10th ANNUAL RESEARCH DAY
April 28th, 2011
ABSTRACT BOOK
We are grateful to Ms. Claire Trias for her outstanding organization and professionalism, without which this event would not be possible.

We are grateful to Touro University-CA for support, Mr. Ralph Cuberos, Mr. Alex Perez, and the Facilities, Information Technology, and Food Services Departments.

The COM Research Department wish to acknowledge the following vendors for their generous support:

A. Gugliucci, MD, PhD
Professor of Biochemistry and Associate Dean for Research
KEYNOTE

12:00 P.M. - 1:00 P.M.

LECTURE HALL A
KEYNOTE SPEAKER

Piotr B. Kozlowski MD, PhD, FCAP
Dean of Research and Professor of Pathology
Touro COM New York, NY

Title of Presentation:
"Introduction to Grant Writing, Part 1: Tame Your Inner Critic"

Dr. Kozlowski received his Doctorate of Medicine degree from the Warsaw Academy of Medicine in 1973 and his PhD in Clinical Neuropathology from the Polish Academy of Sciences in 1979. He was trained in general pathology and neuropathology in the Warsaw Academy of Medicine and later in Anatomic, Clinical and Neuropathology at Downstate Medical Center in Brooklyn, New York. He is board certified in Anatomic Pathology and Neuropathology. He has been a program director at the NIH Institute for Neurological Disorders and Stroke in Bethesda, Maryland and the Director of the Institute for Basic Research in Staten Island, New York. He joined Touro College of Osteopathic Medicine in New York in 2007, first as a founding Pre-Clinical Dean and later as a Dean of Research. Presently, Dr Kozlowski is the Professor of Pathology and Dean of Research at TouroCOM New York.
# POSTERS BY DISCIPLINE

## BASIC SCIENCES

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<td>(1) Touro University - California, College of Pharmacy, Vallejo, California (2) Buck Institute for Age Research, Novato, California (3) University of California at San Francisco, San Francisco, California</td>
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<td>1. Department of Pathology, Louisiana State University–Health Sciences Center, Shreveport, LA. 2. Department of Basic Sciences, College of Osteopathic Medicine, Touro University of California, Vallejo, CA. 3. Department of Cellular Biology &amp; Anatomy, Louisiana State University–Health Sciences Center, Shreveport, LA. 4. Department of Biological Sciences, College of Pharmacy, Touro University of California, Vallejo, CA.</td>
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<td>1. Touro University California, College of Pharmacy, Vallejo, CA 94592.</td>
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<td>1. Public Health Program, College of Education and Health Sciences, Touro University-CA 2. Master’s Program in Graduate Health Sciences and Department of Basic Science, College of Osteopathic Medicine, Touro University-CA</td>
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<td>1. Touro University-California, Basic Sciences Department, Mare Island, Vallejo, California 2. Touro University-California, Information Technology Department, Mare Island, Vallejo, California</td>
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<td>¹College of Pharmacy, Touro University, Mare Island-Vallejo, California ²Metabolomics Core Facility, Genome Center, University of California, Davis, California</td>
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¹Touro University - California, Vallejo, CA

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Russell Caccavello¹, Alejandro Gugliucci ¹
¹Glycation, Oxidation and Disease Laboratory, College of Osteopathic Medicine, Department of Basic Sciences, Touro University-California, Vallejo, USA

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K. Pareja, K. Murphy, B. Olkiewicz, A. Anderson, and A. Miller¹
¹Touro University - California, Vallejo, CA.

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¹Touro University-California, College of Osteopathic Medicine, Vallejo, CA
²University of California San Francisco, San Francisco, CA
³University of California Berkeley College of Letters and Science, Berkeley, CA

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¹1. Touro University, College of Pharmacy, Vallejo, CA.

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²Department of Basic Science, Touro University-California, Vallejo, CA 94592
³Department Of Pharmaceutical Chemistry, University of California San Francisco, CA 94143
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Alison McCormick¹ Jan Kemnade² and David Spencer²
1. Touro University California, College of Pharmacy, Vallejo, CA.
2. Baylor College of Medicine, Department of Immunology, Houston TX

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A. Gugliucci, R. Caccavello, J. Massa, and G.J. Klapstein
Department of Basic Sciences, Touro University-California, Vallejo, USA

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Department of Basic Sciences, Touro University-California, Vallejo, USA

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*Primary Authors. Touro University-CA, Vallejo.

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Melanie Southard, OMS III¹, Patricia Hiserote, D.O.¹, Jeff Belkora, PhD², Kara Gabriel, PhD³, Jennifer Ferrell, D.O¹
1. Touro University College of Osteopathic Medicine, Vallejo, CA.
2. University of California, San Francisco
3. Central Washington University, Ellensburg, WA.

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Christopher Engdahl (MSMHS 2011), Russell Caccavello, Satoshi Kimura, and Alejandro Gugliucci
¹Glycation, Oxidation and Disease Laboratory, College of Osteopathic Medicine, Department of Basic Sciences, Touro University-California, Vallejo, USA.
²Department of Laboratory Medicine and Central Clinical Laboratory,
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² KMT Shirati Hospital Research Center, Shirati, Tanzania | 30   |
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¹ College of Osteopathic Medicine and College of Pharmacy, Touro University-California, Vallejo, CA  
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³ Department of Radiology and Biomedical Imaging, University of California, San Francisco; China Basin, CA | 34   |
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¹Touro University-California, Vallejo, CA, USA. College of Osteopathic Medicine. Glycation, Oxidation, and Disease Laboratory ²Department of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke-City, Tochigi, Japan. | 35-36 |
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<td>J. M. Schwarz¹²</td>
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**OSTEOPATHIC MANIPULATIVE MEDICINE**

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<td>Athena Lin¹²</td>
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<td>¹Department of Osteopathic Manipulative Medicine, Touro University</td>
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<td>New England College of Osteopathic Medicine, Biddeford, ME</td>
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<td>Jonathan Mongold OMS III</td>
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John Glover, DO, Touro University-California College of Osteopathic Medicine;  
Paul Rennie, DO, Touro University-Nevada College of Osteopathic Medicine;  
Heather Ferrill, DO, University of New England College of Osteopathic Medicine;  
William F. Morris, DO, A.T. Still University-School of Osteopathic Medicine Arizona;  
ABSTRACTS BY COLLEGES

College of Education and Health Sciences

B-4 Assessing the role of CASPASE-12 alleles in African-Americans with rheumatoid arthritis
Laura Marshall1 Mohammad Obaidullah2, Evan Hermel2 and Kevin D. Klapstein1
1. Public Health Program, College of Education and Health Sciences, Touro University-CA
2. Master’s Program in Graduate Health Sciences and Department of Basic Science, College of Osteopathic Medicine, Touro University-CA

C-4 Heart Disease: How Insurance Helps, or Does It? Analysis of Two Northern California Counties: Napa and Solano County Heart Disease Rates and the Correlation to Current Health Insurance Status
Dawn Krytusa, R.N.1, Wesley (Brian) Lashbrook1
1. Touro University-CA, Vallejo, CA.

College of Pharmacy

B-1 Human Embryonic Stem Cells Express a Unique Repertoire of Bcl-2 Family Members
David T Madden(1,2), Jimena Davila(2), Krysta Felky(2), Simon Melov(2), Dale E. Bredesen(2,3)
(1) Touro University - California, College of Pharmacy, Vallejo, California
(2) Buck Institute for Age Research, Novato, California
(3) University of California at San Francisco, San Francisco, California

B-2 Overexpression of the Tumor Suppressor Gene CST6 Leads to Reduced Tumor-Induced Angiogenesis
Christopher G. Kevil1, Shayne C. Barlow1, Athena W. Lin2, and Daniel Keppler3, 4
1. Department of Pathology, Louisiana State University–Health Sciences Center, Shreveport, LA.
2. Department of Basic Sciences, College of Osteopathic Medicine, Touro University of California, Vallejo, CA. 3. Department of Cellular Biology & Anatomy, Louisiana State University–Health Sciences Center, Shreveport, LA. 4. Department of Biological Sciences, College of Pharmacy, Touro University of California, Vallejo, CA.

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Hardeep Kaur and Alison McCormick
1. Touro University California, College of Pharmacy, Vallejo, CA 94592.

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Kevin Ita1, Nanik Hatsakorzhian1, Vladimir Tolstikov2
1College of Pharmacy, Touro University, Mare Island-Vallejo, California
2Metabolomics Core Facility, Genome Center, University of California, Davis, California
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Sherri Wykoff-Clary¹, Alison McCormick¹,  
1. Touro University, College of Pharmacy, Vallejo, CA.

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VanishreeRrajagopalan¹, Shengquan Liu¹, Maxwell Murphy², H Michael Ellerby¹  
1. Touro University-College of Pharmacy, Vallejo, CA, 2. Buck Institute for Research on Aging, Novato, CA.

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Alison McCormick¹ Jan Kemnade² and David Spencer²  
1. Touro University California, College of Pharmacy, Vallejo, CA. 2. Baylor College of Medicine, Department of Immunology, Houston TX

College of Osteopathic Medicine

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1. Touro University-California, Basic Sciences Department, Mare Island, Vallejo, California, 2. Touro University-California, Information Technology Department, Mare Island, Vallejo, California

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College of Osteopathic Medicine, Touro University-CA, Vallejo, CA.

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V. Makhijani¹, A. Macrito¹, K. Pareja¹, E. Thara, N. Logemann¹, and A. Miller¹  
1. Touro University - California, Vallejo, CA

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Angela Veh (OMS2), Behnam Vahdati Nia (OMS1), Daniel Lim (OMS1), Amir Ali Sarkeshik (MSHMS), and Shin Murakami.  
Department of Basic Sciences, College of Osteopathic Medicine, Touro University-California, CA.

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Fayha Lakhani, Tamira Elul  
College of Osteopathic Medicine, Touro University-CA, Vallejo, CA.
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Russell Caccavello 1, Alejandro Gugliucci 1
1 Glycation, Oxidation and Disease Laboratory, College of Osteopathic Medicine, Department of Basic Sciences, Touro University-California, Vallejo, USA

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K. Pareja, K. Murphy, B. Olkiewicz, A. Anderson, and A. Miller 1
1 Touro University-California, Vallejo, CA.

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S. Lin 1, A. Dyachenko 1, R. Caccavello 1, M. Wen 2, B. Shan 3, A. Gugliucci 1, J-M. Schwarz 1,2
1 Touro University-California, College of Osteopathic Medicine, Vallejo, CA
2 University of California San Francisco, San Francisco, CA
3 University of California Berkeley College of Letters and Science, Berkeley, CA

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Guangyan Zhou a, Zhuangwu Li a, Dong Wu a, and Miriam Gochin a,b
a Department of Basic Science, Touro University-California, Vallejo, CA 94592
b Department of Pharmaceutical Chemistry, University of California San Francisco, CA 94143

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A. Gugliucci, R. Caccavello, J. Massa, and G.J. Klapstein
Department of Basic Sciences, Touro University-California, Vallejo, USA

Neuronal ischemic sensitivity in a transgenic mouse model of Alzheimer's Disease
Department of Basic Sciences, Touro University-California, Vallejo, USA

The effect of community-based student-initiated projects in reducing incidence of schistosomiasis through treatment and health education in rural Tanzania.
Duong J*, Rosenblatt R*, Bireley B, Macrito A, Rocchi V, and Mahmoud E.
*Primary Authors. Touro University-CA, Vallejo.

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Melanie Southard, OMS III1, Patricia Hiserote, D.O.1, Jeff Belkora, PhD2,
Kara Gabriel, PhD3, Jennifer Ferrell, D.O1
1 Touro University College of Osteopathic Medicine, Vallejo, CA.
2 University of California, San Francisco
3 Central Washington University, Ellensburg, WA.

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1 Glycation, Oxidation and Disease Laboratory, College of Osteopathic Medicine,
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Alejandro Gugliucci¹, Kazuhiko Kotani¹,²,³, Russell Caccavello¹
¹ Glycation, Oxidation and Disease Laboratory, Department of Basic Sciences, Touro University-California, Vallejo, USA ² Department of Laboratory Medicine and Central Clinical Laboratory, Showa University Northern Yokohama Hospital, Tsuzuki-ku, Yokohama City, Japan ³ Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto 612-8555, Japan

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Garima Gupta, MPH OMS II; Alicia Walker, OMS II; James E. Foy, D.O. FACOP Touro University-CA, Vallejo, CA.

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Kazuhiko Kotani¹,²,³, Russell Caccavello², Naoki Sakane³, Toshiyuki Yamada¹, Alejandro Gugliucci²
¹ Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto 612-8555, Japan ² Department of Clinical Laboratory Medicine, Jichi Medical University, Tochigi 329-0498, Japan ³ Glycation, Oxidation and Disease Laboratory, Touro University-California, CA 94592, USA

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Peter Baginsky¹, Megan Jolicoeur¹, Lori Hurlbert¹, Jonathan Revels¹
¹ Touro University-CA, Vallejo, CA

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Russell Caccavello², Kazuhiko Kotani³, Michiaki Miyamoto³, Shun Ishihashi³, Nobuyuki Taniguchi³, Alejandro Gugliucci³
² Glycation, Oxidation and Disease Laboratory, Touro University-California, Vallejo, CA, USA ³ Department of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke-City, Tochigi, Japan

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A. Hench¹, J. Hoppe¹, M. Sullivan¹, J. Magatti², E. Mahmoud¹
¹ College of Osteopathic Medicine, Touro University-California, Vallejo, USA ² KMT Shirati Hospital Research Center, Shirati, Tanzania
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Alejandro Gugliucci 2, Kazuhiko Kotani 1,2,3, Russell Caccavello 2, Kokoro Tsuzaki 3, Naoki Sakane 3, Toshiyuki Yamada 1  
1 Department of Clinical Laboratory Medicine, Jichi Medical University, Tochigi, Japan  
2 Glycation, Oxidation and Disease Laboratory, Touro University-California, CA, USA  
3 Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

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A. Dyachenko 1, S. Patel 1, A. Pham 1, D. Tang 1, S. Lin 1, M. Wen 2, J. M. Schwarz 1,2  
1 Touro University-California College of Osteopathic Medicine, Vallejo, CA  
2 University of California San Francisco, San Francisco, CA

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Alejandro Gugliucci 1, Teresita Menini 1, Kazuhiko Kotani 2, Ricardo Hermo 1, Russell Caccavello 1  
1 Glycation, Oxidation and Disease Laboratory, College of Osteopathic Medicine, Department of Basic Sciences, Touro University-California, Vallejo, USA  
2 Department of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke-City, Tochigi 329-0498, Japan

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A. Pham 1, A. Dyachenko 1, M. Wen 2, M. Rao 2, K. Mulligan 2, J. M. Schwarz 1,2, S. M. Noworolski 3  
1 College of Osteopathic Medicine and College of Pharmacy, Touro University-California, Vallejo, CA  
2 Department of Medicine, University of California, San Francisco; San Francisco General Hospital, CA  
3 Department of Radiology and Biomedical Imaging, University of California, San Francisco; China Basin, CA

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Alejandro Gugliucci 1, Kazuhiko Kotani 2, Russell Caccavello 1  
1 Touro University-California, Vallejo, CA, USA. College of Osteopathic Medicine. Glycation, Oxidation, and Disease Laboratory  
2 Department of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke-City, Tochigi, Japan.

