNA of more opioid addicted individuals
  (b) Identify novel genes and mutations
  (c) Seek double/triple mutations across different genes per individual
  (d) Investigate what is the dominant mechanistic effects (of single and multiple mutations)
Conclusions

• Possible Future Projects for collaboration:
  (a) we hope to identify novel variants associated with opioid addiction risk. Thus characterization of their phenotype will be a future project(s).
  (b) with increase of the “rs” (variants), we plan to study cumulative effect(s) of several variants on cellular networks/pathways. This will be very appealing project, since a single variant typically does not contribute much to the addiction risk.

• Types of collaborators needed:
  (a) wet-lab biochemist(s) to study phenotype of mutants, including intronic mutants (protein-DNA interactions)
  (b) expert(s) in revealing the effects of intronic variants
  (c) statistician(s)

• Resources needed:
  (a) desperately need IRB approval
  (b) funds to support WES sequencing of DNA of about 30 volunteers (Greenwood Diagnostic Lab - $1,300 per WES)
Innovative Treatment for Neonatal Abstinence Syndrome (NAS)

Lori Dickes, PHD
PRTM- MPA
College of Behavioral, Social and Health Sciences
Overview

- Are the hospital length of stay and costs for newborns with NAS who were treated using an innovative model (MAiN) developed at Greenville Health System lower than for other SC infants who were treated with standard care?
Methodology / Research methods

Overview of Methodology

• Retrospective Chart Review 2006 – 2014 (for MAiN)
• Medicaid claims linked with patient encounter and birth certificate data (for comparison group)
• Primary Outcome Measure: Hospital length of stay charges
• Analysis: Propensity score matching technique; Multivariate analyses to examine group differences

Methodological Limitations

• Limitation of retrospective claims data and reliability of medical coding; Design of Experiments

Average Hospital Charges (All Payers) for NAS, 2012

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>NICU</th>
<th>Not NICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU</td>
<td>$106,000 per birth</td>
<td>(1/3 of newborns with NAS or narcotic exposure)</td>
<td>$16,600 per birth (saves $89,400)</td>
</tr>
</tbody>
</table>

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2019 Clemson University Research Symposium

May 9-11, 2019
## Conclusions

<table>
<thead>
<tr>
<th></th>
<th>MAiN (N=110)</th>
<th>State (N=356)</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of stay in days, mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth hospitalization</td>
<td>8.3 (2.8)</td>
<td>13.2 (12.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient readmissions</td>
<td>3.3 (2.2)</td>
<td>9.2 (9.5)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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<th>State (N=356)</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total charges in dollars, mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth hospitalization</td>
<td>10,065.03 (3,027.22)</td>
<td>29,819.71 (35,469.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient readmissions</td>
<td>8,363.13 (7,788.31)</td>
<td>30,705.47 (31,355.70)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Collaboration

Ongoing efforts: MAiN expansion

- Implement the MAiN program in 10 hospitals in SC
- Evaluate the implementation of MAiN across hospital settings and the outcomes of the infants treated with the model
- Partners include GHS, Clemson, and DSS

Collaborations and future projects

- Longitudinal analysis of infant, maternal and family outcomes
- Systems model development for wrap around service delivery for families with SUD
- Health extension follow up for MAiN families model
- Jail, Detention Centers and Prison research around maternal and infant care with SUD
- Development of indices related to pain management in infants
Craniofacial Dysmorphology Associated with Phelan-McDermid Syndrome using Three-Dimensional Morphometrics

Katherine E. Weisensee, Ph.D.
Chair & Associate Professor
Department of Sociology, Anthropology & Criminal Justice
College of Behavioral, Social and Health Sciences
Overview

- Collaborative research funded by NIH R03 – “Small Research Grants for Establishing Basic Science-Clinical Collaborations to Understand Structural Birth Defects.”
  - Kara Powder, Developmental Biologist, Clemson University
  - Curtis Rogers, Senior Clinical Geneticist, Greenwood Genetics Center
- Phelan-McDermid Syndrome (PMS: MIM 606232)
  - Recognized disorder in 2007
  - Over 1500 confirmed diagnoses
  - Autism spectrum disorder and mild dysmorphic features
  - Craniofacial features commonly used in diagnosis, but not well-characterized
Morphometric Shape Analysis

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Clemson University
School of Health Research

Research Symposium
Innovate - Collaborate - Impact

2019 Clemson University
Research Methods

• Characterize mean dysmorphology in PMS
• Understand the impact on growth rates
• Address “diagnostic odyssey”, faster diagnoses, earlier interventions
Developmental Models

• SHANK3 gene deletion is associated with PMS and other ASD
• SHANK3 mouse and zebrafish models exist and have behavioral correlates with ASD, but unknown craniofacial phenotype
• Use animal models to understand multiple outcomes associated with PMS
Conclusions

- Limitations:
  - The collection of scans from young children with developmental delays poses difficulties in capturing quality images with the proper orientation.
  - Limited number of samples that capture normal craniofacial variation across sexes and ancestry groups
  - Small number of patients
- What’s Next:
  - Continue data collection at clinic and family conferences
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Collaboration

