OMM Research – From Bedside to Bench and Back Again

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We Know It Works, But We Need Evidence-Based Studies

• Basic Biomedical
• Animal Studies
• Clinical Studies
Stepping Way Back From The Bedside - Basic Biochemical Studies At The Cellular Level

- Much data on the mild forces of stretch and strain on cellular function
- Ingber Group
  - Tensegrity - Basic forces a cell or tissue is subjected to, that regulates function
  - Changes in ion channel function
  - Gene transcription
  - Changes in mitochondria and ER
  - Changes in oxidative stress
- Endothelial Biology – Endothelial cells do not develop the full complement of receptors and function unless they receive pulsatile stretch
- These same forces apply to what is delivered in OMM
Modeling OMM At The Cellular Level

- **Flex Cell Model**
  - Used by the Standley group at UTSW SOM
  - Much data on cellular level forces, similar to OMM
  - Can be used to replicate repetitive motion injury

- **Cell Injury Controller Model (CIC)**
  - Higher velocity, single rapid impulse
  - Used to mimic trauma initially, but using slower speeds and decreased force may be a model for high velocity OMM
The Flex Cell Model

- Cells grown under tension or lack thereof
- Two dimensional forces can be applied followed by examination of cellular changes
- Standley group – used fibroblasts, found changes in inflammatory mediator production and recovery from repetitive motion injury
Biochemistry of OMM At The Cellular Level

Controls: Maintained with baseline strain of 10%, simulating normal tissue tension.

Repetitive Motion Injury (RMI): Cells maintained at baseline (10%) strain were subjected to an additional 10% strain (total 20%) in repetitive 2 second cycles for 8 hrs, followed by return to baseline.

Myofascial Release (MR): MR was simulated by reducing the strain on the membrane to below the baseline condition of 10%.
Biochemistry of OMM At The Cellular Level –
Decrease In Inflammatory Mediators

Cellular Myofascial Release Improves Resting and Histamine-Stimulated \([Ca^{2+}]\),
After Repetitive Motion Injury

Cellular Myofascial Release Decreases IL-1\(\beta\) and NO Release After Repetitive Motion Injury

* - Sig from Control and MR, \(p<0.01\)
# - Sig from RMI, \(p<0.01\)

* Significant from Control and MR, \(p<0.01\)
# Significant from RMI, \(p<0.01\)
The CIC Model

- Originally designed as a TBI model
- Used high speeds (50 msec and less) and large strain (5-9 mm strain of membrane)
- To mimic OMM, we lowered the speed to 0.5 second pulse and delivered 1 mm strain to induce Cellular Manipulative Therapy, or “CMT”
- Question: Can CMT improve outcome from traumatic injury to neurons?

**Pretreatment Expts:** Delivered “CMT” twice per day, for 3 days, followed by a TBI

**Posttreatment Expts:** Delivered moderate TBI followed by CMT 1, 2, and 3 hrs after TBI.
CMT Improves Neuronal Survival & Function After Traumatic Injury
Sharing the Models

- Models are available, for now, at the Virginia Campus
- We can culture your cells of interest, make lysates, and ship to you for research if you wish.
- Other units may be available as needed
But......Models Must Be Justified

- Organizations such as AOA accept the Flex-Cell model
- For NIH funding, **model justification** is needed
- Must justify that the forces applied are representative of OMM forces
- Critical to establish biomedical engineering collaborations to measure forces applied in real-world OMM
- Strain, direction of strain, strain rate, penetration depth
- Establish consistency with forces applied in cellular models
- Test a range of forces with the cells

- **Model justification will be critical to funding!**
Animal Models

- Same rules apply
- **Must justify forces applied and relevance to real-world OMM**
- Easier to do in larger species
- Smaller species such as rats and mice require sound engineering collaborations to establish what forces to apply and how much
- Forces applied must be measured and aspect ratios should be similar to humans.