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S. Patel 1, A. Dyachenko 1, S. Lin 1, A. Pham 1, D. Tang 1, M. Wen 2, J. M. Schwarz 1,2  
1 Touro University-California, College of Osteopathic Medicine, Vallejo, CA  
2 University of California San Francisco, San Francisco, CA

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A. Gugliucci 1, K. Kotani 1, R. Caccavello 1, T. Yamada 2 and I. Sakurabayashi 2  
1Touro University-California, USA, 2Jichi Medical School, Japan
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D. Tang¹, M. Wen², A. Dyachenko¹, B. Patterson³, J.-M. Schwarz¹,²
¹Touro University, Vallejo, CA
²University of California San Francisco, San Francisco, CA
³Washington University, St. Louis, MO

O-1 OMT and TCM: Comparisons of Manipulative Treatment
*Sophia Chen¹, *Angela Zhang¹, Hung-Rong Yen³, Janet M. Burns¹, Athena Lin¹,²
¹College of Osteopathic Medicine and ²Global Health Program, Touro University-California, Vallejo, USA³Chang-Gung Memorial Hospital, Gueishan Township, Taoyuan County 333, Taiwan (R.O.C.)
*Equally contributing authors

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R-c. Li, J. Hwang, L. Shultz, J. Burns and N. Garcia-Russell
Department of Basic Sciences, Touro University-California, Vallejo, CA

O-3 Osteopathic Medical Student (OMS) Use of Osteopathic Manipulative Treatment (OMT) During School Vacation: A Novel Educational Outcome Measure
Gregg Lund¹, Stacey Pearce-Talsma², R Mitchell Hiserote¹
¹Department of Osteopathic Manipulative Medicine, Touro University College of Osteopathic Medicine, Vallejo, CA ²Department of Osteopathic Manipulative Medicine, University of New England College of Osteopathic Medicine, Biddeford, ME

O-4 Embodying Osteopathy: Integrating Movement through Manual Medicine
Rebecca Wilson OMS V, Coral Peterson OMS V, Priya Shastry OMS IV, Jonathan Mongold OMS III
Touro University-California, Vallejo, CA.

O-5 Frequency of Counterstrain Tender Points in Osteopathic Medical Students: An Osteopathic Educational Research Project
Basic Sciences
Human Embryonic Stem Cells Express a Unique Repertoire of Bcl-2 Family Members.
David T Madden(1,2), Jimena Davila(2), Krysta Felky(2), Simon Melov(2), Dale E. Bredesen(2,3)

(1) Touro University - California, College of Pharmacy, Vallejo, California
(2) Buck Institute for Age Research, Novato, California
(3) University of California at San Francisco, San Francisco, California

Background: Roadblocks to human embryonic stem cell (hESC) based therapeutics include (1) the production of defined cell types at a scale required to meet clinical demand and (2) the limited survival of cells post-transplantation. Cell numbers are determined by the balance of the rates of division and of cell death: Strategies to improve growth could include boosting the rate of division or blunting the rate of cell death. We have focused our studies on the signals that drive hESCs to programmed cell death with the thought that understanding these pathways might well extend to post-mitotic preparations of cells intended for transplantation (e.g. hESC-derived neurons). The decision to die is regulated by a family of related proteins - the Bcl-2 family - that act at the level of the mitochondria. Within this group are molecules that either promote or inhibit cell death. Anti-apoptotic Bcl-2 family members include Bcl-2, Bcl-w, Bcl-xL, Bcl-B, Mcl-1, and A1. Pro-apoptotic Bcl-2 family members include Bax and Bak as well as a group of proteins known as the BH3-only Bcl-2 family which includes Bim, Bid, Puma, Noxa, Bad and others.

Methods: So as to determine which cell death pathways might be most active in hESCs relative to other cell types, we used quantitative PCR to evaluate the basal expression of all members of the Bcl-2 family in hESCs (TE06 and BG01), hESC-derived neural stem cells, seven human primary cell lines including representatives from each germ layer, and two cancer lines. Our hypothesis is that overly abundant Bcl-2 family member transcripts in hESCs would point toward apoptotic and/or anti-apoptotic signaling cascades that are especially active in hESCs. In addition to Bcl-2 family members, we assayed genes that are commonly used as markers of pluripotency and germ layers to serve as an internal control. (Nanog and SOX2 were found to be predominantly expressed by hESCs.)

Results: Our analysis revealed, surprisingly, that expression levels of the pro-apoptotic BH3-only Bcl-2 family members Puma and Noxa are elevated in hESCs compared to other cell-types. The fact that hESCs live while expressing relatively high amounts of the pro-apoptotic molecules Noxa and Puma was surprising; the fact that both Noxa and Puma are regulated by p53 peaked our interest.

Conclusions: What benefit does basal overexpression of Puma and Noxa afford hESCs? Is this expression p53-dependent? If so, what signals are p53 responding to? We hope to answer these and other questions in our future work; doing so should offer insight into the signaling pathways that govern cell survival - insight that undoubtedly will translate to the development of better conditions for both hESC expansion and promotion of cell survival post-transplantation.
Overexpression of the Tumor Suppressor Gene CST6 Leads to Reduced Tumor-Induced Angiogenesis.

Christopher G. Kevil¹, Shayne C. Barlow¹, Athena W. Lin², and Daniel Keppler³,⁴

¹. Department of Pathology, Louisiana State University–Health Sciences Center, Shreveport, LA. ². Department of Basic Sciences, College of Osteopathic Medicine, Touro University of California, Vallejo, CA. ³. Department of Cellular Biology & Anatomy, Louisiana State University–Health Sciences Center, Shreveport, LA. ⁴. Department of Biological Sciences, College of Pharmacy, Touro University of California, Vallejo, CA.

Background: In 2004, we identified CST6 as a novel tumor suppressor gene for breast cancer. This finding has been confirmed by several independent groups and extended to other types of cancers. Our group has further shown that the secreted CST6 gene product, cystatin E/M, was able to alter the gene expression profile of human breast carcinoma cells. In particular, CST6 overexpression led to a 70% reduction in expression of autotaxin, a potent angiogenic enzyme. In the present work, we tested the hypothesis that CST6 overexpression leads to reduced tumor-induced angiogenesis in mice.

Methods: Angiogenic human breast carcinoma MDA-MB-435S cells overexpressing CST6 or vector controls (1 x 10⁶ cells in 200 μL) were injected into Millipore diffusion chambers and implanted subcutaneously into mice. HBSS and VEGF were used as negative and positive controls, respectively. Angiogenic parameters, such as density, size and shape of microvessels in the dermis were measured after a two weeks incubation period. The cells were also analyzed using in vitro angiogenic assays and ELISAs for VEGF and bFGF.

Results: Vector-transfected MDA-MB-435S cells and VEGF elicited a robust angiogenic response, whereas CST6-transfected cells did not stimulate significant angiogenic activity. Ectopic expression of CST6 in MDA-MB-435S cells did not significantly alter production of VEGF or bFGF, and conditioned media from both vector- and CST6-transfected cells increased endothelial cell chemotaxis in vitro. However, conditioned media from CST6-transfected cells significantly attenuated endothelial cell invasion across a reconstituted basement membrane.

Conclusions: Together, these data demonstrate that CST6 preferentially affects tumor angiogenesis by attenuating endothelial cell invasiveness without altering the levels of VEGF and bFGF. We propose that CST6 may exert its tumor-suppressing activity in part through inhibition of tumor angiogenesis.
Uptake and localization of Tobacco Mosaic Virus (TMV) in mammalian dendritic cells.
Hardeep Kaur and Alison McCormick
1. Touro University California, College of Pharmacy, Vallejo, CA 94592.

Background: Virus like particles (VLPs) have gained significant attention in vaccine strategies over live viruses because of their low toxicity, mimicry to viruses, particulate nature and efficiency in cross-presentation of antigens to MHC I molecules. Although they have attractive characteristics, they are still not as efficient in immune induction as live viruses. Reduced immune efficiencies may be due to reduced cell binding, internalization and endosomal escape. So a better understanding of VLP mechanisms of uptake and intracellular trafficking could lead to a rational design of non-viral vectors. We have developed a VLP based on a plant virus, the Tobacco Mosaic Virus (TMV). This particle consists of Semliki Forest Virus (SFV)/RNA transcripts encapsidated by TMV coat protein. We used the nonstructural genes of SFV to drive expression of a vaccine antigen gene of interest. Our long term goal is to use this particle as a vaccine to deliver tumor antigens to immune cells, especially for cancer therapy. In the present study, we wish to study uptake and localization of this TMV particle in mammalian dendritic cells.

Hypothesis: We have observed that mammalian dendritic cells take up TMV by passive mechanisms, and after internalization traffic to acidic endosomal compartments. Our hypothesis is that TMV encapsidated RNA is trapped in endosomes, and this limits RNA translation of vaccine antigen genes. We will test whether conjugation of TMV to endosomal escape peptides will help move the TMV particle out of the endosome into the cytoplasm, in order to improve RNA translation characteristics of TMV VLP particles.

Methods: TMV was fluorescently labeled with Alexa 488, with or without co-conjugation to haemagglutinin (HA2), an endosomal escape peptide which undergoes conformational change at low pH in to facilitate the release of endosomal contents into the cytosol. Dendritic cells were incubated with labeled TMV-A488 or TMV-A488-HA2 for 4h. After exposure, the cells were washed and further incubated for 24h. The acidic vesicles were stained with Lysotracker red and the nuclei with DAPI. The cells were then analyzed by three color fluorescence microscopy.

Results: TMV-A488 was efficiently taken up by dendritic cells in vitro. After entry into the cells, it is co-localized with Lysotracker red in the acidic compartment. When conjugated with the endosomal escape fusion peptide (HA2), it is localized in both endosomal and cytoplasmic compartments.

Conclusions: We were able to regulate the cellular localization of TMV using endosomal escape peptides. Future studies will determine if improved cytoplasmic localization using the HA2 peptide conjugation will improve encapsidated RNA translation in DC’s, which should also improve vaccine efficacy.
Assessing the role of CASPASE-12 alleles in African-Americans with rheumatoid arthritis
Laura Marshall1 Mohammad Obaidullah2, Evan Hermel2 and Kevin D. Klapstein1
1. Public Health Program, College of Education and Health Sciences, Touro University-CA
2. Master’s Program in Graduate Health Sciences and Department of Basic Science, College of Osteopathic Medicine, Touro University-CA

Background: Except in rare cases, the functional CASPASE-12 (CASP12) gene in humans has been identified only in persons of African and Southern Indian heritage. CASP12 has been suggested to play contrasting roles in regulatory responses to bacterial pathogens, and in promoting susceptibility to sepsis by down-regulating the production of inflammatory cytokines, such as interleukin-1. Specifically, the CASP12 single nucleotide polymorphism (SNP) #rs497116 (ter124R) has been clinically associated with an increased risk of sepsis in African-Americans. However, if CASP12 in fact has an anti-inflammatory function, it may then be a protective factor against inflammatory disease. To test this hypothesis, we investigated the distribution of CASP12 in African-Americans (AA) with rheumatoid arthritis (RA).

Methods: The CASP12 SNP rs497116 was genotyped in 296 patients and 100 controls from the Consortium for Longitudinal Evaluation of African-Americans with Early Rheumatoid Arthritis (CLEAR Registry) via a PCR-based SNP assay. DNA from persons who genotyped as CASP12+ was sequenced to verify results. Statistical analyses were performed using the R statistical software program.

Results: We found no significant difference in the overall distribution of CASP12 genotypes within AA with RA. Of male patients who were homozygous for CASP12, there was an approximately eight-year earlier onset of disease than in female patients, but this difference was not statistically significant. However, the odds of CASP12 homozygosity were higher in the AA males with RA than in the controls (AA without RA). Finally, AA males with serologic markers for RA were more likely to be homozygous for CASP12 than controls.

Conclusions: Homozygosity for the CASP12 SNP rs497116 appears to be a risk factor for RA in male African-American patients.
Identifying and minimizing anatomy dissection laboratory information flow bottlenecks towards greater efficiency and student performance

Kenneth Hisley¹, David Eliot¹, Bruce Silverman¹, Kris Andrues¹, Julia Perhac², Jack Madderra²

¹. Touro University-California, Basic Sciences Department, Mare Island, Vallejo, California, ². Touro University-California, Information Technology Department, Mare Island, Vallejo, California

Background: We are exploring methods to increase student course execution efficiency, recall and performance on the practical exams by 1) identifying time-consuming bottlenecks in this flow retarding progress, and 2) providing for simultaneous projection of dissection status coupled with table-by-table flags for excellent anatomical structure presence.

Learning resources include a dissector, atlases and a list of anatomical structure names (termed the “lab list”). The learning process consists of following the dissector instructions detecting, finding and confirming structures included in the lab list using the atlases to guide them. Thus, any given laboratory session involves labor-intensive, time-consuming and cognitively-demanding task sequences involving original exploration, detection, identification and validation of structures based on a well-defined list of features in a very limited time period. We have identified two potential areas for investigation: 1) at the individual table level, given a lab list entry, the time and effort to find index references to and access relevant atlases plates—a critical learning tool—appears much higher than the other tasks facing students, and 2) at the “table group” level, a great deal of time is spent searching for tables with the best examples of dissected structures across all tables. Thus, Hypothesis 1: the addition of faculty-selected atlas plate indexes to each structure name in the lab list will minimize the time to finding correct anatomical structures at the individual table level as journalized and confirmed by faculty.

Hypothesis 2: simultaneous visual access to a dynamically-update laboratory table/lab list status display will increase learning efficiency as measured by improved laboratory practical examination grades.

Methods: We have chosen the pelvis-peritoneum-scrotum laboratory unit to test our theories. The students are usually divided into three equal groups assigned to different days. Group A will be our control group without any changes in lab list or faculty progress checking, Group B will be issued a modified lab list with the addition of relevant atlas plate numbers assigned to each required anatomical structure name and existing faculty progress checking, and Group C will use the existing lab list but with the addition of faculty progress dynamic real-time journaling using mobile tablet/transactional database updates culminating in real-time table status video display visible to the entire group. The use of this database technology will require close coordination for Information Technology Department to ensure campus data security and data traffic support levels. This initial effort will compare and contrast the laboratory practical scores for the pelvis-peritoneum-scrotum lab unit across the three groups by using paired t-tests.

Expected Results: We expect Group A to reflect mean exam scores for this unit accumulated for the past 5 years, Group B to exhibit significant score increases in individual and small student groups, and Group C will show a significant increase in the total class lab practical exam grades.
Liquid chromatographic-tandem mass spectrometric determination of atenolol following transdermal administration
Kevin Ita¹, Nanik Hatsakorzian¹, Vladimir Tolstikov²
¹College of Pharmacy, Touro University, Mare Island-Vallejo, California
²Metabolomics Core Facility, Genome Center, University of California, Davis, California

Background: Although high-performance liquid chromatography is widely used for drug quantitation following transdermal application, low drug concentrations justify the development of alternative techniques to improve sensitivity, precision and accuracy. In the present study, a liquid chromatography-tandem spectrometric method was developed for analysis of atenolol following transdermal administration.

