6th Touro University Annual Research Day

March 7th, 2007

Mare Island, Vallejo, CA 94592

Touro University-California
Office of Research

6th Touro University Annual Research Day

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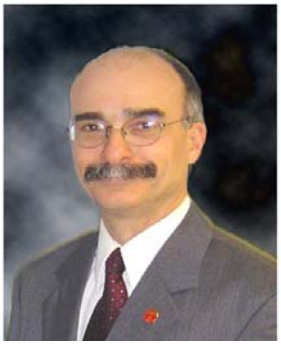

Program Coordinator
Alejandro Gugliucci, MD, PhD
Research Director

Event organized for the campus by the: *Division of Preclinical Education and Research*

Barbara Kriz, PhD
Associate Dean

With the support and participation of the Deans of all the Colleges:

Harvey Kaye, PhD
Provost

Katherine Knapp, PhD
Dean, College of Pharmacy

Michael Clearfield, DO, FACOI
Dean, College of Osteopathic Medicine

Acknowledgements:

Many thanks to the following who contributed to the success of this event:

Touro University for support of research

Facilities Department, Touro University Jay, Ralph and the crew.

Food Service, Touro University Robin Gross and her crew

MIS Department, Touro University

All presenters, investigators, mentors

All attendees.

Special thanks to the organizing crew: Marylyn, Miesha, Miko, Linda, Heather, Jen, Brienna, John, Artem and Chinhnam

John W. Baynes
Carolina Distinguished Professor Emeritus

Keynote speaker

Dr. John Baynes is best known by our students as the author of our required biochemistry textbook, which manages to teach biochemical concepts through their relevance in clinical medicine.

His research areas include biomarkers of aging and chronic disease; chemical basis for the pathology of diabetes, atherosclerosis and aging.

His laboratory applies analytical biochemical techniques to the characterization and measurement of trace chemical modifications of tissue proteins, particularly compounds that are useful as biomarkers of disease and that provide insight into mechanisms of disease and response to therapy.

His numerous awards include the MERIT Award from NIH for research program on "Glycation of Protein in Diabetes," 1989–2012; Basic Science Research Award, University of South Carolina School of Medicine, 1987; Russell Research Award for Science, Mathematics, and Engineering, University of South Carolina, 1996; and Interdisciplinary Basic Science/Clinical Science Research Award, University of South Carolina School of Medicine, 1998.

He is a founding member and past president of the International Maillard Reaction Society (IMARS), which nucleates glycation researchers from around the world.

PROGRAM

March 7th, 2007 from 12 to 5:30 pm

12:00-1:00. Poster Viewing And Pizza. Lander Hall, COP hallway and lounge

ORAL PRESENTATIONS CLASSROOM A

1:00-1:10

Welcome: Harvey Kaye, PhD, Provost. A Gugliucci, MD, PhD, Research Director.

1:10-2:00

JOHN W. BAYNES, PhD, KEYNOTE SPEAKER
Carolina Distinguished Professor Emeritus
Dept of Biochemistry, University of South Carolina ***"Chemical modifications of proteins in aging and disease"***

SPEAKERS

2:10- 2:20

ASSESSMENT OF THE CONTRIBUTION OF LACTATE TO FATTY ACID SYNTHESIS BY MASS ISOTOPOMER DISTRIBUTION ANALYSIS (MIDA)
Dr. Karl Meszaros *and Dr. Jean-Marc Schwarz*

2:25- 2:40

A METALLOPEPTIDE MIMIC OF THE COILED COIL DOMAIN OF CLASS 1 VIRUSES IS A USEFUL TARGET FOR ANTIVIRAL DRUGS
Lifeng Cai, Yanxia Hou and ***Miriam Gochin****

2:45- 2:55

TROJAN HORSE ENCAPSIDATED RNA VACCINES STIMULATE SPECIFIC IMMUNITY
Alison A. McCormick [1,2]***,*** *Tina A. Corbo*[2]*, Sherri Wykoff-Clary*[2]*, Mark L. Smith*[2]*, Long V. Nguyen*[2]*, Kenneth E. Palmer*[2]*, and Gregory P. Pogue* [2]

3:05-3:15

PERMEATION IS A MUCH LARGER DETERMINANT OF BLOCK OF HERG BY QUINIDINE AND CISAPRIDE THAN INACTIVATION.
Cheung K., *Stratton, M.J., Pham N., and Miller A.*

3:15-3:35 COFFEE BREAK, POSTERS. Lander Hall, COP hallway and lounge

3:35-3:50

ACROLEIN INHIBITS PARAOXONASE-1 ACTIVITY : EFFECT OF HEMODIALYSIS AND PUTATIVE ROLE IN ATHEROGENESIS,
Gugliucci, A, *Lunceford, N, .Kinugasa, E.Ogata, H. Schulze, J. Kimura, S.*