- Again, **model justification is key to external funding!**
Moving Back to the Bedside…..How Can the Biomedical Scientist Help the Clinician?

- Measurement of biochemical parameters in human samples – urine, blood
- Cytokines, chemokines and interleukins for inflammation
- Markers of oxidative stress in blood and urine
- Activation states of immune cells in the blood
A Clinician Wants to Determine the Effect of OMM at Improving Resolution of Infection

- Outside of the obvious clinical measurements, biomedical scientists can provide potent supportive data on biochemistry
- Interleukin or cytokine concentrations in the blood.
- Chemokine profiles for activated immune cells
- Activation state of blood neutrophils
- Inflammatory markers secreted in urine (isoprostanes, chemokines)

- Markers such as these can strengthen clinical data!
A Clinician Wants to Determine the Effect of OMM at Improving Functional Capacity in Athletes.

- Athletes are at high levels of oxidative stress, which OMM may relieve.
- Biochemical measurements we can perform:
  - Urine isoprostanes
  - Total antioxidant potential in blood
  - Glutathione ratios
  - Lipid peroxidation products in blood and urine
Yeah, But How Much Does It Cost?

- Most of these assays come in kits, that are run on specialized equipment in the lab
- A panel of 3 cytokines in a patient would cost about $30.00 for supplies
- If you were measuring 3 time points in your study, it would cost about $90 per patient
- Reasonable, supports clinical data
- Collaborate with your friendly biomedical scientist to establish what markers may be best for you to measure
Where To Go For The Funding?

• In House funding key for initial work – model development is NOT routinely funded
• AOA is a first obvious source…..but they can’t fund everything
• **NCCIH is a primary source** – Strategic Plan included in your packet
  - Strong focus on funding studies related to manipulative medicine
  - Nonpharmacologic management of pain
  - Neurobiological manipulation
  - Clinical trials of manipulative medicine
  - Reviews are more critical
  - Often goes to an outside study section (a regular NIH review panel)
  - Choose a panel carefully and seek advise from the program coordinator
  - Be mindful of your models!!!!
  - Justify the model, get biomedical engineering and statistical input/collaboration
Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)
National Institutes of Health (NIH)

Components of Participating Organizations
National Cancer Institute (NCI)
National Institute of Nursing Research (NIINR)
National Institute on Aging (NIA)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
National Institute on Drug Abuse (NDA)
National Institute of Dental and Craniofacial Research (NIDCR)
National Institute of Neurological Disorders and Stroke (NINDS)
National Center for Complementary and Integrative Health (NCCIH)
National Institute on Minority Health and Health Disparities (NIMHD)

Funding Opportunity Title
Mechanisms, Models, Measurement, & Management in Pain Research (R21)

Activity Code
R21 Exploratory/Developmental Research Grant
Department of Health and Human Services

Part 1. Overview Information

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<td>National Center for Complementary and Integrative Health (NCCIH) formerly NCCAM</td>
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<tr>
<td>Funding Opportunity Title</td>
<td>Exploratory Clinical Trials of Mind and Body Interventions for NCCAM High Priority Research Topics (R34)</td>
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<tr>
<td>Activity Code</td>
<td>R24 Exploratory Grant</td>
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Related Notices

- NOT-OD-16-004 - NIH & AHRQ Announce Upcoming Changes to PARs, Instructions and Forms for 2016 Grant Applications (November 10, 2015)
- NOT-OD-16-003 - Simplification of the Multiple Inquiries Section of NIH Grant Applications and Revisions to RFA-OD-16-045 (November 10, 2015)
- June 4, 2015 - Notice NOT-OD-15-014 supersedes instructions in Section III.3 regarding applications that are essentially the same.