Methods: An LC-MS/MS technique was developed for quantitative determination of atenolol following transdermal administration through porcine ear skin. Atenolol transcutaneous flux, determined using the developed LC-MS/MS technique, was 1.8ng/ml/h/cm²

Results: No interfering peak was observed. The chromatograms were free from endogenous matrix interference with atenolol retention time at 1.47min. The present LC-MS/MS method offered a lower limit of quantitation (LLOQ) of 0.1ng/ml.

Conclusions: An LC-MS/MS method was developed and validated for atenolol assay. The method is rapid, sensitive and specific with an LLOQ of 0.1ng/ml. This technique was successfully used to monitor atenolol following transdermal administration across porcine ear skin. It was possible to detect atenolol in the receptor compartment of a flow through cell after 2 hours.
**Wnt and Cadherin factors coordinate to regulate turning behaviors of optic axons and their growth cones in vivo**

Brittney Dautremont, Megan Jolicoeur, Ranjeeta Singh, Andrew Wiley, Michelle Mora and Tamira Elul

College of Osteopathic Medicine, Touro University-CA, Vallejo, CA.

**Background:** Coordination of Wnt with Cadherin signaling likely shapes developing neuronal circuits but the underlying mechanisms are not well understood. Here, we examined whether β-catenin mediates a specific transcription-independent interaction between Wnt and Cadherin downstream factors to pattern pathfinding behaviors of optic axons that steer them toward their target.

**Methods:** We injected GFP-tagged mutants that disrupt β-catenin interactions with Wnt and Cadherin pathway effectors into individual optic neurons in developing embryos. High resolution widefield fluorescence microscopy was then used to image their axons and growth cones navigating towards the target in intact, whole brains taken from young tadpoles. We then quantified left-right patterning or asymmetries in pathfinding behaviors of optic axons and growth cones that steer them specifically towards the optic tectum.

**Results:** Mutants that perturb interactions of β-catenin with the Wnt factor GSK3β and the Cadherin/actin molecular switch α-catenin both abolished left-right patterning in pathfinding behaviors of optic axons in vivo. Specifically, these mutants abolished left-right asymmetries in defasciculation and undulation, as well as in the distribution of filopodial and lamellipodial protrusions in growth cones of optic axons. A transcription (Tcf/LEF) inhibiting mutant of β-catenin did not alter patterning in these axonal pathfinding behaviors.

**Conclusions:** These results suggest that Wnt signals function, in a transcription independent manner, to regulate β-catenin-α-catenin interactions in the Cadherin pathway that pattern optic axon and growth cone pathfinding behaviors as they navigate towards the optic tract. This data supports the idea that a gradient in an non-transcriptional integrated Wnt/Cadherin pathway may normally pattern optic axonal and growth cone behaviors in the optic tract.
Interactions of extracellular potassium, calcium and hydrogen with the potassium channel HERG.

V. Makhijani¹, A. Macrito¹, K. Pareja¹, E. Thara, N. Logemann¹, and A. Miller¹
1. Touro University - California, Vallejo, CA

**Background:** The human ether a-go-go related gene (HERG) encodes a potassium channel that is important in the repolarization of the action potential. HERG is found in a number of tissues, including the brain and the heart. A reduction in the number of cardiac HERG channels has been implicated in Long QT Syndrome, which in some cases can degenerate into the lethal arrhythmia Torsades de Pointes. Many patients present with abnormal serum electrolyte levels due to a variety of conditions including gastrointestinal dysfunction, renal and endocrine disorders, diuretic use, alcoholism, and aging. Changes in extracellular electrolytes and extracellular pH have been shown to reduce HERG channel function and may act at the outer pore of the channel to block the channel. It is not clear if the permeant ion (i.e. potassium) can influence current reduction by other extracellular electrolytes and extracellular pH.

**Methods:** Experiments were performed using two-electrode voltage clamping of Xenopus oocytes expressing wild-type HERG. cRNA of WT HERG was injected into enzymatically defolliculated oocytes and currents recorded 1-5 days after injection.

**Results:** Increasing extracellular calcium from 0.1 mM to 10 mM as well as decreasing extracellular pH from 7.0 to 6.0 resulted in a greater decrease in HERG current when extracellular potassium was reduced from 20 mM to 0 mM. Additional experiments showed that the decrease in current due to increasing calcium was different at different extracellular pH. The Drosophila voltage-gated potassium channel, *Shaker*, showed a smaller decrease in current by extracellular calcium which was not dependent on extracellular potassium.

**Conclusions:** Although the mechanism by which both extracellular calcium and extracellular pH reduce current through HERG channels is not clear, one plausible explanation is pore block by these cations. The results presented here suggest that potassium, calcium, and hydrogen may interact at the outer mouth of HERG such that block of HERG by calcium and hydrogen depends on the concentration of other extracellular cations. There is evidence that the outer mouth of the HERG channel is different than other voltage-gated potassium channels and thus these interactions may be unique to the HERG channel. This study has implications for an increased risk of cardiac arrhythmias in patients with hypokalemia.
Oxidative stress and toxicity of the sod-4 extracellular superoxide dismutase mutation in C. elegans: an implication for evolutionary theories of aging

Angela Veh (OMS2), Behnam Vahdati Nia (OMS1), Daniel Lim (OMS1), Amir Ali Sarkeshik (MSHMS), and Shin Murakami.

Department of Basic Sciences, College of Osteopathic Medicine, Touro University-California, CA.

Background: The principle of the evolutionary theories of aging is that the force of natural selection diminishes late in life. Based on the principle, two popular theories of aging predict the genes that contribute to aging. The mutation accumulation theory predicts accumulation of the genes (or mutations) with late harmful effects. The antagonistic pleiotropy theory predicts a similar but more focused set of the genes that have early beneficial effects at the cost of late harmful effects (referred to as pleiotropic genes).

Methods: An in vivo imaging for ROS was developed and used for genetic screening for mutants that can increase ROS. Lifespan assays and general worm procedures were also used.

Results: Using genetic screening combined with in vivo imaging analysis for reactive oxygen species (ROS), we have identified the sod-4 mutation. The sod-4 gene is the only C. elegans gene for extracellular superoxide dismutase (EC-SOD), which can scavenge deleterious reactive oxygen species (ROS). Mutations in sod-4 caused embryonic lethality, delayed development and reduced fertility. Surprisingly, the sod-4 mutant showed increased lifespan during adult phase.

Conclusions: It was concluded that inactivation of sod-4 show unusual antagonistic pleiotropy, that is, early deficits and late life extension. Since recent results questioned the role of age-related oxidative stress in aging, this study offers a first step for more detailed understanding of oxidative stress and aging.
Filopodial and Lamellipodial Interaction in Axon Guidance and Growth Cone Directionality

Fayha Lakhani, Tamira Elul
College of Osteopathic Medicine, Touro University-CA, Vallejo, CA.

Background: Axon development relies on the pathfinding abilities of the growth cone, which is a dynamic structure at the tip of the growing axon. The route that the growth cone takes involves steering maneuvers via signaling pathways at the growth cone cytoskeleton. The interactions between microtubules and actin filaments, which make up filopodia and lamellipodia, are important for axon growth and growth cone turning. Here, we examined the relationship between filopodia and lamellipodia in growth cone pathfinding and motility.

Methods: We used an in vivo time-lapse video of retinotectal axon pathfinding in Xenopus Laevis made by Sonia Witte, Cambridge University, to quantify the interaction between filopodia and lamellipodia and growth cone directionality. We measured the length/width of the growth cone to determine the relationship between filopodia and lamellipodia. In addition, we measured the angle of the axon as it developed to determine the correlation of directionality with filopodia or lamellipodia.

Results: Our observations and measurements of L/W ratio for growth cones indicate that there is an antagonistic relationship between filopodia and lamellipodia. As a filopodia protrudes out from the growth cone, a lamellipodia retracts. Also, the growth cone spends different amounts of time in filopodial or lamellipodial morphology. Specifically, we found that the growth cone spends more time in the lamellipodial morphology than the filopodial morphology. Additional observations show that there is a bias in direction of both filopodial and lamellipodial extension that correlates with the direction of the growth cone motility.

Conclusions: The interaction of filopodia and lamellipodia allows the growth cone to progress and reach its target. Filopodia likely respond to guidance cues by stabilizing when they encounter an attractive guidance molecule or by retracting on contact with a repellent guidance molecule. The intracellular cues sensed by the filopodia facilitate the directionality of the growth cone. Lamellipodia appear to be the actual motor portion of the cell that then acts to pull the cell forward during the process of axon migration. These data provide basic kinematic measurements of optic axonal growth cone motility in vivo for future studies involving molecular and biomechanical perturbations.
Towards a functional assay of HDL subclasses: A new method to simultaneously analyze HDL subclasses, their paraoxonase activity and their apolipoprotein composition

Russell Caccavello¹, Alejandro Gugliucci ¹

¹Glycation, Oxidation and Disease Laboratory, College of Osteopathic Medicine, Department of Basic Sciences, Touro University-California, Vallejo, USA

Background: Alterations in plasma apolipoproteins levels can influence the composition, content, and distribution of plasma lipoproteins that affect the risk of atherosclerosis. PON-1 is a promiscuous esterase carried by HDL, which protects LDL from oxidation and decreases homocysteine-thiolactone damage via its lactonase activity, which is considered the physiological, cardioprotective function of PON1. Different HDL subclasses have been linked to different degrees of cardioprotection. Little is known about the distribution of PON1 across HDL subclasses.

Aims of this study: To develop a method to analyze PON1 activity in different HDL subclasses and correlate with size and apolipoprotein composition.

Methods: This study assessed the relationship between HDL subclass distribution PON1 activity in situ and apolipoproteins (apo) AI, E, CII. The contents of plasma HDL subclasses were determined by native gel electrophoresis and enzymatic detection of activity in situ (coupled reaction that yield a color product-patent pending-) followed by Coomassie staining and sequential immunodetection of apolipoproteins in a Western blot. HDL subfractions were also analyzed in non-denaturing tube gels using the Lipoprint HDL system. Nine classes of HDL sizes can be quantified using this procedure. After development the method has been applied in a pilot cross-sectional study where we sequentially enrolled 16 healthy subjects (7 males, 9 females) with HDL-cholesterol ranging from 30-110 mg/dl.

Results: Our method allows for detection of PON1 activity in HDL subclasses, shows differential distribution of the activity in different subjects, with a tendency for the activity to be higher in HDL3 and HDL2b, which is in agreement with our indirect correlation study using Lipoprint. The separation of subclasses by their apo AI, E and CII and B content yields both qualitative and quantitative separation that are superior to the commercial method. Some subjects display PON1 activity in a VLDL fraction, a preliminary result under intense investigation.

Conclusions: We have developed a method for the analysis of HDL subclasses of a serum sample in a native gel that is more discriminative than the commercial method that only shows lipid distribution. Our method displays the whole apolipoprotein profiles and it adds the functionality of PON1 activity. Our data show that specific HDL particles are responsible for most PON1 activity, that this varies among subjects and pave the way for future studies on the inter-phase of HDL subclasses, interaction between apolipoproteins and PON1 activity and may become a practical tool to unravel the functionality of HDL.
Role of the Activation Gate in Determining the Extracellular Potassium Dependency of Block of HERG by Trapped Drugs

K. Pareja, K. Murphy, B. Olkiewicz, A. Anderson, and A. Miller

Touro University - California, Vallejo, CA.

Background: One form of Long QT syndrome, referred to as acquired Long QT syndrome, has been shown to primarily result from a reduction in the cardiac potassium channel HERG (human ether-a-go-go related gene) by a large number of pharmaceutical compounds. In some instances Long QT syndrome will degenerate into the potentially lethal arrhythmia Torsade de Pointes, characterized by a rapid heart rate and severely compromised cardiac output. Many patients requiring medication also present with abnormal serum electrolyte levels due to a variety of conditions including gastrointestinal dysfunction, renal and endocrine disorders, diuretic use, alcoholism, and aging. Extracellular electrolytes, in particular extracellular potassium, have significant influence on HERG channel behavior and have been shown to alter drug block of HERG. However, the mechanisms by which drug block is altered in different extracellular solutions are not well understood.

Methods: Experiments were performed using two-electrode voltage clamping of Xenopus oocytes expressing either wild-type HERG or the HERG mutant D540K. cRNA was injected into enzymatically defolliculated oocytes and currents recorded 1-5 days after injection.

Results: We have previously shown that block of HERG by quinidine, a drug that is not trapped after channel deactivation, is reduced with increased extracellular potassium and that HERG block by quinidine correlates better with the permeant ion than with inactivation. These results indicate that quinidine block is destabilized by the permeant ion. We show here that block of HERG by terfenadine and bepridil, drugs shown to be trapped in the channel after channel deactivation, is not altered with an increase in the extracellular potassium concentration. Furthermore block by both terfenadine and bepridil of the HERG mutant D540K, which opens with both depolarization and hyperpolarization, is decreased with increased extracellular potassium, similar to the effect of extracellular potassium on block of WT HERG by quinidine. In addition, block of D540K by bepridil at -120 mV, a voltage at which D540K is open and does not inactivate is similar in 0 mM extracellular K and 20 mM NH4 and reduced in 20 mM extracellular K and 20 mM extracellular Cs.

Conclusions: Given that the permeability sequence through HERG is $P_K > P_{Cs} > P_{NH4}$, these results suggest that the permeant ion is not able to destabilize a trapped drug but is able to destabilize a drug that is not trapped and suggest a possible role for the activation gate in determining the extracellular potassium dependency of block of HERG by certain compounds. This study has implications for the increased risk of cardiac arrhythmias in patients with hypokalemia.
A Method to Distinguish Hepatic from Intestinal de novo Lipogenesis
S. Lin1, A. Dyachenko1, R. Caccavello1, M. Wen2, B. Shan3, A. Gugliucci1, J-M. Schwarz1,2
1 Touro University-California, College of Osteopathic Medicine, Vallejo, CA
2 University of California San Francisco, San Francisco, CA
3 University of California Berkeley College of Letters and Science, Berkeley, CA

Background and Hypothesis: Excess fructose consumption may be associated with many metabolic conditions such as obesity and diabetes1,2. In children, both fructose consumption and obesity prevalence have increased significantly in the past three decades3,4. Recent studies suggest that de novo lipogenesis (DNL), the conversion of sugars to fat, is a key mechanism that may link fructose consumption and fatty liver and hypertriglyceridemia5. DNL is known to be an active pathway in human hepatic and adipose tissue. Based on a previous study that reported the existence of DNL in the intestine of hamsters6, we hypothesize that DNL occurs in the human intestine as well. The analyses described in this report focus on fructose consumption and hepatic versus intestinal DNL. We present evidence suggesting that the intestine is a lipogenic tissue modulated by diet and that changes in intestinal DNL can be detected using newly developed methodology.