- Collaborators needed:
  - Visualization of three-dimensional variation
  - Clinicians and researchers with expertise in other disorders associated with craniofacial dysmorphology

- Resources needed:
  - Additional 3dMD cameras would allow larger capture area
  - Lab space
  - GeoMagic software
RF Sensing For Health

Pingshan Wang
Professor
Electrical and Computer Engineering
The College of Engineering, Computing and Applied Sciences

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Overview

Label free detection and differentiation of molecules, particles, cells and diseased tissue
- Rapid diagnostic test (RDT) of disease
- Real-time monitoring of IV drugs and metabolites

RF sensing
- Tunable RF interferometry: sensitivity and specificity (intrinsic physical and electrical properties)
- Results to date: RF liquid analyzers, flow cytometers, gas detectors, and electron-spin spectrometers
  - Molecules: DNA
  - Particles, cells, and GUVs
Tunable RF interferometry and DNA measurement


Measuring nanometer thick GUV membrane domain
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Particles and Cells

4 µm silica

Human breast cell mixture measurement at ~3.42 GHz.
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Cells and VOCs

H. Li et al., IEEE Sensors J., 2017

PGMA/POEGMA copolymer: 70 nm Ø LOD: 50 ppm for aceton ppb is easily achievable

S. Cerevisiae vs. S. Pastorianus

J. Osterberg (to be published)
Material: 0.2 µg DPPH at room temperature

At $f = 7.7$ GHz, SNR = 121; sensitivity: $1 \times 10^{11}$ spins/GHz$^{1/2}$

Commercial instrument: $5 \times 10^{10}$ spins/GHz$^{1/2}$ at low temperature
Collaboration

• Possible future projects for collaboration
  – Build a database: molecules, cells, fluids, and tissues
  – Identify RF fingerprints: machine learning (AI) and big data
  – Rapid diagnostic test (RDT) of disease: body fluids
  – Real-time monitoring of IV drugs and metabolites
  – Non-invasive imaging of diseased tissues: skin cancers and brain stroke
  – Bioelectronic medicine
Use of functionalized magnetic nanoparticles as a tool for disease detection and treatment.

Thompson Mefford
Materials Science and Engineering
mefford@clemson.edu
Meffordresearch.com
Assembling, Pulling, and Twisting of Magnetic Nanoparticles as a Collaborative Tool


• Ligand or material may not be biocompatible or dispersible.
  • e.g., Aliphatic ligands, toxic materials, isoelectric point.
• Remedy via ligand exchange, grafting to, grafting from.
• Water dispersible and stable in buffers and protein rich environments.
• Add functionality

Conde João et al., Revisiting 30 years of biofunctionalization and surface chemistry of inorganic nanoparticles for nanomedicine, Frontiers in Chemistry, 2, 48, 2014
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Designing Polymer-Particle Systems for Varied Applications

- Homogenous Distributions of Particle Size
- Stable Binding of Polymers on the Surface
- Suitable polymer brush for colloidal stability
- Functionality of Polymer Groups is Critical for Long Term Success

Use of functional particles to treat antibiotic resistant pathogens

Treatment of K99 for 120 minute treatment time results in a 3 log reduction CFU/ml

- 31 kA/m at 207kHz
- Over 3 log reduction in CFU/ml of K99.
- No decrease in cell viability with untargeted particles.
- Much quicker than conventional antibiotics.
- Clinically relevant decrease in CFU.

**Poly(ethylene oxide)** – PEO
GM3 glycoconjugate
EC K99 interacts with GM3
EC O157 does not interact
Heparin Fe₃O₄ for Prevention of Restenosis

T2 Weighted MRI for Circulation and Distribution

- Circulation is encouraging as heparin binds rapidly to cellular sites.
- Return to normal after 1hr 30min
- Animal showed no toxicity based issues.

Staining demonstrate phenotypic change of VSMCs from synthetic to contractile

- Nuclear number increased matching with MTS and live/dead assay.
- No change in appearance or expression.

Circulation is encouraging as heparin binds rapidly to cellular sites. Return to normal after 1hr 30min. Animal showed no toxicity based issues.
Conclusions

- Precise Synthesis of:
  - Particle Size
  - Anchoring Chemistry
  - Polymer Brush Length
  - Availability of Additional Modification

- Multifunctional Platform for:
  - Imaging
  - Therapy
  - Discovery

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Acknowledgments

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Thompson Mefford
Materials Science and Engineering
mefford@clemson.edu
Meffordresearch.com

Mark Bolding,
UAB-Radiology

Delphine Dean,
Bioengineering

Jeremy Tsang,
Biological Science

Brian Powell,
Environmental Science

Thomas Crawford,
USC-Physics

Rachel Getman,
Chemical Engineering

Jiro Nagatomi,
Bioengineering

Sapna Sarupria,
Chemical Engineering

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Collaborative Opportunities

A platform for discovery: What would you do?

Thompson Mefford
Materials Science and Engineering
mefford@clemson.edu
Meffordresearch.com

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Mothers with Addiction

Mary Ellen Wright, PhD, APRN, CPNP-BC
Mothers with Addiction and Recovery Nursing
College of Behavioral, Social and Health Sciences
Overview

Research Question
What is the experience of pregnant and parenting mothers who are affected by substance use disorder?