3:55-4:05

HEALTH-RELATED QUALITY OF LIFE (HRQoL) IN PRIMARY CARE PATIENTS WITH TYPE 2 DIABETES MELLITUS AND DEPRESSION
Bijal M. Shah *and Katherine K. Knapp*

4:10-4:20

EFFECTS OF OXIDIZED LOW DENSITY LIPOPROTEIN ON HSP 70 EXPRESSION IN THE CEREBRAL CORTEX OF HUNTINGTON'S DISEASE TRANSGENIC MICE
D. H. Lee, T. D. Hulbert, *K. D. Klapstein, J. Schulze, T. Menini, and G. J. Klapstein*

4:25-4:35

CARDIOVASCULAR DISEASE PREVENTION THROUGH ACTIVE EDUCATION
J.Santhan, *M. Winkleby, Judith Ned, Greg Troll,*

4:40-4:50

NEW PHARMACIST SUPPLY PROJECTIONS: LOWER SEPARATION RATES AND INCREASED GRADUATES BOOST SUPPLY ESTIMATES
K.K. Knapp[1], *J.M. Cultice*[2]

4:55-5:05

SIMPLE SPECTROSCOPIC MONITORING OF LIQUID SURFACE CURVATURE CHANGES IN THIN WELLS
Lifeng Cai[1] *and Miriam Gochin*[1,2]

5:10-5:25

GENETIC AND BIOCHEMICAL ANALYSIS OF HUMAN CASPASE 12
Evan Hermel[1]*, Mehdy Yavari*[1]*, Katayoun Edalat Parsi*[1]*, Annie Lim*[1]*,Kevin Daniel Klapstein*[2].

5:30- 5:40

MUTATION OF THE PHOSPHOLIPASE CATALYTIC DOMAIN OF THE *PSEUDOMONAS AERUGINOSA* CYTOTOXIN EXOU ABOLISHES COLONIZATION PROMOTING ACTIVITY AND REDUCES CORNEAL DISEASE SEVERITY
D. J. Evans[1, 2]***,*** *C. Tam*[2]*, S. Lewis*[2]*, W. Li*[2]*, E. Lee*[2]*, S. M. J. Fleiszig*[2]

POSTERS

BASIC SCIENCES

1. **SEPARATION OF L- AND D-LACTATE ENANTIOMERS: A METHOD TO DETECT ENDOGENOUS GLYCATION**
   A. Dyachenko [1], E. Everhart [2], K. Meszaros [1], A. Gugliucci [1], J.M. Schwarz [1,2]
   1. Touro University-California, Vallejo, CA. 2. University of California, San Francisco, CA.

2. **FREE SERUM ACROLEIN LEVELS IN SEVERAL DISEASE STATES ASSOCIATED WITH OXIDATIVE STRESS OR INFLAMMATION.**
   C. Hathuc[1], A. Gugliucci[1], E. Kinugasa[4], M. Ogata[4], M Tsuji[4], N. Ikeda[3], J. Schulze,[1] S. Kimura[2]
   1) Touro University College of Osteopathic Medicine, Vallejo, CA.
   2) Department of Laboratory Medicine,
   3) Department of Neurosurgery,
   4) Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama, Japan

3. ***PROPHAGE INDUCTION IN SALMONELLA ENTERICA SEROVAR TYPHIMURIUM***
   N. Garcia-Russell, Touro University-California, Vallejo, CA.

4. ***TAMM HORSFALL PROTEIN (UROMODULIN) IS RESISTANT TO CARBONYL AND NITROSATIVE STRESS: A COMPARATIVE STUDY WITH MODEL ABUNDANT SERUM PROTEINS.***
   L. Tran, M. Rose, J.Schulze, A. Gugliucci. Touro University-California, Vallejo, CA.

5. **POSSIBILITIES OF A PERIAPICAL GRANULOMA**
   Robert B. Howe, DDS and David J. Eliot PhD Touro University-California, Vallejo, CA.

6. **IL*EX PARAGUARIENSIS* "MATE" PROTECTS HDL PARAOXONASE ACTIVITY. MATE DRINKING INCREASES PARAOXONASE-1 ACTIVITY IN NORMAL SUBJECTS: A PILOT STUDY**
   B. Cross, J. Schulze, A. Murphy, A. Gugliucci Touro University-California, Vallejo, CA.

7. **TOWARD THE MECHANISM OF ANESTHETIC-INDUCED AMNESIA: ANESTHETICS SHUT DOWN MEMORY CONSOLIDATION BY INHIBITING HIPPOCAMPAL *ARC*-PROTEIN SYNTHESIS IN THE RAT.**
M. T. Alkire, T. Beydoun, T. Miyashita, J. McReynolds, J. Guzowski;
University of California, Irvine, Orange, CA.