Methods: These analyses were performed in samples collected from three participants in a study of dietary fructose restriction in obese children who have a history of excessive fructose consumption. Subjects underwent stable isotope tracer studies in the Pediatric Clinical Research Center at UCSF before (baseline) and after 10 days of outpatient fructose restriction during which complex carbohydrates were substituted for fructose. Hepatic and intestinal DNL were measured before and after the fructose-restricted phase. During the metabolic studies, subjects consumed shakes containing a stable isotope tracer. Collected plasma samples were ultracentrifuged to isolate triglyceride-rich lipoproteins (TRL)7, which were subsequently separated into apoB48 (chylomicrons) and apoB100 (VLDL) via immunoprecipitation (Abstract B10, Touro Abstract Book 2010). Triglycerides (TG) were extracted via thin layer chromatography (TLC) and were subsequently derivatized for GC/MS analysis.

Results: Fractional hepatic and intestinal DNL rates can be measured by this method. Using data from these three subjects, intestinal DNL tended to be higher with high fructose diets (8-11%) compared to low-fructose diets (1-5%).

Conclusions: Our preliminary results demonstrate our ability to separately measure hepatic and intestinal DNL. The clinical significance and regulation of intestinal vs. hepatic DNL warrant further study.

7Lemieux et al. J. Lipid Res. 1999 ; 40: 2111--

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**Antibodies Conjugated To TMV As A Fusion Partner In Vaccine Studies**

Sherri Wykoff-Clary, Alison McCormick

1. Touro University, College of Pharmacy, Vallejo, CA.

**Background:** Antibodies and peptides are often fused to other proteins to improve the immune response they generate. Tobacco Mosaic Virus, TMV, has many potentially useful properties as a conjugate for vaccines. It is a rod-shaped plant virus which is not infectious in mammals. Unlike mammalian viral carriers, such as adenovirus, it can be used for repeated doses, allowing for booster shots, and cannot spread from person to person. Unlike adjuvant carriers such as KLH, TMV is small enough to visualize on a gel, and easy to work with in the lab. It is also inexpensive to produce and easy to purify. In order to use TMV with a maleimide linker, a modified TMV, called 1295.10, was created which expresses an N-terminal lysine (ref: Smith, et al, 2005). We tested a tumor antigen chemically conjugated to TMV, and compared vaccine efficacy to a similar KLH conjugate by two methods. First, we immunized mice and tested antibody responses by ELISA. Second we immunized mice, and determined if vaccination protected mice from lethal tumor challenge.

**Methods:** 2 forms of anti-tumor antibody A20, murine and human, were reduced to provide free cysteines and conjugated to both TMV 1295.10 and to KLH using a maleimide linker, sulfo-SMCC. Equal masses of TMV*Ab and KLH*Ab were injected into mice, along with PBS only, Ab only, KLH-g-Ab (gluteraldehyde conjugated) and A20CDR3 peptide*TMV. Serum was collected after each vaccine, and analyzed for antigen specific immune responses by ELISA. After 3 vaccinations, the mice were injected with A20 tumors at 1 x 10⁵ cells/animal. Tumor growth and animal survival was monitored over 11 weeks and graphed.

**Results:** The A20-human constructs generated higher Ab levels than their corresponding A20-murine constructs did. Serum antibody levels against the TMV conjugates were equivalent to the corresponding KLH conjugates as measured by ELISA assay. In the tumor challenge, A20CDR3 peptide*TMV was essentially equivalent to PBS. A20m*TMV and A20m*KLH both significantly reduced tumor growth. A20h*KLH significantly reduced tumor growth, while the tumor growth reduction seen in A20h*TMV was not significant. Subsequent to this study, methods of optimizing conjugation of TMV to Ab were examined, beginning with varying the TMV:Ab ratio in the conjugation reaction. Ratios of 10:1, 4:1, 2:1 and 1:1 TMV:Ab were conjugated and analyzed by ELISA, showing 1:1 to have the highest proportion of Ab to TMV.

**Conclusions:** Serum antibodies to the TMV conjugates were equivalent to the corresponding KLH conjugates. In the tumor challenge, with A20m, both the TMV and KLH constructs significantly reduced tumor growth, but with A20h, only the KLH significantly reduced growth. By using ratios of 1:2, 1:10 etc, TMV:Ab it may be possible to improve the percentage of Ab conjugated in the Ab*TMV product, thereby improving its efficaciousness. Also, this study used doses of equal total protein mass. Since KLH and TMV have different numbers of conjugation sites available, this does not necessarily result in an equivalent dose of Ab being administered. The study will be repeated using ratio optimized Ab*TMV, and equalizing by dose of Ab administered, rather than by total mass of protein administered. TMV is still far cheaper and easier than KLH, and is still worth pursuing as a conjugation partner in commercial vaccines.
Discovery of Indole Compounds as Novel Inhibitors of Gp41
Guangyan Zhou\textsuperscript{a}, Zhuangwu Li\textsuperscript{a}, Dong Wu\textsuperscript{a}, and Miriam Gochin\textsuperscript{a,b}
\textsuperscript{a}Department of Basic Science, Touro University-California, Vallejo, CA 94592 \textsuperscript{b}Department of Pharmaceutical Chemistry, University of California San Francisco, CA 94143

Background: The core crystal structure of gp41 revealed that there is a deep hydrophobic pocket located in the groove formed by the trimeric N-terminal heptad repeats (NHR). Small molecule binding inside this pocket will block the fusion process mediated by gp41. We have previously identified a series of indole compounds as low to mid-\(\mu\)M inhibitors of gp41 through a structure-guided drug design approach.

Hypothesis: In order to improve binding affinity and cell-cell fusion inhibition activity, we carried out lead optimization. The strategy was: (1) keeping the –COOH group, which was confirmed to be essential for binding; (2) extending the length of the compound to occupy more of the groove formed by NHR, in order to block the protein–protein interaction between the NHR and CHR; (3) designing the shape of the new compound to be compatible with the groove contours.

Methods: The 3D coordinates of each ligand were generated from their SMILES strings using OMEGA2 and SZYBK1. AutoDock4.2 (Scripps Research Institute) was used for docking. Docking on the indole series compounds was performed with four receptor structures of gp41: 2r5d, 3p7k, 1if3 and 2kp8. Suzuki-coupling reaction was employed to build the scaffold of our compounds. The target compounds were purified by HPLC and characterized by LCMS and \(^1\)H NMR.

Results: Experimental binding affinities of the compounds for the hydrophobic pocket were strongly correlated to fusion inhibitory data (\(R^2 = 0.83\)), clearly confirming the hydrophobic pocket as a valid binding site and the mechanism of action as hydrophobic pocket binding. The most active compound II-3 had binding affinity ~0.6 \(\mu\)M and IC\textsubscript{50} for inhibition of cell-cell fusion 0.8 \(\mu\)M. A common binding mode for the inhibitors was established by docking studies using the four structures of gp41.

Conclusions: From our lead optimization process, we have obtained activity improved significantly in both \(K_i\) for binding and IC\textsubscript{50} against HIV-1 fusion. That confirmed that our design strategy was effective. Our studies not only identified novel chemical structures as inhibitors against gp41, but also established a solid foundation for future optimization.
Differential Cell Viability Effects of Compound SL-01-03 in Prostate Cancer Cell Lines
Vanishree Rajagopalan¹, Shengquan Liu¹, Maxwell Murphy², H Michael Ellerby¹
¹. Touro University-College of Pharmacy, Vallejo, CA. ². Buck Institute for Research on Aging, Novato, CA.

Background: Chemotherapy still remains the principal treatment option to treat majority of cancers. Due to the nonspecific cytotoxic mechanisms of chemotherapeutic drugs, patients have to endure adverse side effects that negatively impact their quality of life. Compound SL-01-03 is a small molecule designed on our laboratory aimed at being cytostatic rather than cytotoxic. If such cytostatic agents are combined with cytotoxic drugs, in principle, we should be able to lower the dose of the cytotoxic agent while delivering the same therapeutic effect but with reduced adverse effects.

Methods: MTS cell viability assays were carried out using Compound SL-01-03 in three prostate cancer cell lines: DU-145 (hormone independent), PC-3 (hormone independent) and LNCaP (hormone dependent).

Results: A dose dependent (0.5 -10 μM) decrease in cell viability of up to 50% was observed in LNCaP cell line, while cell viabilities of DU-145 and PC-3 cell lines were not affected by Compound SL-01-03.

Conclusions: These preliminary results suggest that Compound SL-01-03 causes growth inhibition in hormone dependent cells, while, no such inhibition is seen in hormone independent cells. We speculate that hormone receptors may play a role in regulating the cellular effects of Compound SL-01-03. Further studies are ongoing to test this hypothesis.
**Tobacco Mosaic Virus (TMV) interacts directly with mammalian immune cells in vivo.**

Alison McCormick\(^1\) Jan Kemnade\(^2\) and David Spencer\(^2\)

1. Touro University California, College of Pharmacy, Vallejo, CA.
2. Baylor College of Medicine, Department of Immunology, Houston TX

**Background:** In the past decade VLP vaccines based on a plant virus, Tobacco Mosaic Virus (TMV) have shown utility in infectious disease and cancer vaccine therapeutics. We have developed whole antigen fusions to TMV, as well as peptide antigen fusions, and shown they are very effective at stimulating protective immunity in many different animal models of disease (See Sherri Wykoff-Clary's poster). One question that has persisted is: How does a plant virus stimulate immunity in a mammalian host? One reason this question is compelling is that TMV is a rigid rod shaped virus that is uncharacteristic of mammalian virus types, is unenveloped, does not have a receptor for internalization, and yet it is highly immunogenic in vivo. The question is worth answering, because TMV virus is intrinsically safe as a vaccine carrier, because it is not infectious at 37°C, cannot replicate in mammalian cells, cannot integrate into mammalian DNA, and is easily propagated in plants. So, TMV has little potential for causing disease, or transmitting unknown mammalian infectious material. Also, very importantly, TMV is extremely cost effective for vaccine production at large scale in tobacco crops. All of these characteristics are in contrast to typical mammalian viral vectors such as adenovirus, which are potentially infectious, are produced in mammalian cells at great expense, can carry over unknown mammalian pathogens, and can integrate into host DNA. We wanted to better understand how TMV interacts with mammalian immune cells, especially antigen presenting dendritic cells, in order to better characterize and expand TMV's vaccine potential.

**Hypothesis:** TMV will be taken up directly in vitro and in vivo by immune cells, especially professional antigen presenting cells (APC's) like dendritic cells (DC's). Our second hypothesis is that APC's and DC's will become activated to present antigens after TMV uptake.

**Methods:** Mice were immunized with Alexa 488 fluorescently labeled TMV and draining lymph nodes were recovered on days 2, 5 and 15. Analysis included determining the type of cells involved in TMV uptake, their relative numbers, and whether or not cells were activated. TMV-A488 levels were measured by fluorescence activated flow cytometry and cells were counter stained for immune cell surface markers that identify immune cell lineage (B cells, T cells and DC's), activation state (CD40 and CD86), and the ability to present antigen through upregulation of MHC class I and class II receptors.

**Results:** In vivo, ~20-50% of cells in draining lymph nodes, including DC's, had taken up TMV-A488. Interestingly, TMV uptake also recruited T-cells to lymph nodes, demonstrating that local activation of APC's was sufficient to stimulate migration of effector cells into lymphoid tissues. TMV uptake induced potent immune cell activation, by measurement of CD40 and CD86 co-receptor upregulation, and upregulation of MHC I and II. Time course analysis demonstrated that activation persisted up to 15 days in some types of immune cells.

**Conclusions:** Even though it is a plant virus, TMV efficiently interacts with and is capable of activating mammalian immune cells in vivo. We want to continue this work by identifying pathways of uptake and localization (See Dr. Hardeep Kaur's poster), identify cytokine mediators, and downstream signaling pathways that promote TMV vaccine efficacy.
High density lipoprotein changes in the 3xTg-AD triple transgenic mouse model of Alzheimer’s disease

A. Gugliucci, R. Caccavello, J. Massa, and G.J. Klapstein
Department of Basic Sciences, Touro University-California, Vallejo, USA

Background: Cardiovascular changes, especially in the cerebral microvasculature, have been implicated in the pathophysiology of Alzheimer’s disease (AD). It has been suggested that oxidative stress such as low-density lipoprotein (LDL) oxidation may play an important role in the progression of the disease as it facilitates the formation of atherosclerotic plaques. The enzyme paraoxonase (PON1), a major constituent of high density lipoprotein (HDL), is one of the key players in the regulation of LDL oxidation. It is also reported to be a potent cholinesterase inhibitor and an arylesterase, combating organophosphate poisoning and metabolism of environmental neurotoxins which might contribute to age-related neurodegeneration. Interestingly, PON1 also acts as a Hcys-thiolactonase, converting highly neurotoxic homocysteine-thiolactone (also associated with AD) to its biologic precursor homocysteine.

Hypothesis: We hypothesized that PON enzymatic activity is lower in symptomatic 3xTg-AD mutant mice than in age-matched background strain controls.

Materials and methods: The 3xTg-AD mouse model of AD incorporates an APP/PS1/tau triple gene mutation, and is one of the most aggressive models of AD symptom development. These mice develop amyloid plaques at about 2-3 months of age, and behavioral memory deficits and deficiency in long-term potentiation by 6 months. Serum was collected from mice ex-vivo at various ages (4-18 months). Serum PON1 triesterase activity was determined and HDL subclasses were analyzed with Lipoprint.

Results: Our results show that symptomatic mutant 3xTg-AD mice exhibit reduced serum paraoxonase activity (20-30%) at all ages tested (P<0.001). No changes were observed in total cholesterol, apoA-I or PON immunoreactivity and only minor changes were seen in HDL cholesterol, however there were significant shifts in HDL subclasses, with a significant increase in intermediate size fractions. Since reduced paraoxonase activity has also been found in human AD patients, this mouse model may be a good choice for testing drugs that increase PON1 activity to determine whether this is a rational target for AD pharmacotherapy.
Neuronal ischemic sensitivity in a transgenic mouse model of Alzheimer's Disease
Department of Basic Sciences, Touro University-California, Vallejo, USA

Background: A strong correlation has been demonstrated between stroke and Alzheimer's Disease (AD), and each exacerbates the severity of the other. It has been suggested that cardiovascular changes in AD contribute to this phenomenon. The goal of this project was to investigate whether brain tissue from a transgenic AD mouse model exhibits altered intrinsic neuronal sensitivity to ischemia. We modeled ischemic damage using oxygen-glucose deprivation (OGD; an in vitro global cerebral ischemia model) in brain slices from 3xTg-AD mice with an APP/PS1/tau triple gene mutation, an aggressive AD model. These mice develop amyloid plaques at about 2-3 months of age, and behavioral memory deficits by 6 months. The acute brain slice preparation allows direct examination of neuronal synaptic properties under controlled conditions, obviating the need for the vascular system for delivery of oxygen and glucose.