Funding Opportunity Announcement (FOA) Number | PAR-14-182

Companion Funding Opportunity | None

Number of Applications | See Section III.3: Additional Information on Eligibility

Catalog of Federal Domestic Assistance (CFDA) Number(s) | SS 213

Funding Opportunity Purpose | The goal of this funding opportunity is to support early phase clinical trials of mind and body interventions that have been identified by NCCAM as high priority research topics. This funding opportunity is intended to support exploratory clinical trials, which will provide data that are critical for the planning and design of a subsequent controlled clinical study. Clinical efficacy of effectiveness study, or a pragmatic trial. The data collected should be used to fill gaps in scientific knowledge necessary to develop a persuasive full-scale clinical trial. This FOA is not appropriate for support of exploratory clinical trials to test or determine efficacy or effectiveness. Applications that propose solely to write a protocol or manual of operations or to develop infrastructure for a clinical trial are not appropriate for this announcement. The subsequent larger trial should have the potential to make a significant impact on public health.

Department of Health and Human Services

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<td>Biology of Manual Therapies (R21)</td>
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<td>R21 Exploratory/Developmental Research Grant</td>
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Related Notices

- NOT-OD-16-004 - NIH & AHRQ Announce Upcoming Changes to PARs, Instructions and Forms for 2016 Grant Applications (November 10, 2015)
- NOT-OD-16-005 - Simplification of the Vertebrate Animals Section of NIH Grant Applications and Contract Proposals (November 10, 2015)
- June 4, 2016 - Notice NOT-OD-15-014 supersedes instructions in Section III.3 regarding applications that are essentially the same.

Funding Opportunity Announcement (FOA) Number | PAR-14-167

Companion Funding Opportunity | None

Number of Applications | See Section III.3: Additional Information on Eligibility

Catalog of Federal Domestic Assistance (CFDA) Number(s) | 33723

Funding Opportunity Purpose | This FOA encourages research grant applications (R21) from institutions/organizations that propose to investigate the basic science and mechanisms of action under the neurophysiological (especially the central nervous system responses), immunological, endocrinological and/or biomechanical consequences of manual therapies, such as spinal manipulation, mobilization and massage therapy.


**Department of Health and Human Services**

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  National Institute of Nursing Research [NINR]  
  National Center for Complementary and Integrative Health [NCCIH]  
  National Cancer Institute [NCI] |

**Funding Opportunity Title**

Advancing the Science of Geriatric Palliative Care (R01)

**Activity Code**

R01, Research Project Grant

**Announcement Type**

New

**Related Notices**

- October 14, 2014 - Notice of Change &Expiration Date for PA-13-364. See Notice NOT-AG-14-035.
- NOT-AI-14-016 - NIAAA: Notice of Change to NIAAA Requirements for R01 and R21 Grant Applications: November 16, 2015.

**Funding Opportunity Announcement (FOA) Number**

PA-13-354

**Companion Funding Opportunity**

PA-13-355, R21 Small Grant Program  
PA-13-356, R21 Exploratory/Developmental Grant

**Number of Applications**

See Session II.1, Logistical Information on Eligibility.

**Catalog of Federal Domestic Assistance (CFDA) Number(s)**

83.656, 83.657, 83.658, 83.659

**Funding Opportunity Purpose**

This Funding Opportunity Announcement (FOA) encourages research grant applications focused on palliative care in geriatric populations. This FOA emphasizes studies in a variety of settings, including ambulatory care, hospitals, and specific sites within hospitals, including specialty wards, intensive care units and emergency departments, assisted living facilities, and short- and long-term care facilities. However, inpatient and end-of-life settings are not included within the scope of the FOA, as they are the subject of other NIH programs. Rather, this FOA highlights research on palliative care in settings and to the events earlier in geriatric patients’ decades of disability, including hospice care. Types of studies may include observational, quasi-experimental, or interventional studies using primary data collection and secondary analyses. Leveraging ongoing cohorts, intervention studies, metaanalyses, data and...
Don’t Forget Foundations!

• Check with the VCOM Office of Research for Foundation opportunities!

• Good luck to us all!