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Food for Thought: A Public Health Approach to the School Food Environment

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Areas of Interest:
Childhood obesity prevention, specifically school-based research examining school lunch and school breakfast programs in order to decrease or prevent obesity in children and adolescents.
Nutrition + Disease

- Type II diabetes
- Overweight and obesity
- Hypertension
- Dental cavities
- Certain types of cancer
- Iron deficiency
- Osteoporosis
Why Schools?

*The public health approach*

95%

50%
(Some) Previous Studies

• School-based salad bars and fruit and vegetable consumption
• Implementation science of school-based salad bars
• Statewide (Utah) parent breakfast survey
Utah ranks last in school breakfast participation

By Wendy Leonard, Deseret News

Published: Saturday, March 19 2016 5:15 p.m. MDT
Updated: Saturday, March 19 2016 5:16 p.m. MDT

Sammy Creel and other students at Granite District’s James E. Moss Elementary School eat their breakfast in their classroom after school has started for the day, Friday, March 18, 2016.

Scott G Winterton, Deseret News

(Some) Future Ideas

• Difference in perception between parents and food service directors/staff on healthy foods served at school
• Which is healthier: school breakfast or home breakfast
• How does serving school breakfast after the bell affect cognition?
Opportunities for Collaboration

- App development experts
- Child development experts
- Psychology experts
- Many more!
Divalent Copper Complexes as Anti-Influenza Agents


Dept. of Physiology and Developmental Biology and Dept. of Chemistry and Biochemistry
M2 Wild-Type (WT) and S31N

Wild-Type

S31N

Amantadine

Val27 valve
Ala30, Ser31
Ala34
Entry cluster
His-box
Bridging cluster
Trp-basket
Exit cluster
Asp44, Arg45

viral exterior

viral interior

NH₂
Novel Complexes

- Need equivalent efficacy as free Cu$^{2+}$
- Need Cu$^{2+}$ tightly bound and protected
- Needs to be stable in solution
- Needs to be pure
- Needs to have known concentration
Stability: UV Absorbance Spectra

Water

ACSF (NaH₂PO₄, NaHCO₃, glucose)

Barths (NaHCO₃, MgSO₄)

Cu(CO-IDAA)

Cu(CO-IDA)

Cu(AMT-IDAA)

Cu(AMT-IDA)
Experiments & Data: Two-Electrode Voltage Clamp

- **Wild-Type M2**
  - AMT 100 uM

- **S31N Mutant**
  - AMT 100 uM

- **No Imidazoles (H37A)**
  - CuCl₂ 100 uM
Experiments & Data: Two-Electrode Voltage Clamp

Cu(CO-IDAA) 100 uM

Cu(AMT-IDAA) 100 uM

S31N Mutant

S31N Mutant/No Copper On Compound

No Imidazoles (H37A)
Experiments & Data: Two-Electrode Voltage Clamp

- Cu(CO-IDA) 100 μM
- Cu(AMT-IDA) 100 μM

S31N Mutant

S31N Mutant/ No Copper On Compound

No Imidazoles (H37A)
Experiments: Mini-Plaque Viral Assay

- MDCK culture
- 33 °C/16 hour Incubation
- Fluorescent labeled (FITC) antibodies