Materials and methods: Transverse hippocampal brain slices (400 µm) were prepared from 3xTg-AD mice and age matched WT controls ranging from 1-10 months of age, and placed in a temperature controlled recording chamber (34 ± 0.5 °C) superfused with artificial cerebrospinal fluid (ACSF) in an atmosphere of 95% O₂, 5% CO₂. Stimuli were delivered every 15 seconds via a bipolar stimulating electrode placed in the stratum radiatum of area CA1. Excitatory post-synaptic potentials were recorded using a glass microelectrode placed in the apical dendritic field of CA1 pyramidal neurons. Oxygen glucose deprivation was applied by switching to ACSF with an equimolar substitution of sucrose for glucose, and an atmosphere of 95% N₂, 5% CO₂.

Results: Our results show similar rates of recovery between mutant and wild type mice subjected to 5 minutes of OGD in 2-3 month or 7-9 month cohorts, however there was a significant difference in electrical DC potential shifts between mutant and WT preparations in the 7-9 month cohort, indicating possible changes in cellular regulation of ionic currents associated with ischemia.
CLINICAL SCIENCES
The effect of community-based student-initiated projects in reducing incidence of schistosomiasis through treatment and health education in rural Tanzania.

Duong J*, Rosenblatt R*, Bireley B, Macrito A, Rocchi V, and Mahmoud E.

*Primary Authors. Touro University-CA, Vallejo.

Hypothesis: Schistosomiasis is a chronic parasitic infection affecting approximately 176 million Africans. This tropical disease deserves attention not only because of the multitude of people it affects, but also because it leads to abdominal symptoms in the short term and hepatosplenomegaly and portal hypertension upon advancement.1 Due to limited access to hospital care and education, lakeside villagers are not only untreated, but also simply unaware of precautions against schistosomiasis. By providing yearly on-site screening, education and treatment, the incidence of schistosomiasis in rural Tanzania can be reduced.

Methods: As a response to the need to decrease rates of Schistosomiasis in villages along Lake Victoria, Tanzania, a longitudinal study was carried out. Minigo, a village along Lake Victoria with a population of 3635, visited yearly since 2006, was provided with educational sessions on the basics of Schistosomiasis, including how it's contracted as well as how to modify daily activities to minimize their exposure. On location screening for S. haematobium and S. mansoni was provided through physical exam and fecal and urine sample testing. Praziquantel 40 mg/kg bodyweight was prescribed for those who tested positive and prophylactically for those in prolonged contact with the waters. Those who tested positive with complications were provided with an ultrasound and peripheral blood smear to determine the morbidity of the disease in order to inform the patient if additional treatment is needed. A second village, Masonga (Pop. 2000), was also educated, screened, and treated starting in 2010.

Results: The incidence rate was 30% in 2007, 14% in 2009, and 10% in 2010 in Minigo. Masonga (Pop. 2000), providing a basis for comparison, had an incidence of 20%.

Conclusion: This study demonstrates the effectiveness of providing access to treatment at the community level and preventative education in the reduction of disease prevalence, yielding a 67% decrease of Schistosomiasis in Minigo. Additionally, the incidence of Schistosomiasis in Masonga reiterates the value of intervention and education by providing a baseline rate two times higher than that of Minigo. Further follow-up in both villages will include continual screening, treatment, and education in hopes to observe a similar decline of Schistosomiasis infection in Masonga to confirm the efficacy of this intervention.

1 WHO, Schistosomiasis Fact Sheet, Feb 2010.
Developing a Shared Decision Making Model for the Touro University Medical Center
Melanie Southard,OMS III1, Patricia Hiserote, D.O.1, Jeff Belkora, PhD2, Kara Gabriel, PhD3, Jennifer Ferrell, D.O1
1. Touro University College of Osteopathic Medicine, Vallejo, CA.
2. University of California, San Francisco
3. Central Washington University, Ellensburg, WA.

Background: The prevalence of diabetes, heart disease, and asthma continues to grow in underserved populations. This, in part, may be due to low health literacy among such patients that complicates their understanding of their disease and treatment options. Facilitating patient-physician interactions may also aid in greater patient understanding and treatment adherence.

Methods: While initial plans were to provide a phone service for patients to access with questions about their disease, the success of shared decision-making programs at the Breast Care Center at UCSF resulted in the implementation of that model system at Touro University Medical Center. Patients were paired with first year medical students who provided guided assistance in developing question lists and accompanied patients to their appointments to advocate on their behalf.

Results: Completed patient surveys indicated that patients appreciated having someone help them identify questions and record their office visit. Physicians indicated that they feel that patients were more comfortable asking questions and expressing concerns.

Conclusions: Providing a shared decision-making service to underserved populations improves both patient and physician perceptions of their interactions and may, ultimately, enhance patient care outcomes.
Paraoxonase-I Rescue Phenomenon During Hemodialysis is Not Caused by Changes in High Density Lipoprotein Subclasses
Christopher Engdahl (MSMHS 2011), Russell Caccavello, Satoshi Kimura, and Alejandro Gugliucci

Glycation, Oxidation and Disease Laboratory, College of Osteopathic Medicine, Department of Basic Sciences, Touro University-California, Vallejo, USA.

Department of Laboratory Medicine and Central Clinical Laboratory, Showa University Northern Yokohoma Hospital, Tsuzuki-ku, Yokohama City, Japan.

Background: A growing amount of research suggests that paraoxonase-1 (PON-1), a component of high density lipoproteins (HDL), plays a cardioprotective role in humans. In fact this enzyme could be the key to the healthful benefits of HDL by its prevention of atherosclerotic plaque formation. It has been previously documented that the activity of PON-1 decreases in renal failure patients. However, PON-1, activity has been shown by our laboratory to increase with hemodialysis (HD). The mechanism for this PON-1 rescue phenomenon is presently unknown. Could it be due to changes in the HDL subclasses? The research attempted to answer this question.

Hypothesis: We tested the hypothesis that PON-1 activity increases after hemodialysis due to changes in HDL subclasses.

Methods: HDL samples from a random sampling of HD patients from the Department of Internal Medicine and Laboratory Medicine at Showa University, Yokohama, Japan were first tested for PON-1 enzyme activity (n=35). PON-1 activity was measured kinetically by arylesterase assay on both pre and post hemodialysis samples. Specimens were then subjected to HDL subclass analysis using a Lipoprint™ LDL and HDL Subfractionation System. The results of this were analyzed with Lipoware software to determine the HDL subclass content of the samples. This data was then analyzed and plotted for trends.

Results: This research confirms previous work demonstrating that PON-1 activity increases after HD. In this case, a 45.1% increase in postHD PON-1 activity (55.9 ± 22.5 vs. 81.1 ± 27.4 U/L, p = 0.000000027) was observed. Subsequent Lipoprint analysis yielded the following results: large-HDL profile (48.1 ± 13.3 % vs. 44.4 ± 19, p = 0.36), intermediate- (41.9 ± 6.8 % vs. 41.9 ± 9.9, p = 0.37), and small-HDL profile increased by 19.4% (11.4 ± 6.9 vs. 13.6 ± 11, p = 0.37). These results suggest that the HDL subfractions remain relatively unchanged through the course of HD therapy, although a trend for a shift towards smaller particles after dialysis became apparent.

Conclusions: Our work provides new insights into the rescue of HDL/PON-1 activity produced by hemodialysis. The findings suggest that this increase in activity is unrelated to changes in the HDL subclass distribution. Instead this could be the consequence of the removal of metabolic waste products that would otherwise inhibit PON-1 activity. At the same time, we cannot discount the fact that this could be the result other metabolic signals. A prime candidate for this would be the Peroxisome Proliferator-Activated Receptor Gamma (PPARG) system. Future investigation will attempt to replicate and quantify these findings in non-Japanese populations. Additionally we plan to investigate the possibility of PON-1 inhibition by metabolic waste products and the role PPARG plays in this system.
Heart Disease: How Insurance Helps, or Does It?
Analysis of Two Northern California Counties: Napa and Solano County Heart Disease Rates and the Correlation to Current Health Insurance Status
Dawn Krytusa, R.N.¹, Wesley (Brian) Lashbrook¹
¹. Touro University-CA, Vallejo, CA.

Background: Coronary heart disease, or heart disease, has become an increasing problem in the United States. Estimated prevalence rates for 2006 were 36% of the adult population (age 20+), in the United States, according to the American Heart Association (Heart, 2009). There has been minimal research on direct correlations between health insurance and heart disease status; however, recent literature suggests associations between the variables.

Methods: Data was retrieved from the California Health Interview Survey (CHIS). In this study, these associations in Napa and Solano counties in Northern California were statistically tested by crude odds ratios and crude chi-square analyses. Currently, a logistic regression is being performed to control for demographic confounders and should be completed by 02/05/11.

Results: The results show an increased risk for heart disease for those that have insurance. These results also depict significant effect modification by county location with Solano county residents being at a higher risk. Results from the logistic regression, which will control for demographic confounders, are expected to obtain similar results.

Conclusions: Although insurance was found to be a significant risk factor for heart disease, further studies must be done. Some additional confounders that may have affected the results, that were not accounted for and were not available in this survey, were the length of time the patient had insurance and patient compliance with a medical regimen if their current status was insured.

Aspirin esterase activity correlation with HDL subclasses and paraoxonase1 activity: the lipid connection in aspirin metabolism
Alejandro Gugliucci1, Kazuhiko Kotani1,2,3, Russell Caccavello1
1Glycation, Oxidation and Disease Laboratory, Department of Basic Sciences, Touro University-California, Vallejo, USA
2Department of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke-City, Tochigi 329-0498, Japan
3Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto 612-8555, Japan

Background: Accelerated atherosclerosis and atherothrombosis are the leading causes of morbidity and mortality. Aspirin (acetylsalicylic acid) is one of the most widely used drugs for the purpose of preventing thrombosis. Our previous results support the contention that an association exists between changes in AE activity and metabolic shifts in cholesterol. Our data suggest that glucose and lipid control may contribute to alleviate aspirin resistance and improve aspirin effectiveness in patients with DM. The association between cholesterol and AE needed further exploration, notably with regards to HDL and its functionality.

Hypothesis: Serum AE activity is associated with lipid parameters, especially HDL subclasses and paraoxonase in healthy volunteers.

Materials and Methods: In this cross-sectional study we sequentially enrolled 30 healthy subjects (14 males, 16 females) with HDL-cholesterol ranging from 20-110 mg/dl. PON1 activity was explored with 4 substrates. PON1 triesterase activity was determined using paraoxon as a substrate. PON1 lactonase activity was measured with 5 (thiobutyl)butyrolactone (TBBL) as well as dihydrocoumarin. PON1 mono-esterase activity was measured using phenylacetate as a substrate. HDL subfractions were analyzed in non-denaturing tube gels using the Lipoprint HDL system from Quantimetrix. Nine classes of HDL sizes can be quantified using this procedure. Aspirin esterase is analyzed by following hydrolysis of acetylsalicylic acid kinetically in a temperature controlled plate reader SpectraMax UV with SOFTmax PRO software (Molecular Devices, Sunnyvale, CA, USA). Samples were kinetically read at 300 nm at 37°C for 15-minutes. Results are expressed in nmoL of acetylsalicylic acid hydrolyzed per minute and per milliliter (nmol/mL/min). The intra-assay variation is 4% and the inter-assay variation is 5%.

Results: The present study confirmed our previous data of an association of AE activity and total cholesterol and lack of a correlation with HDL cholesterol. The new important findings are: strong correlation between AE and PON1 lactonase and esterase activity. AE correlates with intermediate density HDL (HDL3 and small HDL2). As this is a cross-sectional study we can assess the presence of correlations, not causations. Nevertheless this is the first report showing an association of aspirin metabolism in plasma with individual HDL subclasses and paraoxonase activity.

Conclusions: In short, the present study shows that serum AE activity correlates with total cholesterol, HDL 3 and small HDL2 subclasses and strongly with PON1 activities. No association is found with HDL-cholesterol and many other lipid or metabolic parameters. These results suggest that a link exists between HDL function and aspirin metabolism in plasma. Our work may be thus provide the basis for future studies to confirm the data in larger samples and to elucidate the mechanisms.
The effects of food environment on childhood obesity in Vallejo, Ca
Garima Gupta, MPH OMS II; Alicia Walker, OMS II; James E. Foy, D.O. FACOP
Touro University-CA, Vallejo, CA.

Objective: The goal of this study is to examine the prevalence of childhood obesity in elementary school children in Vallejo, California in relation to the elementary school food environment. The study compares the prevalence of obesity amongst elementary school children in select schools, and evaluates the correlation between the rates of obesity and food density, specifically for children ages 5-11.

Background: Low-income neighborhoods are reported to have 2.5 times more exposure to fast food as compared to more affluent areas. According to Block et al., American families consume fewer and fewer calories from home cooked meals. “In 1995, ‘away from home’ foods provided 34% of caloric intake and 38% of total fat intake compared to 18% for both categories in 1977-1978.” According to Glanz et al., there is a lack of scientific literature that directly addresses how poor food environments contribute to childhood obesity. Childhood obesity is more prevalent in low-income neighborhoods (Glanz et al., 2008). However, the authors did not conclude that this was directly related to increased exposure to fast food restaurants and convenience stores in these neighborhoods.

Methods: Elementary schools were chosen based on differences in school reported rates of low income students in attendance. Elsa Widenmann reports that 65% of students are considered low income while Glen Cove Elementary reports 25% of their students as from low-income backgrounds. This is compared to 35% low income students at the county level. Food environment was determined using drive-by survey of one square mile around Glen Cove and Elsa Widenmann Elementary School in Vallejo, Ca. Food establishments were classified into locally owned food vendors, chain food vendors, convenience stores, and grocery stores. Height and weight data was obtained via retrospective medical record review for children born from years 2000-2004 who have been seen at local clinics from 2008-2011 and attend either Glen Cove (n=31) or Elsa Widenmann Elementary School (n=35). BMI percentile was determined using the CDC website “Child and Teen BMI Calculator.” BMI percentiles were subsequently compared for the two groups.

Results: The drive-by survey revealed that within one square mile of Glen Cove Elementary, there was one locally owned food vendor. Within one square mile of Elsa Widenmann Elementary there were 19 total food vendors: 9 locally owned food vendors, 2 chain food vendors, 5 convenience stores, and 3 grocery stores. These two schools display dichotomous food environments. Of the 30 children from Glen Cove Elementary, 7 children had a BMI percentile between 85-95, putting them in the overweight category, and 3 children had BMI percentiles above 95, putting them in the obese category. Of the 36 children at Elsa Widenmann Elementary, 5 children had a BMI percentile between 85-95, putting them in the overweight category, and 9 children had BMI percentiles above 99, putting them in the obese category. However, the overall difference between BMIs at Elsa Widenmann and Glen Cove is not statistically significant (t = 0.82, df = 64, p-value = 0.42, 95% CI: -1.15, 2.73). In addition, the prevalence of obesity in elementary schools is not correlated with a higher food density in this study (X-squared = 1.57, df = 1, p-value = 0.21).