• Paradigm to focus on the maternal-infant dyad
• Inform future studies by understanding:
  social contexts of use
  identification of types of poly-substances used in pregnancy
  influences for pursuit of recovery.
• Inform studies of the longitudinal effects on the infant/child from perinatal exposures
• Theoretical framework Nursing as Caring (Boykin and Schoenhofer) and Bronfenbrenner’s Ecological System Theory.
Methodology and Research Method

• Overview of Methodology
  Qualitative study using Story telling
  • mothers recruited by posters in recovery centers
  • Participants anonymously called a designated cell phone
  • N = 11 mothers stories ranged from 1 – 3 hours

Narrative inquiry using ATLAS
ti qualitative analysis program

Classroom Award from ATLAS
ti.
  Creative inquiry students participated in data collection, transcription and coding of the data.
  Colleague Dr. Heide Temples
Conclusions

• Positive social support (both informal and formal) co-occurrence with women active in recovery in all levels of social ecological systems.
  Changing paradigm of “hitting rock bottom”
• Motivational factor of motherhood with pursuing recovery and expressions of genuine concern for the child by the mothers and the affect on the child.
  Raising awareness of maternal infliction on the infant
• Past and current trauma
• Chronic nature of addiction
• Poly-substance use that includes prescribed substances for treatment and illicit substances
Future Projects for collaboration

1. Effectiveness of formal social support programs focused on mothers and infants
2. Co-morbidities of post-partum depression, abuse and recidivism
3. Toxicology identification of poly-substances
Needs for Collaboration

• Longitudinal effects on infant brain from perinatal substance exposure and effects of environment on longitudinal effects

Collaborators:
  Pharmacy  Pathology  Neurology
  Lab availability to measure biomarkers of brain compromise

Predictors such as the Genetic predictors presented today

Anthropology, sociology as partners on the social environmental factors and co-morbidity studies
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Impacting Population Health Management

Amanda Moore
Associate Director of the Social Media Listening Center
Department of Communication
College of Behavioral, Social and Health Sciences
Overview

• Research Question:
  • How can Prisma Health reach individuals who might be pre-diabetic or diabetic?

• Importance of research question
  • South Carolina ranks as the 5th highest state for diabetes.

• Research findings to date – In process
  • Prisma Health launched a health assessment survey.
  • The SMLC has been providing strategic suggestions.
Methodology / Research methods

- **Overview of Methodology**
  - Survey
    - Distributed via Social Media
    - Distributed via Email Marketing
    - Distributed via in-person (traditional marketing)
  - Next Steps
    - Based on information collected, we will conduct a formal research study.
    - Use social media to implement strategic messaging to target audiences.
Conclusions

- Important findings to date
  - Strategic messaging has improved the reach of Prisma Health’s social media posts.
- Limitations of current research
  - In preliminary phases of research.
  - Not everyone has access to social media or internet.
- Next steps
  - Working to construct formal research projects.
Collaboration

• Possible Future Projects for collaboration
  – Projects centered on health information accessibility.
  – Projects centered on effective health messaging.

• Types of collaborators needed
  – Seeking health researchers to assist with long-term projects.
  – Considering involving undergraduates – potentially a CI.

• Resources needed
  – Project could benefit from more advanced software.
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Treating Intellectual Disability in South Carolina

Modi Wetzler
Department of Chemistry
College of Science
Overview

- Creatine Transporter Deficiency (CTD) affects ~2M people worldwide
  - Severe intellectual disability (IQ 20-50)
- Completely untreatable
  - No intellectual disability is treatable with a synthetic drug
- Biochemically very well understood
- Needed: creatine analog that enters the brain despite nonfunctional transporter, still active with creatine kinase (CK)

\[
\text{Creatine kinase:} \quad \text{ATP} + \text{ADP} \rightarrow 4 \text{mM}
\]
\[
\text{Phosphocreatine:} \quad \text{Creatine} \quad \sim 40 \text{mM}
\]
Methodology / Research methods

Uptake of first four compounds in wild-type zebrafish

- **Positive control for uptake**: CRA1
- **Negative control for activity**: CRA2
- **Taken up (shown)**: CRA3, active with CK (not shown)
- **Natural [Cr] concentration**
- **Brain [Cr]**
- **Brain [Analog]**
- **Head [Cr]**

Creatine

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Conclusions

- Uptake into wild-type zebrafish brains demonstrated
- Breeding of ortholog & homolog mutant zebrafish almost complete (Susan Chapman, Biological Sciences)
- Rescue of metabolic phenotype in patient-derived cells (Charles Schwartz, Greenwood Genetic Center)
- Laura Baroncelli (CINR, Italy) has mouse model
- We are significantly scaling up syntheses
- Has been well-funded, currently in the translational research funding gap
- Gene to compound to clinic in South Carolina?
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- Interdisciplinary research teams at Clemson that are peptide focused
- (e.g., >1000 peptide hormones in your body right now)