<table>
<thead>
<tr>
<th></th>
<th>CuCl₂</th>
<th>Cu(IDA)</th>
<th>Cu(IDAA)</th>
<th>Cu(Amt-IDA)</th>
<th>Cu(Amt-IDAA)</th>
<th>Cu(CO-IDA)</th>
<th>Cu(CO-IDAA)</th>
</tr>
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<tr>
<td>A/CA/07/09 H1N1</td>
<td>3.8 ± 0.9</td>
<td>8.2 ± 2.0</td>
<td>4.4 ± 0.6</td>
<td>6.9 ± 1.2</td>
<td>4.9 ± 0.8</td>
<td>0.7 ± 0.1</td>
<td>11.6 ± 1.1</td>
</tr>
<tr>
<td>A/W5/33 H1N1</td>
<td>4.3 ± 1.0</td>
<td>4.7 ± 1.1</td>
<td>7.2 ± 5.3</td>
<td>2.4 ± 0.3</td>
<td>4.1 ± 2.4</td>
<td>2.1 ± 0.7</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>A/Victoria/03/75 H3N2</td>
<td>1.1 ± 0.3</td>
<td>4.4 ± 2.2</td>
<td>16.3 ± 8.4</td>
<td>4.2 ± 1.7</td>
<td>7.0 ± 1.2</td>
<td>3.7 ± 0.9</td>
<td>8.4 ± 0.7</td>
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<th></th>
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<th>Cu(Amt-IDAA)</th>
<th>Cu(CO-IDA)</th>
<th>Cu(CO-IDAA)</th>
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<td>MDCK Cell Vulnerability</td>
<td>19 ± 6</td>
<td>115 ± 9</td>
<td>64 ± 6</td>
<td>64 ± 7</td>
<td>52 ± 5</td>
<td>147 ± 38</td>
<td>180 ± 15</td>
</tr>
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</table>
Summary

- Majority of influenza A strains have the mutated M2 channel; No M2 blockers
- We have synthesized, purified, and characterized four new copper complexes: \( \text{Cu(Amt-IDA)}, \text{Cu(Amt-IDAA)}, \text{Cu(CO-IDA)}, \text{and Cu(CO-IDAA)} \)

- Most promising is \( \text{Cu(CO-IDA)} \):
  - Stable
  - >90% block
  - Sub-micromolar EC\(_{50}\)
  - Low cytotoxicity
Acknowledgement

Kelly McGuire       Greg Mohl       McKenzie Hart & Andrew Belnap
Spencer Wallentine  Jonathan Lynch & Steven Walker
McKay Jensen        Natalia Garcia   Dallin Gillette  Michael Scott
Roger Hamison PhD
Cardiovascular Epidemiology
Evan Thacker
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- Connections of heart health with cognition
- Time trends and geographic patterns in heart disease statistics
- Other stuff like diabetes, hormones, smoking, obesity, healthy aging, etc
Cardiovascular health

- Diabetes
- Hypertension
- Triglycerides
- Cholesterol
- Obesity

Cerebrovascular Disease
- Oxidative Stress
- Inflammation
- Neuronal Degradation
- β-amyloid aggregation
- Neurofibrillary tangles

Vascular Cognitive Aging
Heart failure & cognitive decline

(with BYU statistics student Christa Schank Hammond)
Leptin, BMI & cognitive impairment

(with BYU public health student Reena Karki
And BYU statistics student Rachel Marker)
Heart disease vs cancer mortality rates

(with BYU public health student Michael Harding)
Other current & near-future projects

Coronary heart disease
CABG surgery
Cardiovascular health metrics
Adiponectin
Hemostasis biomarkers
ECG parameters
Cardiorespiratory fitness

Cognitive decline & cognitive impairment

~ Some of these projects involve (or will involve) BYU students ~
Interests for the future

• More of the same ...
  ... and also ...
• Infection biomarkers and cognition
• US maps of cardiovascular health & cognition
• Cardiovascular disease & brain MRI
• Cardiovascular disease & neuropathology
Diabetes, Insulin Secretion, and Beta Cell Function

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Areas of Interest:
Nutrient metabolism and biochemistry; metabolic disorders that cause human diseases
Molecular pathways of β-cell function and proliferation

Jeffery S. Tessem, Ph.D.
Department of Nutrition, Dietetics and Food Science
Brigham Young University
Type 1 and Type 2 Diabetes are increasing worldwide

Worldwide 2015: 415 million people with diabetes

- North America and Caribbean:
  - 2015: 44.3 million
  - 2040: 60.5 million

- Europe:
  - 2015: 59.8 million
  - 2040: 71.1 million

- Middle East and North Africa:
  - 2015: 35.4 million
  - 2040: 72.1 million

- South and Central America:
  - 2015: 29.6 million
  - 2040: 48.8 million

- Africa:
  - 2015: 14.2 million
  - 2040: 34.2 million

- South East Asia:
  - 2015: 78.3 million
  - 2040: 140.2 million

- Western Pacific:
  - 2015: 153.2 million
  - 2040: 214.8 million
β-cell mass is lost in T1D and T2D