Conclusions: There was no statistically significant relationship between the food environment and prevalence of obesity in this sample. According to the National Health and Nutrition Examination Survey, it is estimated that 19.6% of children between the ages of 6-11 are obese. Rates of obesity in this pilot study are comparable at 18%. The prevalence of obese and overweight children in this population, at the local and national level, is alarming. This study confirms the findings of Block et al. and Glanz et al. in that the food density...
around elementary schools in low-income neighborhoods is strikingly different from that of schools in more affluent regions. Elsa Widenmann Elementary had far more food vendors and fast food options within one square-mile of the school than Glen Cove Elementary. The lack of statistical significance in this study may lead us to consider that, for this age group, food environment alone is not a major factor in rates of obesity. It is important to examine additional confounders such as home diet, school meal plans, and levels of physical activity between students from lower socioeconomic status backgrounds versus those from higher socioeconomic brackets. However, the low power of the number of medical records reviewed is a significant limitation in determining a potential correlation. This pilot study examined only two of the sixteen elementary schools in the Vallejo Unified School District. It is necessary to evaluate the food density around more schools and have more subjects to determine if a correlation between prevalence of obesity and food environment exists.
Influence of ezetimibe monotherapy on ischemia-modified albumin levels in hypercholesterolemic patients
Kazuhiko Kotani 1,2,3*, Russell Caccavello 2, Naoki Sakane 3, Toshiyuki Yamada 1, Alejandro Gugliucci 2
1 Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto 612-8555, Japan
2 Department of Clinical Laboratory Medicine, Jichi Medical University, Tochigi 320-0498, Japan
3 Glycation, Oxidation and Disease Laboratory, Touro University-California, CA 94592, USA

Background: Ischemia-modified albumin (IMA) is a novel biochemical marker of atherosclerosis-induced ischemia-in vivo. Ezetimibe, a new-concept agent, is a selective inhibitor of intestinal cholesterol transport, which suppresses the absorption of dietary and biliary cholesterol thereby reducing circulating concentrations of low-density lipoprotein cholesterol (LDL-C). Although little is known about whether ezetimibe reduces oxidative stress, more recent studies using some oxidative stress-related markers of lipids, lipoproteins and proteins (i.e., oxidized low-density lipoproteins, protein carbonyl, 8-isoprostane) have indicated that this agent may improve oxidative stress environments.

Aims of the study: To investigate the influence of ezetimibe treatment in patients with hypercholesterolemia on circulating levels of IMA, in addition to other atherosclerotic risk factors used in daily practice.

Materials and Methods: The study included 31 hypercholesterolemic patients with serum LDL-C concentrations of ≥ 3.64 mmol/L (male/female = 13/18; mean age = 65.7 ± 5.6 years), who received 10 mg/daily ezetimibe during a 12-week treatment period. These patients had no history of cardiovascular, thyroid, kidney or liver diseases, and they did not receive any other lipid-lowering agents. The study was approved by the ethics committee of Kyoto Medical Center and each subject gave informed consent. After an overnight fast, both in the pre treatment and post treatment phases of this study, standard atherosclerotic risk markers were measured. Serum IMA was measured by the decrease in cobalt 2+ binding. Paired t-test was used to compare the pre- and post-treatment levels of respective markers. Simple and multiple linear regression analysis, controlled for age, gender, smoking and all measured markers, were used to observe the correlations between changes in the respective markers’ levels (Δ: post- minus pre-data).

Results: During the treatment period, the levels of IMA (0.57 ± 0.52 vs 0.55 ± 0.62 AU, p 0.036) and LDL-C (3.98 ± 0.58 vs 3.18 ± 0.56, p< 0.0001) were significantly reduced. There were small changes in the other atherosclerotic risk markers. Simple regression analysis revealed that ΔIMA levels were not significantly correlated with those of the other atherosclerotic risk markers: Multiple regression analysis failed to show significant correlations between ΔIMA levels and those of the other markers: β-coefficient (P value), ΔBMI 0.152 (0.484); ΔMBP 0.213 (0.299); ΔLDL-C -0.062 (0.786); ΔHDL-C -0.178 (0.449); ΔTG -0.219 (0.332); Δglucose -0.039 (0.877).

Conclusions: The new finding of the present study is a significant reduction of IMA levels during a period of ezetimibe treatment on hypercholesterolemic patients. IMA is a surrogate marker for atherosclerotic-mediated ischemic ROS-mediated damage and ezetimibe may reduce this oxidative pathway in an atherosclerosis-prone population. While the present study appears to provide insight into daily lipid management in hypercholesterolemic patients, more studies are necessary to confirm the clinical relevance of the present findings and to verify the mechanisms underlying the relationship.
Skin Autofluorescence: A tool for identification of prediabetes (preDM) and diabetes (DM)
Peter Baginsky¹, Megan Jolicoeur¹, Lori Hurlbert¹, Jonathan Revels¹
¹Touro University-CA, Vallejo, CA

**Background:** While 24 million Americans have DM, 57 million others have preDM. They are at increased risk of developing DM, and thus are candidates for intensive prevention efforts. Laboratory testing is inconvenient, expensive, and not available to many. A non-invasive test would make widespread screening for preDM and DM far more feasible. The advanced glycation endproducts (AGE) reader may offer such a test. The reader detects accumulated AGEs in tissue, by measuring skin autofluorescence (AF) when the volar forearm is illuminated by ultraviolet light. Skin AF is elevated in DM patients compared to controls, and it is particularly elevated in those with complications, including coronary heart disease, and microvascular complications. Thus, measuring AGE levels may allow early detection of DM, DM complications, and preDM.

**Methods:** Our goal was to determine whether elevated levels of AGEs, as measured by skin AF, would identify individuals with preDM, and thus be a useful non-invasive screening method. Subjects were adults receiving care at an outpatient clinic. Those with skin phototype V or VI were excluded, as little reflectance could be measured. During 2009-2010, 143 patients were tested using a Diagnoptics reader. 44 of these had no chart evidence of glucose measurement, and were excluded. The remaining 99 patients were analyzed. Subjects were age 18-85, 20% were male.

**Results:** 55 patients had normal glucose. The remaining 45 had either known DM or preDM, or had abnormal fasting or random glucose or gestational DM. To account for normal increasing AF with age, skin AF was adjusted for age according to the controls previously reported. AF was considered elevated if above the following levels of arbitrary units (AU) for each age category:

- **<49 years:** 1.84 AU
- **50-59:** 2.12 AU
- **60-69:** 2.50 AU
- **70-79:** 2.76 AU
- **≥80:** 2.89 AU

Of 45 subjects with DM or preDM, 34 were identified by elevated AF levels. As a means of detecting either DM or preDM, AF had sensitivity of 76%, specificity of 46%, positive predictive value of 54%, and negative predictive value of 69%.

**Conclusions:** Although it lacks specificity, AF testing is a sensitive test for prediabetes or diabetes, and is useful for widespread screening.
Influence of a short-term change in glucose and lipid concentrations on aspirin esterase activity in patients with type 2 diabetes mellitus: a pilot study
Russell Caccavello a, Kazuhiko Kotani a,b, Michiaki Miyamoto a,c, Shun Ishibashi c, Nobuyuki Taniguchi a, Alejandro Gugliucci a
a Glycation, Oxidation and Disease Laboratory, Touro University-California, Vallejo, CA, USA b Department of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke-City, Tochigi, Japan c Division of Endocrinology and Metabolism, Jichi Medical University, Shimotsuke-City, Tochigi, Japan

Background: There are some issues on the use of aspirin; for instance, the optimal dose that confers maximal anti-platelet action without increased risk of bleeding remains to be determined, and aspirin resistance exists in metabolic disorders such as DM. Although few studies have investigated the intrinsic mechanisms of these resistance, changes in serum aspirin esterase (AE) activity, which participates in aspirin pharmacokinetics, may account for part of the mechanisms. We have recently reported that the AE levels may not always be high in DM patients, and there seems to be a discrete but not too strong association between AE and lipids in these patients relative to non-DM subjects [1].

Aims of the study: To investigate the influence of a short-term change of plasma glucose and serum lipid concentrations on serum AE activity in DM patients.

Materials and Methods: A total of 10 Japanese patients (women/men = 5/5, mean age = 54.4 ± 9.3 years) with diagnosed type 2 DM were studied. They were admitted for a 2-week educational program on glycemic control, which included energy- and nutrition-balanced diet therapy (25-30 kcal/ideal weight [kg]; carbohydrates 50%, proteins 30%, fat 20%) and 30-minutes of walking per day. All patients were in treatment with oral hypoglycemic agents, but the agents were not changed during the program, even though the dosage was modified. They did not use any other drugs including aspirin. The fasting plasma glucose, serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride concentrations were measured by standard enzymatic methods. Hemoglobin A1c (HbA1c) were measured by a HPLC method. Serum AE activity was measured kinetically, as described previously. The method was modified in our laboratory and adapted to 96-well microplates. The reagent buffer contains Tris-HCl (0.6 mol/L) and CaCl₂ (0.4 mol/L) at pH 7.6-7.7.

Results: Age and sex-adjusted linear regression analysis for AE revealed that all the variables were correlated with AE at a statistically non-significant level. The correlations between the change in the levels (Δ values) of AE and other metabolic variables in the pre- and post-intervention phase of the program are presented in Table 1. The single linear regression analysis for the changes of AE revealed that the changes in total cholesterol, triglyceride and glucose were significantly and positively correlated with those of AE.

Thereafter, the age- and sex-adjusted linear regression analysis for the changes of AE revealed that the changes in total cholesterol, triglyceride and glucose remained to be correlated significantly and positively with those of AE. These correlation coefficients for AE and glucose in particular, were high (coefficient > 0.8).

Conclusions: In short, the present study shows that the change in blood glucose, total cholesterol and triglyceride concentration was remarkably and positively associated with the change of serum AE activity in DM patients after an intervention to ameliorate metabolic control. These results suggest that improvement of glucose and lipid parameters toward target values may contribute to aspirin effectiveness in these patients. Our work may be thus provide the basis for future studies to confirm the data in larger samples and to elucidate the mechanisms of aspirin-resistance issues in DM.
Leprosy: Rehabilitation Through Community-Sustainable Income Generation
A. Hench1, J. Hoppe1, M. Sullivan1, J. Magatti2, E. Mahmoud1
1 College of Osteopathic Medicine, Touro University-California, Vallejo, USA
2 KMT Shirati Hospital Research Center, Shirati, Tanzania

Background: Incidence of leprosy has declined in Tanzania; however, the physical and psychosocial manifestations of the disease have long-term effects on a patient’s quality of living, social status, and family life. While it is commonly acknowledged that poverty increases the risk of contracting the bacterial infection, it is seldom recognized how the disease perpetuates poverty. The implementation of community-rehabilitation has been shown to decrease the perpetuation of leprosy-associated disabilities.

Methods: Phase I concluded that long-term facilities relying on charity resources are insufficient without a form of supplemental income generation. Phase I established a clean water supply, resources for food self-sufficiency, and the beginnings of income generation. These actions have been a positive force in the community’s health and well-being. Based on the questionnaire findings from Phase I, Phase II supplied materials to address the physical needs of the lepers. The goal of Phase II of the Leprosy Project was to implement and apply the primary needs assessed in Phase I and to devise and solidify a method of generating a steadier and more reliable income.

A focus group was held with the patients residing in the leprosy camp to evaluate how to increase their group income. The able-bodied residents maintain maize and millet crops near Lake Victoria, whose harvest is a major source of revenue for the camp.

Results: Unanimously, the nine leprosy camp residents agreed that a gasoline-powered water pump would allow year-round farming and therefore establish steady income generation. The camp generated 100,000 Tanzanian Shillings from the past season’s maize and millet harvest and hope to double that by growing throughout the year. Phase II evaluated the findings of Phase I and provided the items that addressed the physical needs of affected individuals. During Phase II a water pump was provided, which will allow water access to crops during the dry season and increase income generated from the camp’s millet and maize crops.

Conclusions: Phase II evaluated Phase I’s findings and provided clothing, hats, and sunglasses in order to address some of the resource deficits. In addition, Phase II purchased a water pump with the goal of solidifying and increasing the income generated from the camp’s millet and maize crops. Phase III of this study will continue the efforts of Phase I and II in working to improve the self-sustainability of the camp, focusing on income generation. Phase III will include evaluating the efficacy of provision of support to income generation project in decreasing the perpetuation of leprosy-associated disabilities.
Influence of physical activity intervention on circulating soluble receptor for advanced glycation end products in elderly subjects
Alejandro Gugliucci 2 Kazuhiko Kotani 1,2,3, Russell Caccavello 2, Kokoro Tsuzaki 3, Naoki Sakane 3, Toshiyuki Yamada 1
1 Department of Clinical Laboratory Medicine, Jichi Medical University, Tochigi, Japan
2 Glycation, Oxidation and Disease Laboratory, Touro University-California, CA, USA
3 Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization
Kyoto Medical Center, Kyoto, Japan

Background: Inflammation caused by advanced glycation end products (AGEs) may be quenched by the soluble receptor for AGEs (sRAGE). The aim of the present study was to investigate the influence of physical activity on circulating sRAGE, and the association between changes of circulating sRAGE and paraoxonase1 (PON1) activity (as an antioxidative enzyme) in a physical activity intervention study on an elderly subject cohort.

Methods: Serum sRAGE, PON1 activity and cardiometabolic variables were measured in 30 community-dwelling healthy Japanese volunteers (15 men/15 women, mean age 65 years) in the pre- and post-phase of a 6-month interventional program for physical activity increase.

Results: The levels of body mass index and sRAGE (1103 ± 496 to 1030 ± 437 ng/L, P < 0.05) were reduced during the intervention period. In addition, the change of sRAGE was significantly and inversely correlated with that of PON1 activity, independent of the other cardiometabolic variables (β = -0.511, P < 0.01).

Conclusions: The present study showed a reduction of sRAGE levels, and an inverse correlation between sRAGE and PON1 activity, after a 6 month intervention study increasing physical activity on an elderly cohort. These findings may represent an adaptive regulation of sRAGE in this type of exercise intervention, future studies are warranted on the clinical relevance of sRAGE changes in physical activity.
Impact of Oral Glucose Tolerance Test (OGTT) on de novo lipogenesis
A. Dyachenko\textsuperscript{1,} S. Patel\textsuperscript{1,} A. Pham\textsuperscript{1,} D. Tang\textsuperscript{1,} S. Lin\textsuperscript{1,} M. Wen\textsuperscript{2,} J-M. Schwarz\textsuperscript{1,2}
\textsuperscript{1} Touro University-California College of Osteopathic Medicine, Vallejo, CA
\textsuperscript{2} University of California San Francisco, San Francisco, CA

**Background and Hypothesis:** The liver plays a vital role in glucose homeostasis by producing and taking up glucose. One possible fate of glucose taken up by the liver is its conversion to fat via the de novo lipogenesis (DNL) pathway. The OGTT is a diagnostic test for diabetes. It consists of giving a 75g oral glucose load and taking regular blood samples during the following two or three hours to determine how glucose is cleared from the blood. The aim of this study is to measure the amount of hepatic DNL after a 75g glucose load (OGTT). This methodology will estimate how much glucose is taken up by the liver and converted into lipids through DNL after an OGTT.

