Research in Osteopathic Medicine – New Horizons

Brian F. Degenhardt, DO, C-NMM/OMM
A.T. Still Research Institute, Director
Assistant Vice-President for Osteopathic Research,
AT Still University, Kirksville, MO
AOA Council on Research
Rocky Mountain Integrative Medicine
• Kirksville College of Osteopathic Medicine
• Established 2001
• Mission:

“To advance whole person healthcare and wellness through the development and support of premier clinical and translational research”
The goal of the A.T. Still Research Institute is to explore and advance the scientific evidence base of osteopathic medicine and associated health professions within the A.T. Still University.
Osteopathic Medicine

- Reform movement
- Fastest growing healthcare profession
- Manipulative Medicine
- Holistic Medicine
- Prevention
- Optimizing intrinsic healing processes
- Mind, Body and Spirit concerns and interventions
- Primary Care
- Integrated throughout healthcare specialties & facilities
- Integrated throughout healthcare specialties & facilities
Disclosures

• Trained as a clinician and evolved into a clinician researcher
• Osteopathic medicine remains committed to prioritizing patient care/primary care
• The profession is committed to an active participation in advancing knowledge/patient care through science
• Can not cover the full scope of research with the osteopathic profession
• Purpose: Inform - promote discernment
Overview -

- Discuss some of the leading research programs within the osteopathic profession
- Discuss dual degree opportunities
- Discuss research within the AT Still Research Institute
- Discuss research opportunities for undergraduates at the institute and grad students within AT Still University
Current Areas of Leading Research
Brian J. Balin, PhD

Director, Center for Chronic Disorders of Aging (CCDA)

Director, Adolph and Rose Levis Foundation Laboratory for Alzheimer’s Disease Research

Professor, Department of Bio-Medical Sciences
Philadelphia College of Osteopathic Medicine
Alzheimer Disease Projects

Evaluation of how infectious agents may be involved with initiating early changes in the brain such as inflammation that results in protein accumulations (amyloid and tau) – the main components of the pathologic entities found in this disease.
Respiratory Infection
Olfactory pathway
Systemic via blood
Specific infectious agents

- *Chlamydia pneumoniae*
- Herpes simplex virus -1
- *Borrelia burgdorferi* – Lyme disease
- *Helicobacter pylori* – Ulcers, stomach cancer
- *Porphyromonas gingivalis* - Periodontitis
Analysis of infection in AD

- Human brain tissues and fluids (CSF & Blood)
  - PCR, qRT-PCR immunohistochemistry, electron microscopy

- Cell culture models using human cell lines and/or primary cells (neurons, glial cells, monocytes, endothelial cells, olfactory neuroepithelial cells)
  - Inflammasome and innate immunity analysis
  - Apoptosis (cell death pathway) and autophagy (self-eating pathway) analysis
  - Alzheimer disease specific gene and protein change analysis (eg, amyloid, tau)
  - Therapeutic potential of peptide (acALY18) in clearing infection

- Animal models using normal non-transgenic mice (BALB/c and C57BL/6 strains)
  - Analysis of specific pathways of infection into the brain
  - Analysis of amyloid and tau changes
  - Analysis of persistence of organisms in brain tissues
Analysis of infection in AD

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Summary of CCDA Accomplishments
1/1/2007 - 7/1/2013

<table>
<thead>
<tr>
<th>Activity</th>
<th>Number</th>
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</thead>
<tbody>
<tr>
<td>Intramural Grants</td>
<td>67</td>
</tr>
<tr>
<td>Symposia and Lectureships</td>
<td>32</td>
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<tr>
<td><strong>Scholarly Activity</strong></td>
<td></td>
</tr>
<tr>
<td>➢ Extramural grant proposals funded (eg, NIH, PA Dept Com &amp; Econ Dev, PA dept Health, DoD, AOA)</td>
<td>35</td>
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<tr>
<td>➢ Peer-reviewed publications</td>
<td>100*</td>
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<tr>
<td><strong>Directors’ Activities (eg, invited presentations, collaborations, student mentoring and committees, etc)</strong></td>
<td>&gt;85</td>
</tr>
<tr>
<td><strong>Sponsorships (faculty, student development, community)</strong></td>
<td>70</td>
</tr>
<tr>
<td><strong>Ongoing and New Collaborative Efforts</strong></td>
<td>&gt;15</td>
</tr>
<tr>
<td>New Research Initiatives (eg, peanut allergy, stem cell, etc)</td>
<td>~4</td>
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* Does not include pubs in press
Basic/Clinical/Translational Research Projects