Increasing β-cell mass could be used as a treatment for all forms of diabetes

Islet transplantation—potential cure for diabetes

Major obstacle to greater use of islet transplantation is the availability of beta-cells

More β-cells are needed

Discovery and manipulation of β-cell proliferation pathways
Tessem Lab Goal:
Identify genes & pathways that govern the preservation and expansion of functional \(\beta\)-cell mass
Where can we get more $\beta$-cells?
Our experimental methodology

- *INS-1 β-cell line*
- *Primary rat islets*
- *Primary human islets*

- Manipulate with adenoviral gene transfer, shRNA knockdown, pharmacological modulators, nutritional factors
- Measure for phenotypic changes in β-cell proliferation, insulin secretion, and cell survival
- Determine the mechanism and molecular pathways that result in the observed phenotypes through biochemical, metabolic, transcriptomic, biochemical and histological techniques.
- All studies begin in the INS-1 cells, and then are transitioned to the rat and human islets
Working model for how Nr4a’s enhance functional β-cell mass

Nkx6.1 → Nr4a1, Nr4a3

- Mitochondrial Function
- E2F1, Cyclin E1, B1, A1, A2, AURKA
- CDK5r1
- Ube2c, Ube2s, Cdc20
- p21

Insulin Secretion

Cell Cycle Progression & Proliferation

Tessen, et al. PNAS 111: 5242, 2014
Reynolds, et al. AJP-Endo, 2016
Potential collaborations

• What can we provide?
  • **Young vs. Old Wistar Rat colony**- we only use the pancreas, open to collaboration with other tissues
  • **Knock out mice**
    • Nr4a1 full body- we only use the pancreas, looking for collaboration with other tissues
    • Nr4a3 full body- we only use the pancreas, looking for collaboration with other tissues
    • Nr4a1 Floxed- If you have a tissue specific Cre we can see the effect of Nr4a1 KO in your tissue of interest
    • RIP-Cre-ERTM β-cell knock out- Do you have a floxed animal that you would like to check the effect in the beta cell?
  • **Tissue culture** - We have β-cell, α-cell and hepatocyte lines.
  • **Feeding Studies** - We have Nr4a1, Nr4a3 and Nr4a1 β-cell knock out on high fat and low fat diet-open to looking at your gene or system of issue.
  • **Adenovirus and Lentivirus** - we have over 100 adenovirus and lentivirus for gene overexpression and knockdown, and expertise in building these constructs.
  • **Islet isolation** - would you like to know if your gene of interest or experimental model affects the β-cell? Let us help you find out
  • **Techniques that we use frequently**- RT-PCR, Histology, Respiration, ChIP, microarray, mitochondrial assays, metabolite measurements, etc.
Potential collaborations

• What are we interested in?

  • What are the molecular mechanisms that permit β-cell mass to increase in pregnancy?
  
  • Do different β-cell subtypes exist?
  
  • What genes control Nkx6.1 expression in the β-cell?
  
  • How can manipulating β-cell vasculature increase β-cell proliferation?
  
  • Why do aged β-cells lose their ability to replicate?
  
  • What are the effects of Nr4a1 or Nr4a3 loss in other tissues?
  
  • What are the binding partners of Nkx6.1, Nr4a1 and Nr4a3?
  
  • What are the transcriptional targets of the Nr4a’s?
  
  • How does unsaturated versus saturated fatty acids affect Nr4a function (putative ligand)?