**Methods:** A healthy adult male volunteer was admitted to the Clinical Research Center (CRC) at San Francisco General Hospital (SFGH). The subject underwent intensive tracer studies to measure hepatic DNL. Blood samples were taken every 30 minutes for 5 hours. The subject remained at the CRC with restricted physical activity. Collected plasma samples were ultracentrifuged to isolate triglyceride-rich lipoproteins (TRL). Triglycerides (TG) were extracted via thin layer chromatography (TLC) and were subsequently derivatized for GC/MS analysis.

**Results:** This poster will show that a small part of the OGTT load is converted to lipids by hepatic DNL.

**Conclusions:** By quantifying how much glucose is converted to lipids in the liver this method will determine one of the possible fates of total hepatic glucose uptake after an OGTT.
Serum Paraoxonase Esterase and Lactonase Activities Correlate with Intermediate Size HDL Particles
Alejandro Gugliucci 1, Teresita Menini 1, Kazuhiko Kotani 2, Ricardo Hermo 1, Russell Caccavello 1
1 Glycation, Oxidation and Disease Laboratory, College of Osteopathic Medicine, Department of Basic Sciences, Touro University-California, Vallejo, USA
2 Department of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke-City, Tochigi 329-0498, Japan

Background: PON-1 is a promiscuous esterase carried by HDL, which protects LDL from oxidation and decreases homocysteine-thiolactone damage via its lactonase activity, which is considered the physiological, cardioprotective function of PON1. Different HDL subclasses have been linked to different degrees of cardioprotection. Little is known about the distribution of PON1 across HDL subclasses.

Hypothesis: We tested the hypothesis that there might be differential distribution of PON1 activity across different HDL subclasses.

Methods: in this cross-sectional study we sequentially enrolled 30 healthy subjects (14 males, 16 females) with HDL-cholesterol ranging from 20-110 mg/dl. PON1 activity was explored with 4 substrates. PON1 triesterase activity was determined using paraoxon as a substrate. PON1 lactonase activity was measured with 5 (thiobutyl)butyrolactone (TBBL) as well as dihydrocoumarin. PON1 mono-esterase activity was measured using phenylacetate as a substrate. HDL subfractions were analyzed in non-denaturing tube gels using the Lipoprint HDL system. Nine classes of HDL sizes can be quantified using this procedure.

Results: HDL subclasses were stratified as high size (HDLa-c, Rf 0-0.15, HDL 2b), intermediate size (HDLd-f, Rf 0.20-0.29, HDL 2a-HDL3a), and low size (HDLg-1, Rf 0.38-0.53, HDL3b-c). All PON1 activities correlated significantly and positively with intermediate size HDL concentrations (both relative and in concentration of cholesterol): lactonase r= 0.72, p 0.0005; triesterase r= 0.69, p 0.001; arylesterase r= 0.70, p 0.001. No correlation was found with high or low sized HDL subclasses.

Conclusions: We show that PON1 lactonase and other activities strongly correlate only with a discrete size distribution of HDL, namely particles with intermediate sizes compatible with HDL3 and small HDL2 for the most part. Our data suggest that specific HDL particles are responsible for most PON1 activity and pave the way for future studies on the isolated particles themselves as well as to research on the inter-phase of HDL subclasses and PON1 activity to make better predictions for human disease.

(Substrate kindly provided by Dan Tawfik, Weizmann Inst. of Science, Rehovot 76100, Israel).
Liver Fat Measured by Magnetic Resonance Spectroscopy and Biomarkers of Liver Disease.
A. Pham¹, A. Dyachenko¹, M. Wen², M. Rao², K. Mulligan², J.M. Schwarz¹², S.M. Noworolski³.

¹College of Osteopathic Medicine and College of Pharmacy, Touro University-California, Vallejo, CA
²Department of Medicine, University of California, San Francisco; San Francisco General Hospital, CA
³Department of Radiology and Biomedical Imaging, University of California, San Francisco; China Basin, CA

Background: Proton magnetic resonance spectroscopy (H-MRS), which has been developed as a non-invasive alternative to liver biopsies for research, can be used to measure intrahepatic lipid content.¹ Non-alcoholic fatty liver disease (NAFLD) has a 33% prevalence in developed countries (REF), paralleling with the epidemic of obesity and type-2 diabetes. Studies have shown NAFLD to be associated with insulin resistance and metabolic syndrome. The purpose of this study was to investigate the relationship between MRS measures of liver lipids and serum measures of metabolic function in a volunteer population without known liver disease and without excessive alcohol consumption.

Methods: X subjects underwent screening for a metabolic study in the CTSI Clinical Research Center at San Francisco General Hospital (SFGH). After being consented, subjects had fasting blood tests of metabolic function. They underwent MRS to determine the lipid-to-water ratio in their liver using a 3T magnet and sequence parameters of: PRESS selection, TR/TE = 2500 /30 ms, 64 acquisitions, and respiratory motion correction². For this analysis, subjects were grouped according to their lipid-to-water ratio, 0-5%, 5-10%, 10-20% and above 20%.

Results: X% (a/b) of the subjects had liver lipids-to-water ratio > 10%, suggesting steatosis. Wilcoxon/Kruskal-Wallis tests showed a significant positive association between the liver fat groups and the liver enzymes aspartate aminotransferase (AST), alanine transaminase (ALT) and alkaline phosphatase (P <0.05) with fasting triglycerides, insulin, albumin and white blood cell levels (P <0.05).

Conclusions: Liver enzymes like AST and ALT, which are used in liver function tests, are often elevated in people with steatosis. In this study, an elevated lipid/water ratio, suggestive of fatty liver, is also associated with components of the metabolic syndrome, including increased fasting insulin and triglyceride levels.


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Correlation between ischemia-modified albumin and intermediate-density lipoprotein in hemodialysis patients: preliminary data
Alejandro Gugliucci\textsuperscript{1}, Kazuhiko Kotani\textsuperscript{2}, Russell Caccavello\textsuperscript{1}
\textsuperscript{1}Touro University-California, Vallejo, CA, USA. College of Osteopathic Medicine. Glycation, Oxidation, and Disease Laboratory  \textsuperscript{2}Department of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke-City, Tochigi, Japan.

**Background:** End-stage renal disease (ESRD) is associated with an increased rate and incidence of atherosclerosis leading to cardiovascular disease (CVD). Several underlying mechanisms are at play, including abnormal lipid/lipoprotein metabolism. It is well-known that while plasma/serum total and/or low-density lipoprotein cholesterol are rarely elevated, intermediate-density lipoprotein (IDL) is markedly elevated in ESRD patients. Ischemia-modified albumin (IMA) is a new biomarker of CVD. Increased IMA levels can reportedly predict mortality (mostly from cardiac disorders) in ESRD patients. Furthermore, the modification of albumin not only by acute but chronic oxidative stress as well (e.g., diabetes oxidative/ischemic conditions. and hyperlipidemia) has been recently documented. The IDL particle also has atherogenic properties that lead to or are exacerbated in oxidative stress.

**Aims of the study:** This preliminary study was aimed at examining the association between IMA and IDL accumulation in ESRD, which has not been previously characterized.

**Materials and Methods:** ESRD patients (7 men/8 women; mean age 60 years) on maintenance hemodialysis (a mean course of 7 years) were enrolled in this study. All patients were dialyzed three times per week on a non-reprocessed synthetic polysulfone dialyzer. Patients were non-smokers and free of acute illness, and those with a history of CVD, thyroid disorder, cancer and liver abnormalities were excluded. Fasting blood samples were obtained by venipuncture before the dialysis. Total cholesterol, high-density lipoprotein cholesterol and triglyceride were enzymatically measured. Lipoprotein subfractions were analyzed using a commercial kit utilizing disc-electrophoresis (LipoPhor system; Quantimetrix, CA, USA). Serum IMA was measured by the decrease in cobalt \textsuperscript{2+} binding. Briefly, sample was added to a solution of cobalt chloride. After adding dithiothreitol, the absorbance of mixture was determined (IMA is expressed in absorbance units). The intra-assay coefficient of variation was 5.0% at a mean absorbance of 0.51 units. For the correlations between IMA and the other variables, we used Pearson’s coefficient test as well as an age- and gender-adjusted partial correlation test. Because triglyceride had a skewed distribution, the values were logarithm-transformed in analyzing. A \( P \) value \( \leq 0.05 \) was considered significant.

**Results:** Mean levels of respective measured variables (median level in triglyceride) were as follows: total cholesterol 4.66 mmol/L; high-density lipoprotein cholesterol 1.42 mmol/L; triglyceride 1.10 mmol/L; IMA 0.56 absorbance units; low-density lipoprotein subfraction 41.8%; IDL subfraction 10.6%; very low-density lipoprotein subfraction 16.7%; high-density lipoprotein subfraction 30.9%.

In univariate correlation tests, IMA was significantly and positively correlated with the IDL subfraction and not with the other lipid variables. An age- and gender-adjusted partial correlation test thereafter revealed a significant positive correlation between IDL percentage and IMA \( (r = 0.523, P = 0.034) \). Thus, the present study showed a significant positive correlation between IDL and IMA levels among hemodialysis patients with ESRD. As expected, higher percentage of IDL (> 10% in average) was observed in these patients as
compared with age- and gender-matched non-ESRD controls ($n = 15, 1.1\%$; $P < 0.001$). In addition, the controls exhibited a lower level of IMA in (0.48 absorbance units; $P = 0.050$), similarly to our prior study, and that prior report demonstrated that the IMA levels were unchanged after hemodialysis, suggesting that IMA could be a biomarker that is not very largely influenced by renal filtration.

**Conclusions:** In summary, this study found a significant positive relationship between IDL and IMA in hemodialysis patients with ESRD. Albeit this is a preliminary study, it provides suggestive evidence of a link between the characteristic dyslipoproteinemia found in ESRD and IMA, and if confirmed in larger series, should pave the way for further work on pathogenic mechanisms and exploratory studies on the potential of the IDL-IMA ratio as a biomarker in hemodialysis patients with ESRD.
Impact of Oral Glucose Tolerance Test (OGTT) on Hepatic Glycogen

S. Patel¹, A. Dyachenko¹, S. Lin¹, A. Pham¹, D. Tang¹, M. Wen², J. M. Schwarz¹, ²
¹Touro University-California, College of Osteopathic Medicine, Vallejo, CA
²University of California San Francisco, San Francisco, CA

Background and Hypothesis: The liver plays a vital role in glucose homeostasis by producing and taking up glucose. During hypoglycemia, the liver releases glucose from glycogen via glycogenolysis and/or uses lactate, pyruvate, glycerol and amino acids to synthesize glucose via gluconeogenesis (GNG). After feeding, the liver can uptake glucose directly and store it as glycogen (direct pathway)ⁱ, ² or can take up gluconeogenic substrates to generate new glucose to be stored as glycogen (indirect pathway)⁵. Animal studies suggest that the indirect pathway is a preferred pathway to replenish hepatic glycogen (“glucose paradox”)². The aim of this study is to compare the contribution of the direct and indirect pathway to overall glucose flux stored as hepatic glycogen after a 75g glucose load from an oral glucose tolerance test (OGTT). The OGTT assesses how glucose is cleared from the blood and it is used to diagnose diabetes. After absorption, glucose can be stored as hepatic glycogen before reaching the blood. The amount taken by the liver and stored as glycogen may vary with health status. This method will assess hepatic glycogen flux, a component of glucose uptake after an OGTT.

Methods: A healthy adult male subject was admitted to the Clinical Research Center (CRC) at San Francisco General Hospital. The subject underwent intensive tracer studies to measure hepatic uridine diphosphate (UDP)-glucose flux. D-glucose-1d was infused to label the hepatic UDP-glucose pool, which in turn was sampled using acetaminophen, serving as a “pharmacological probe”. Acetaminophen was conjugated with UDP-glucose in the liver to form acetaminophen glucuronide (GlcUA), which was subsequently excreted in the urine³. ²¹³ C glycerol was infused to estimate GNG. Urine and blood samples were collected regularly from 0 to 300 minutes after the OGTT. The subject remained in the CRC with no physical activity. Labeled urinary GlcUA was isolated by HPLC, and derivatized for GC/MS analysis. The tracer dilution method will be used to calculate the flux of UDP-glucose. The UDP-glucose flux or glycogen flux is a quantification of the amount of glucose per hour that is stored as glycogen.

Results: This poster will present the total UDP-glycogen flux and the origin of the glucose stored as glycogen: glucose from OGTT (direct pathway) versus new glucose made by hepatic GNG (indirect pathway).

Conclusions: This method will determine how much of the OGTT taken up by the liver is stored as hepatic glycogen.

¹McGarry et al. Annual Reviews of Nutrition 1987; 7; 51-73.
³Hellernstein et al. Journal of Clinical Investigation 1997; 100; 5; 1305-1319.
Paraoxonase 1 status in Tangier's disease: case report
A. Gugliucci¹, K. Kotani², R. Caccavello¹, T. Yamada² and I. Sakurabayashi²
¹Touro University-California, USA, ²Jichi Medical School, Japan

Background: Tangier disease (TD) is a hereditary disorder characterized by the severe deficiency or absence of high-density lipoprotein cholesterol (HDL-C). TD is caused by mutations in the ATP-binding cassette transporter A1 (ABCA1) gene. No previous study on PON-1 status in patients with this disorder had been reported. We had previously described the first case of TD carrying a missense mutation in a transmembrane alpha-helix of ABCA1. A 31-year-old Japanese woman had an extremely low level of HDL-C (1mg/dl) and yellowish tonsillar swelling, leading to the diagnosis of TD. The patient is homozygous for a point mutation of T4978C in exon 37, which results in the substitution of cysteine-1660 to arginine (C1660R) in the 8th transmembrane segment of ABCA1. Her parents, grandmother, and brother were found to be heterozygous for the same mutation.

Aims: We conducted this study to evaluate PON1 status in this patient.

Methods: We measured PON-1 activity using TBBL (lactonase), phenylacetate and paraoxon.

Results: In all cases, the activity in the patient was 18-26% that of the mean for a control Japanese population. Western blots showed very low levels of apoA1 and about 20% of PON-1 immunoreactivity. We measured the 3 PON-1 activities in lipoprotein depleted serum and confirmed that essentially the remaining PON-1 activity in this case of TD, is free PON-1. PON-1 and apoA-1 were undetectable in urine.

Conclusions: This is the first report on PON-1 activity and mass status in Tangier's disease. It suggests that a dysfunctional ABCA1 impairs HDL formation and that, in turn impairs PON-1 binding to the particle. The only PON-1 in the circulation of these patients is free and it amounts to a very low activity for all main substrates. Low PON-1 mass and activity may be another contributing factor to the increased atherogenesis in TD patients.