Alzheimer’s Disease
Parkinson’s Disease
Multiple Sclerosis
Cardiovascular/Ischemia-reperfusion
Transplantation and Wound Repair
Stem Cell Research
Bone and Cartilage Research
Osteoarthritis
Rheumatoid Arthritis
Osteopenia/Osteoporosis
Diabetes
Gingivitis/periodontitis
Hormonal Dysfunction
Quality-of-Life/Long Q-T wave
Rowan’s Vision for Next Decade

- ↑ enrollment from 12,200 to 25,000
- ↑ operating budget $350 M to $1B
- ↑ sponsored research $24 M to $100 M
- ↑ endowment $160 M to $500 M
Alzheimer’s Disease
Early Diagnosis at Mild Cognitive Impairment

Robert Nagele, Ph.D.
NJ Institute for Successful Aging
and
Department of Medicine
RowanSOM
Autoantibody production

1. Neurons die – which type of neurons depends on brain region affected
2. Dead neurons release their debris into the surrounding cerebrospinal fluid (CSF)
3. Debris enters bloodstream and activates the immune system
4. Immune system generates many autoantibodies to clear debris
5. We detect disease-specific autoantibodies as biomarkers

Alzheimer’s Disease - The First Test

Preparation and Processing

- Slide with human protein antigen targets
- Incubation with human serum
- Fluorescent-labeled secondary antibodies bind to autoantibodies
- Autoantibody biomarkers bind to targets
- Analysis of fluorescent signal patterns and detection of disease-specific autoantibody biomarkers

Sensitivity – 96.0%
Specificity – 92.5%

Nagele et al., 2011
Alzheimer’s Disease Results
Mild-moderate disease

1. Detected **451 autoantibodies** showing significantly higher prevalence in AD compared to controls (p < 0.01) – these are potentially useful as AD biomarkers.

2. Selected **the top 10 autoantibodies** showing the largest difference in group prevalence as our diagnostic indicators.

3. Using only the top 10 indicators, AD sera were distinguished from control sera with a **sensitivity of 96.0% and specificity of 92.5%**
Diagnosis of Alzheimer's Disease Based on Disease-Specific Autoantibody Profiles in Human Sera

Eric Nagele¹#, Min Han²³#, Cassandra DeMarshall²,
Benjamin Belinka¹, Robert Nagele³*

¹ Durin Technologies, Inc., New Brunswick, New Jersey, United States of America, ² Graduate School of Biomedical Sciences, School of Osteopathic
Applying the same strategy identifies autoantibodies as highly accurate diagnostic indicators for mild-moderate Parkinson’s disease (PD).

**Results:**

PD sera were differentiated from control sera with a 97.1% overall accuracy; sensitivity of 93.1% and specificity of 100%.
Detection of AD at the Mild Cognitive Impairment Stage

Our goal is to detect Alzheimer’s disease in earlier, MCI and pre-symptomatic phases

Alzheimer’s pathology is underway 8-10 years before symptoms appear

Early Detection Allows Early Treatment (prior to appearance of symptoms)

Currently funded by the Osteopathic Heritage Foundation
<table>
<thead>
<tr>
<th>MSU Portfolio of Research</th>
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<tbody>
<tr>
<td><strong>ALZHEIMERS &amp; DEMENTIA</strong></td>
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<td><strong>ASTHMA</strong></td>
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<tr>
<td><strong>BIOMECHANICS</strong></td>
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<td><strong>CARDIOVASCULAR</strong></td>
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<td><strong>EAR, NOSE, THROAT</strong></td>
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<td><strong>GENETICS</strong></td>
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<tr>
<td><strong>IMMUNOLOGY; INFECTIOUS DISEASES</strong></td>
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<tr>
<td><strong>MALARIA</strong></td>
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<tr>
<td><strong>NEUROSCIENCE</strong></td>
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<td><strong>NUTRITION &amp; OBESITY</strong></td>
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<td><strong>STEM CELL</strong></td>
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<td><strong>DMC RESEARCH</strong></td>
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Expanding Osteopathic Research to Address 21st Century Medical Needs

Andrea Amalfitano DO, PhD, FABMG
Osteopathic Heritage Foundation
Professor of Pediatrics, Microbiology and Molecular Genetics
College of Osteopathic Medicine
Michigan State University
POMPE DISEASE

• Synonyms
  – Glycogen storage disease type II (GSD-II)
  – Acid maltase deficiency (AMD)
  – Glycogenosis, type II
POMPE DISEASE - PULMONARY

- Respiratory distress/insufficiency
  - Arterial blood gas
  - Sleep studies
- Infections
- Ventilator support
  - Avoid Trach!
  - Prefer:
    nighttime/
    daytime IPPV

Why not GENE THERAPY?
Adenovirus as a “work-horse” gene transfer vector:

Your favorite gene
ClinicalTrials.gov
Identifier: NCT01147965

A Phase I/II Study of Active Immunotherapy With Ad5[E1-,E2b-]-CEA Vaccine in Patients With Advanced or Metastatic Malignancies Expressing CEA

The Expanding DO/PhD Training Program

MSUCOM program to train Osteopathic medical students from non-MSU COMs to become physician scientists through the MSUCOM DO-PhD Program.
Virginia COM Research

- Mild Traumatic Brain Injury
- Congestive Heart Failure
- Microbiology and nanoparticles
- Diseases caused by free radicals
- Environment on neonatal health
Research In Osteopathic Manipulative Medicine
Journal Publication Record for OMM Research

![Bar chart showing the number of publications from 1945 to 2012, with categories for JAOA and non-JAOA publications.](chart)

- **# of publications**
- **JAOA**
- **non-JAOA**

- **45-49**
- **50-59**
- **60-69**
- **70-79**
- **80-89**
- **90-99**
- **2000-2009**
- **2010-2012**
Projection for Publication Productivity

No. Clinical Articles Published

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<thead>
<tr>
<th>Year Range</th>
<th>Number of Articles</th>
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<tr>
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<td>150</td>
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<tr>
<td>2010-2019</td>
<td>250</td>
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Scope of Research in OMM
MUSCULOSKELETAL & NEUROLOGICAL PAIN DISORDERS RESEARCH DIVISION

• Aims to elucidate the causes, effects, and psychological aspects of musculoskeletal and neurological pain disorders.
• Mechanistic research
• Clinical trials
  – orthopedics, pain management, behavioral medicine, and rehabilitation medicine

HEALTHY AGING RESEARCH DIVISION

• Aims to understand the biologic mechanisms behind reductions in neuromuscular and musculoskeletal form and function in seniors.
• Determine the effectiveness of pharmacologic and non-pharmacologic interventions designed to promote physical function in seniors.
• Develop innovative techniques to more accurately quantify bone fragility.
University of North Texas Health Sciences

- Systematic reviews of the literature, conducts population-based surveys and analyzes national health care databases to determine the unique practice characteristics of osteopathic physicians.

- Largest study on spinal manipulation (NIH: K24 AT002422) from the National Institutes of Health-National Center for Complementary and Alternative Medicine

- Evaluate the effectiveness of osteopathic manipulative treatments (OMT) at modulating the immune response during infection, inflammatory diseases and cancer. 
  *NIH: U19 AT002023, R01 AT004361, AOA: 06-11-547, 08-11-573*
• Osteopathic Manual Treatment and Ultrasound Therapy for Chronic Low Back Pain: A Randomized Controlled Trial

• doi: 10.1370/afm.1468 Ann Fam Med March/April 2013 vol. 11 no. 2 122-129
OSTEOPATHIC Trial

• **METHODS:** A randomized, double-blind, sham-controlled study evaluating OMT and UST for nonspecific chronic low back pain. The 455 patients were randomized to OMT (n = 230) or sham OMT (n = 225) main effects groups, and to UST (n = 233) or sham UST (n = 222) main effects groups. Six treatment sessions were provided over 8 weeks.

• **CONCLUSIONS** The OMT regimen met or exceeded the Cochrane Back Review Group criterion for a medium effect size in relieving chronic low back pain. It was safe, parsimonious, and well accepted by patients.
OMT: Otitis Media
Cranial Osteopathic Manipulation in Recurrent Otitis Media

Study Flow Chart

- **Charts screened for episodes**

- **Eligible?**
  - Yes: Consent?
  - No: Exclusion Log

- **Consent?**
  - Yes: Audiology
  - No: Exclusion Log

- **Randomize**

- **OMT**
  - Initial OMT evaluation followed by 9 visits
    - 3 approximately weekly
    - 3 approximately biweekly
    - 3 approximately monthly
  - Final visit: + audiology + OMT Evaluation

- **Control**
146 patients referred
- 102 met criteria
- 44 failed criteria
- 26 refused
- 76 accepted
  - 31 OMT
  - 45 controls
    - 6 dropouts
    - 19 dropouts
    - 25 OMT participants
    - 32 control participants
Results

Average Monthly Episodes of Otitis Media
Change Over Time - one mo washout

Average Monthly Antibiotic Prescriptions
Change Over Time - one mo washout
Ear-related Surgery

- 8 control patients
  @ 2 months for 2
  @ 3 months for 4
  @ 4 months for 1
  @ 6 months for 1