• If you have any ideas for collaborations, please contact me!
Increased Functional \( \beta \)-cell Mass

*Fos*

*Nkx6.1*

Maternal Overnutrition

Mitochondrial Function

*VGF*

*Nr4a1/Nr4a3*

*AURKA, HDAC1, Cdk5r1*

Apoptosis

*GSIS*

Cocoa epicatechins

Tommy Rowley

Matt Ballard

Aaron Leifer

Increased Functional \( \beta \)-cell Mass

Jason Ray

Ben Bitner

Kyle Kener

Anson Crum

Carrie Draney

Emily Barrett

Daniel Lathen

Will Utsch

Adam Wynn

Sam Grover

Courtney Smith

Kevin Garland

Jessica McClintock
Helper T cell role in immunity to infection

Scott Weber
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Microbiology and Molecular Biology Department

I am an Immunologist using molecular, biochemical, and cellular techniques to understand T cell activation and use this to improve the immune response to infection, cancer, and prevent asthma development.
Central role of helper T cells in immunity to infection
T cell activation controlled on numerous levels

1) T cell receptor: T cell function dependent upon affinity of TCR-peptide MHC
2) Cell signaling: Signaling cascade regulates the T cell response to antigen
3) Co-receptors: Co-receptors have a critical role in T cell inhibition and activation
① Improving T cell memory response to infectious disease

② Engineering immunological proteins with improved function

③ Understanding the molecular basis of T cell activation

Examine environmental exposure and asthma development
Model system: Two TCR transgenic mice specific for Listeria

**LLO118**
- **LLO190-205/I-Ab**
- **Vα2, Vβ2**

**LLO56**
- **LLO190-205/I-Ab**
- **Vα2, Vβ2**

**TCRtg mice**
- **LLO118 Ly5.1**
- **LLO56 Thy1.1**

- TCRs differ by 15 amino acids (10 in the CDR3β)

- **CD4^+ cells**
Improving T cell memory response to infectious disease

Key finding: LLO118 better in primary response and LLO56 better in secondary response

- How can helper T cell memory formation be improved?
- What role does cell death have on memory cell generation?
- How does TCR affinity affect recognition of infectious agents?
- What is the role of CD5 in T cell function?
Why use yeast display?
1) Generate cancer and infectious disease therapeutic and diagnostic reagents.
2) Increase biological understanding of T cell activation.
3) Stabilized TCRs are amenable to affinity and structural studies
Calcium ions are involved in numerous cellular events:

- Fertilization
- Transcription
- Lymphocyte activation
- Muscle contraction
- Cell death

How is calcium influx and T cell activation altered in memory cells and high affinity T cells?
The importance of environmental exposures in the development of asthma is most exquisitely illustrated by epidemiologic studies conducted in Central Europe that show significant protection from asthma and allergic disease in children raised on traditional dairy farms. In particular, children's contact with farm animals and the associated high microbial exposures have been related to the reduced risk. A recent New England Journal of Medicine article examined Amish and Hutterite populations and found the dramatic differences in asthma development in these related populations appears to be due to different endotoxin levels in the dust caused by different types of farming techniques. The endotoxins stimulate the innate immune system and are protective from asthma.
Pediatric Malnutrition

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Areas of Interest:
Clinical Malnutrition Screening and Assessment, Pediatric Nutrition, and Nutrition Education
Pediatric Malnutrition
Pediatric Malnutrition (Undernutrition)

• 6 to 41% hospitalized children malnutrition

• Pediatric malnutrition consequences
  • Increased length of stay
  • Increased infections
  • Increased costs
  • Increased mortality rates

• Diagnose and identify
Academy of Nutrition and Dietetics/American Society of Parenteral and Enteral Nutrition 2014 Pediatric Malnutrition Consensus Statement
Primary Indicators

• Weight for height z score
• BMI for age z score
• Length/height z-score
• Mid-upper arm circumference
Handgrip Strength

• Functional measurement related to nutritional status
• Reacts sooner to nutritional changes
• Easy to measure and non-invasive
• No normal reference ranges in large pediatric populations exist
Study Questions

• Does HGS differ in hospitalized children ages 6 to 14 years within 48 hours of admission and non-hospitalized children?

• Is there a difference in HGS of children with cystic fibrosis during hospitalization compared to follow-up appointment?
Collaboration Ideas

• Obtaining HGS measurements in a wider population of children

• Comparing HGS with body composition (muscle mass) measurements

• Your ideas!