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Lipoprotein Kinetics: Measurements of Very Low-density Lipoproteins and Chylomicrons by Chemical Extraction of Apolipoprotein B100/B48 Leucine with Butanol Isopropyl Ether
D. Tang¹, M. Wen², A. Dyachenko¹, B. Patterson³, J.-M. Schwarz¹²
¹Touro University, Vallejo, CA
²University of California San Francisco, San Francisco, CA
³Washington University, St. Louis, MO

Background: Studying lipoprotein kinetics can reveal links between diets and risks for dyslipidemia. The isolation of apolipoproteins can provide kinetic information for very low density lipoprotein (VLDL, apoB100 from liver) and chylomicron (apoB48 from the intestine) production and breakdown. A common way of isolating these apolipoproteins is by using gel electrophoresis. We are proposing a simpler method to replace the tedious process of running gels.

Methods: Triglyceride-rich lipoprotein samples from a subject who consumed stable isotope-labeled leucine were aliquotted into two sets. In one set of samples, affinity columns were used to first separate out apoB100 and apoB48. Then, butanol isopropyl ether was used to precipitate out the apoB proteins, thereby separating them from apoC proteins, apoE proteins, and triglycerides. The other set of samples was subjected to gel electrophoresis to separate the apoB proteins. Subsequent acid hydrolysis denatured the apoB proteins into amino acids, of which leucine was derivatized and run on a gas chromatography-mass spectrometer (GC/MS) to measure isotope enrichment values.

Results: Both methods illustrate that the concentration yield is poor and that in some cases the recovery of amino acids from apolipoproteins may hamper our ability to have sufficient material for GC/MS analysis. The data presented show that comparison of enrichment obtained by each method was similar and did validate the precipitation method.

Conclusion: Considering the entire sample processing commitment of each method, chemical extraction provides a more efficient, yet equally accurate way of accomplishing the same goal. However, more test-runs must be performed to refine its protocol so that its maximum benefits are achieved.
OSTEOPATHIC
MANIPULATIVE
MEDICINE
OMT and TCM: Comparisons of Manipulative Treatment

*Sophia Chen¹, *Angela Zhang¹, Hung-Rong Yen³, Janet M. Burns¹, Athena Lin¹²
¹College of Osteopathic Medicine and ²Global Health Program, Touro University-California, Vallejo, USA ³Chang-Gung Memorial Hospital, Gueishan Township, Taoyuan County 333, Taiwan (R.O.C.)
*Equally contributing authors

Background: With the exception of acupuncture, very little literature is available that compares Osteopathic Manipulative Medicine (OMM) to Traditional Chinese Medicine (TCM). Most just explained what OMM is or introduced the different categories of TCM involved. Osteopathic Manipulative Therapy (OMT) aims to facilitate the body’s ability to heal itself. It achieves this by targeting somatic dysfunction through techniques that manipulate soft tissue and bone to optimize function. In TCM there is a modality of treatment that also utilizes the hands, namely the 4,000-year-old practice of Tui-Na, which means “push” and “grab.” Its holistic methods of healing include soft tissue techniques, such as myofascial rolling, as well as musculoskeletal manipulation.

Methods: Through the Touro University Global Health Program, we shadowed physicians of various sub-specialties in the TCM department at Chang Gung Memorial Hospital in Taiwan for one week, followed by extensive literature review. We evaluated TCM Tui-Na techniques by comparing them to OMM techniques. Videotaped treatments performed by a TCM practitioner were later evaluated with OMM faculty at Touro and translated into OMM concepts and terminology.

Results: We interpreted Tui-Na treatments on asthma, low back, shoulder, and neck pain. For asthma the technique involved inhibition and kneading along the paravertebral muscles overlaying the sympathetic chain ganglia. Low back pain involved a soft tissue technique in which the back of the hands was utilized in a rolling fashion, applying light pressure sequentially from medial to lateral along acupuncture meridians. Shoulder pain involved an articular technique beginning with the rotator cuff and ending with joints of the distal upper extremities. Neck pain diagnosis resembled a more global technique and treatment involved kneading and stretching with active flexion and extension.

Conclusions: We found that TCM Tui-Na and OMT soft-tissue and articular techniques share the most similarities. The differences, as best as we can describe, lay in the intention of their palpation. Tui-Na, like osteopathy, tries to improve function by manipulating structure. However, it takes this to a further dimension and utilizes manual techniques to influence acupuncture meridians. We hope that this stimulates interest in future research that compares the two practices and enables osteopathic physicians to utilize complementary concepts in approaching patient care and improving clinical outcomes.
Evaluation of osteopathic manipulative medicine pre-treatment for the prevention of acute mountain sickness

R-c. Li, J. Hwang, L. Shultz, J. Burns and N. Garcia-Russell
Department of Basic Sciences, Touro University-California, Vallejo, CA

Background: Acute Mountain Sickness (AMS) is a common illness seen in unacclimatized persons shortly after ascent to high altitude. While the exact mechanisms remain unclear, the pathogenesis of AMS seems to be multifactorial and arises from the body's inadequate response to hypoxia. In the present study, we use Osteopathic manipulative medicine (OMM) to treat somatic dysfunction and optimize structural function prior to exposure of high altitude. While these adjustments may not be significant at sea level, they may change the subject's ability to respond to high altitude hypoxia.

Methods: This study is designed as a double-blind, randomized, sham-controlled trial. Osteopathic treatment or sham protocol will be performed within 48 hours prior to arrival to high altitude. The Lake Louise scoring system will be periodically used to evaluate the occurrence and severity of AMS symptoms during a 2 day, 2 night stay at high altitude. In addition, heart rate, ventilatory parameters, and hemoglobin O2 saturation will also be periodically monitored.

Results: Four subjects were able to participate in two separate sessions, which each serving as their own control in a cross-over design. Among all the parameters studied, only the oxygen saturation level (SaO2) demonstrated a treatment effect. The subjects that received OMT had much higher SaO2 compared to the sham group (p=0.068). The rest of the analysis (pulse, respiratory frequency, tidal volume, lake louise score) did not show any significant difference between OMT or sham.

Conclusions: Our findings imply that Osteopathic Manipulative Medicine has an effect in increasing oxygen saturation at altitude. By correcting somatic dysfunction, OMM seems to better prepare the body to compensate for a hypoxic environment. Phase II of this study will widen the number of subjects as well as investigate differences in oxygen consumption in OMT and sham treated patients.
Osteopathic Medical Student (OMS) Use of Osteopathic Manipulative Treatment (OMT) During School Vacation: A Novel Educational Outcome Measure
Gregg Lund1, Stacey Pearce-Talsma2, R Mitchell Hiserote1
1. Department of Osteopathic Manipulative Medicine, Touro University College of Osteopathic Medicine, Vallejo, CA 2. Department of Osteopathic Manipulative Medicine, University of New England College of Osteopathic Medicine, Biddeford, ME

Background: The use of OMT in clinical practice by Osteopathic Physicians is decreasing, even in light of increased evidence of OMT efficacy. This decrease is likely multi-factorial. One factor suggested is OMS interest in OMT use. Characterization of student interest in OMT has been difficult, especially when OMT use during clinical rotations is used as a surrogate measure. Clinical rotation OMT use may be determined more by the culture of the clinical rotation site or interest of supervising physicians, than OMS decision making. However, OMT during school vacation is the student’s decision and may be a better measure of their interest. The purpose of this study was to determine the feasibility of surveying students about their OMT use during winter vacation.

Methods: Following IRB approval at both institutions, paper questionnaires were distributed to first and second year OMS during Osteopathic Manipulative Medicine class, soon after the students returned from winter vacation in January 2011. The survey asked for information on whether they used OMT, for those treated what were their chief complaints, what OMT model was used and the results of treatment. For those that did not use OMT, the reason for not treating was asked. Results were entered into a Microsoft Access database for analysis.

Results: 407 (79.0%) survey were returned. OMT was used by 66.1% of students. A break down for the two colleges and classes are listed below

<table>
<thead>
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<th>Surveys Retuned</th>
<th>Students Using OMT</th>
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<tbody>
<tr>
<td></td>
<td>COM 1</td>
<td>COM 2</td>
</tr>
<tr>
<td>Class of 2014</td>
<td>94.3%</td>
<td>83.3%</td>
</tr>
<tr>
<td></td>
<td>58.6%</td>
<td>36.3%</td>
</tr>
<tr>
<td>Class of 2013</td>
<td>83.6%</td>
<td>63.4%</td>
</tr>
<tr>
<td></td>
<td>60.4%</td>
<td>59.6%</td>
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For the students with opportunities to use OMT, the top reasons for not using OMT and the percent of respondents giving that reason (may have more than one reason per student): No place to treat (80.4%), No time to treat (57.9%), Not confident in OMT use (54.2%), Did not want to treat (37.4%), Did not feel OMT would be helpful (17.8%). Complete report of type of OMT used, chief complaints, and perception of efficacy data will follow in full presentation.

Conclusions: Using the paper survey was feasible. Further analysis of data may identity differences as students advance in school, effects of curriculum and modifiable factors to increase OMT use. Follow-up studies may identify the associations between early student directed OMT use and its use later in training and clinical practice.
Embodying Osteopathy: Integrating Movement through Manual Medicine
Rebecca Wilson OMS V, Coral Peterson OMS V, Priya Shastry OMS IV, Jonathan Mongold OMS III
Touro University-California, Vallejo, CA.

Background: The fourth Osteopathic tenet is; rational treatment is based upon an understanding of the basic principles of body unity, self-regulation, and the interrelationship of structure and function. Providing Osteopathic medical students support for this tenet in addition to the materials taught in class, may have a positive effect on the changes they will integrate into both their personal and professional lives. Toward that end we investigated the possibility of teaching theories and techniques of postural movement and breathing exercises in parallel to the student’s Osteopathic manipulative medicine (OMM) curriculum. In this way, students utilized these theories, techniques, and exercises to develop an anatomical awareness of their own body. Our goal was to allow opportunity for integration of Osteopathic treatment techniques with basic movement and breathing exercises to explore osteopathic technical concepts internally. Additionally, a forum for discussion accompanied each class. Students were encouraged to link not only the course work and supplemental activities, but also integrate their own philosophy with the Osteopathic tenets. This exploration will lend itself to promotion of student-physician self-care during the medical education years.

Methods: For one semester, weekly classes were designed to explore various techniques and anatomical regions to fulfill the following objectives:

1. Provide a space for internal exploration of anatomical knowledge and connectivity.
2. Explore exercises adapted from different osteopathic techniques to remove restrictions, restore balance, and maximize neuromusculoskeletal function and integrity.

Following each class, participants had the opportunity to discuss and reflect on their experiences. This was fostered in two formats, group discussion or individualized one on one conversation, based on the participant’s preference.

Retrospectively and informally we attempted to evaluate the program outcomes; 1) Characterization of student selected discussion topics, 2) form of feedback (group or one on one discussion) used and 3) whether competing stressors of student life (i.e. tests) modified participation. We also noted the changes in topic preferences for these discussions over the course of the semester.

Block exam classes were focused on exploring the heart center and the core link in order to release and move through the upper cross syndrome and deep flexion of the cervical spine caused by exam preparations.

Results: Data was not quantitatively gathered, but it appeared that over the course of the semester, participants were more aware of the osteopathic connection through various forms of postural movement and breathing exercises. We also noted the change in topics for these discussions over the course of the semester (i.e. Beginning of the semester with foundational work and the core link; block exam weeks were focused on exploring the heart center and upper cross syndrome (areas that easily can fall into dysfunction during exam preparation)). During block exams participation in classes was equal or greater than other parts of the semester.

Conclusions: It appears that this is a possible model to help students integrate OMM and the Osteopathic tenets. Potentially most interesting, block exams are the most stressful time of the semester, and students appear to avoid all non-essential activities. Regardless of any educational benefit, it was noted that attendance and discussions did not decrease, and on occasion increased. Clearly students found this of great value. Further inquiry into what aspect of the possible interplay of mind, body and spirit during stressful times is warranted.
Frequency of Counterstrain Tender Points in Osteopathic Medical Students: An Osteopathic Educational Research Project

Background: In the world of medical education, the quantity of information that must be taught in the first-and second-year curriculum increases with every new advance in medicine. To make room in the curriculum for new material, each discipline must evaluate what should be taught and what should be left for self-study or clerkships. Within the osteopathic manipulation medicine (OMM) curriculum, a wide variety of diagnosis and manipulative treatment techniques must be taught to prepare students for both practical use and their licensing exams. Counterstrain is one of the many osteopathic manipulative techniques students must learn, but it encompasses over 120 separate tender points. To maximize the impact of teaching counterstrain in the OMM curriculum, this study aims to identify a core group of high yield tender points to teach for each body region. By maximizing the experiential value of the material, the investigators hope to enhance student learning and improve future use of the technique.

Research and Design Methods: Procedures: First and second year osteopathic medical students at 5 different osteopathic medical schools were surveyed during their regularly scheduled OMM laboratory classes about whether they personally had any of the tender points that were covered during the laboratory sessions. Scannable forms were handed out at the beginning of each laboratory session involving those counterstrain tender points; students documented the tender points and retruned the forms by the end of class that day. In most cases, each student’s laboratory partner recorded the presence or absence of surveyed tender points on the student’s form as the partner practiced didiagnosing and treating the countersrain tender points that were taught during the laboratory session. The data was collected over 12 months. The number of laboratory sessions dedicated to counterstrain varied by institution, ranging from 6 to 12-separate sessions, and included tender points from the head, cervical, thoracic, lumbar, sacrum, pelvis, rib, upper extremity, and lower extremity body regions. This study was reviewed by the institution review board at each school and student participation was voluntary.

Inclusion Criteria: All medical students in the first and second-year curriculum at the following osteopathic schools were eligible for participation in this project: ATSU-KCOM, ATSU-SOMA, Touro University – California, Touro University – Nevada, and UNECOM.

Exclusion Criteria: Students who were not present at the regularly scheduled time period for OMM laboratory periods were not included in the study.
**Data Collection:** The survey forms included basic demographic information, such as age, sex, height, weight, race, demographic information, such as age, sex, height, weight, race, ethnicity, history of symptomatology in the region (current new symptoms, intermittent or recurrent symptoms, or chronic longstanding problems), and history of significant injury in the region. The information obtained for the various tender points included the relative location of the tender point (right, left, or notn) and the severity of the tenderness at the point (mild or significant).

**Data Analysis:** Fisher exact tests were used to test for differences between males and females on the prevalence of the tender point.

**Discussion:** With two-thirds of the data analyzed, wide variation in the prevalence of these tender points was observed, ranging from 20% to 95%. When differences were seen between men and women, tender points were more commonly found in women except for certain locations. Positive tender points offer students the experience of palpating tissue texture abnormalities in their relatively healthy colleagues, while providing an opportunity to assess the physical changes that occur with successful counterstrain treatment. This experience may ultimately reinforce the value of the technique for future clinical practice.

**Study Limitations:** There were two main limitations to this study. The first limitation is that 6 different counterstrain reference textbooks were used in the OMM courses at the 5 participating osteopathic schools. Different textbooks describe the locations of some of the named tender points slightly differently. The second limitation is that the examiners of the tender points were novice osteopathic medical students who have not been exposed to the tender point locations prior to the date of the surveys. This likely affects overall accuracy and, thus applicability to outside populations. However, the tender points that were commonly found are likely common tender points that are easy to find, making them ideal for OMM curriculums.