- 1 treatment patient
  @ 6 months

\[ P = .03 \]
Baseline Hearing in Decibels

Final Hearing in Decibels
Overview of Significant Results

• Prospective, randomized, physician blinded
• 32 non-OMT + routine care; 25 OMT + routine care
• Fewer average episodes AOM (p=.04)
• 1/25 OMT; 8/32 non-OMT got “tubes” (p=.03)
• Longer average surgery-free months (p=.01)
• More normal tympanograms (a+c), p=.02
Implications

• “..suggests that OMT served a beneficial purpose” (Pichichero, Arch Ped Adol Med 2003;157:852-3)
Therapeutic Goals of Osteopathic Manipulation

- Improve rib cage and diaphragm dynamics
- Relieve tissue tension around nerve structures
- Improve circulation

Research Design
Non-Healthcare-Associated Community-Acquired Pneumonia Subgroup Analysis

Subjects (n=306)
- Osteopathic Manipulative Treatment (OMT) Group (n=105)
- Light-touch (Sham) Treatment (LT) Group (n=98)
- Conventional Care Only (CC) Group (n=103)
Antibiotic Use

- Compliance with IDSA & ATS Consensus Guidelines
  - 2000/2003: 87%
  - 2007: 96%
- Not significantly different between groups (P=0.71)
- Not related to age (P=0.21) and Pneumonia Severity Index class (P=0.76)
Subjects (n=306)

OMT Group (n=105)
- Twice daily
- 7 days a week
- 15 min duration

LT Group (n=98)

CC Group (n=103)

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Community-acquired pneumonia subgroup analysis
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CC Group (n=103)

Research Design
Community-acquired pneumonia subgroup analysis
82 Treatment Providers

- 20 Osteopathic Neuromusculoskeletal Medicine / OMT Specialists

- 62 Residents
  
  12 residencies
  
  - Emergency Medicine
  - Family Medicine
  - Family Medicine / ONM
  - General Surgery
  - Internal Medicine
  - Internal Med / Emergency Med
  - Interns
  - Obstetrics and Gynecology
  - Orthopedic Surgery
  - ONM
  - PM&R
  - Psychiatry
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Outcomes:
1) Length of Hospitalization
2) Adverse Events

Age groups (years)
- 50-74
- ≥75
Palpatory Skills & Diagnosis
A Century of OMM Teaching

- Present background information
- Demonstrate Techniques
A Century of OMM Teaching

• Present background information
• Demonstrate Techniques
• Independent practice of techniques
Thoracic Pump with Activation

- Hands are placed on the subjects’ anterior, superior portion of the rib cage.
- During exhalation, physicians apply a rapid alternating pressure - rate of approximately 120 compression/relaxation cycles/minute on chest wall.
- Some pressure is maintained while the patient inhales. Pressure on patients’ chest cage increases with each successive exhalation, and it is sustained with the subsequent inhalation.
- At approximately the first one-third to one half of the inhalation, the physicians briskly remove their hands from the rib cage.
TP Pressure Processing
Group Data

Baseline: 982 N (932-1033)
Peak: 1697 N (1674-1721)
Midpoint: 2.7 secs (2.1-3.3)
Slope: 70 N/sec (59-80)
Clinician Researcher Development Program
Established 2009
Goals

• To provide meaningful research experiences to students

• To develop and establish an on-going program that will support the development of future clinicians and the progress of current research.

• To train clinicians who will actively engage and provide leadership in clinical research as a regular aspect of their clinical practice.

• To train clinicians who will have the foundation to become leaders in directing evidence-based healthcare in America
Overview of Program:

• Two Entry Points
  – Undergraduate students
  – ATSU graduate students

• Two Time Periods
  – Summer Program
  – Academic year program
Undergraduate Students

- Experience equivalent to approximately 200 hours
- Work within an established research team
- Attend weekly meetings where updates and strategic planning occurs
- Attend workshops
- Given specific assigned projects and timelines
- Presentation of work
- Funded spots are limited
ATSU Students

- **Level I: SRI Intern**
  - Undergraduate

- **Level II: Assistant Clinical Research Extern**
  - Second year intern and first or second year ATSU student
    - greater responsibility within a project.

- **Level III: Associate Clinical Research Extern**
  - Upper class (3rd or 4th years in clinical rotations)
    - Individualized projects with more self-directed training

- **Level IV: Clinical Research Postdoctoral Fellow**
Participants

- 31 Interns
- 21 Undergraduates from 5 states
- 10 ATSU students within KCOM
Osteopathic Medicine
Reform movement

Integrated throughout healthcare specialties & facilities

Optimizing intrinsic healing processes

Research

Primary Care

Holistic Medicine

Prevention

Osteopathic Medicine

Fastest growing healthcare profession

Manipulative Medicine
Thank you!!

Any Questions?