8. **MECHANISM OF ACTION OF N-TERMINAL DOMAIN OF β-CATENIN ON OPTIC AXON BRANCHING**
Michelle Mora, Andrew Wiley and Tamira Elul Touro University College of Osteopathic Medicine, Vallejo, CA.

9. **ACROLEIN DECREASES PARAOXONASE 1 (PON-1) ACTIVITY IN HDL: PROTECTION BY CYSTEINE**
J.Schulze, N. Lunceford, M. Rose, L. Tran, A. Gugliucci. Touro University College of Osteopathic Medicine, Vallejo, CA.

10. **STRUCTURE-ACTIVITY RELATIONSHIPS OF FLEXIBLE HETEROAROTINOIDS AS POTENTIAL ANTICANCER AGENTS**
Shengquan Liu, College of Pharmacy, Touro University – California, Vallejo

11. **HIPPOCAMPAL MRNA LEVELS OF THE PLASTICITY RELATED IMMEDIATE-EARLY GENE *ARC* ARE NOT SUPPRESSED BY AN AMNESIC DOSE OF SEVOFLURANE IN THE RAT**
T. Beydoun, T. Miyashita, J. McReynolds, J. Guzowski, M. T. Alkire;
Univ of Calif, Irvine, Orange, CA.

12. **TRANSDERMAL DELIVERY OF PENBUTOLOL: IN VITRO CHARACTERIZATION**
K.B.Ita, A.K.Banga, College of Pharmacy, Touro University, Mare Island-Vallejo, California
Department of Pharmaceutical Sciences, Mercer University, Atlanta, , Georgia

13. **EFFECTS OF EXERCISE INTENSITY ON GLYCEMIA CONTROL AFTER A DIETARY GLUCOSE CHALLENGE**
T. S. Wong, Touro University-California, Department of Basic Science, Vallejo, CA 94592.

14. DEVELOPING NEW TREATMENTS FOR ALCOHOLISM: POTENTIAL ROLE OF THE NEUROKININ-1 RECEPTOR.

P.Steensland[1], K. Young[2], A. Motamed[3], J Simms[1], J. Whistler[1] and S.E. Bartlett[1,2]
[1]Ernest Gallo Clinic and Research Center at the University of California San Francisco
[2]College of Pharmacy and [3]College of Osteopathic Medicine, Touro University-California, CA.

15. TRIPLE JUMP SUMMATIVE EVALUATION: A STRATEGY FOR LONGITUDINAL ASSESSMENT OF STUDENT ACADEMIC PROGRESS.

Karna Mc Donald. *College of Pharmacy and [3]College of Osteopathic Medicine, Touro University-California, CA.*

16. ARE TAMM-HORSFALL PROTEIN (UROMODULIN) LEVELS IN CAUCASIAN THAN IN ASIAN POPULATIONS? A PILOT STUDY

M. Rose, L. Tran, C. Hathuc, J.Schulze, S. Kimura and A. Gugliucci.Touro University College of Osteopathic Medicine, Vallejo, CA. and * Department of Laboratory Medicine Showa University Northern Yokohama Hospital, Yokohama, Japan*

POSTERS

CLINICAL SCIENCES

1. **LONG TERM USE OF BETA BLOCKERS IN WHITE AND BLACK PATIENTS AFTER ACUTE MYOCARDIAL INFARCTION**
   Mitchell Barnett, PharmD, MS[1,2], Mary Vaughn-Sarazin, PhD[1], Gary Rosenthal, MD[1]

2. **ISCHEMIA-MODIFIED ALBUMIN LEVELS ARE HIGHER DURING THE FIRST WEEK AFTER AN ACUTE ISCHEMIC STROKE: A PILOT STUDY.**
   S. Kimura[1], N. Ikeda[2], T. Menini [3], J. Schulze[3], A. Gugliucci[3]
   Touro University-California, Vallejo, CA. Showa University, Yokohama, Japan.

3. **COPING STRATEGIES, METABOLIC CONTROL AND DEPRESSIVE SYMPTOMS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: IS THERE A RELATIONSHIP?**
   Bijal M. Shah and Katherine K. Knapp Touro University-California, Vallejo, CA.

4. **RISK OF CEREBROVASCULAR EVENTS IN ELDERLY VA DEMENTIA PATIENTS: COMPARISON BETWEEN ANTIPSYCHOTIC AND NON-ANTIPSYCHOTIC USERS.**
   Mitchell Barnett, PharmD, MS[1,2], Heidi Wehring, PharmD[2], and Paul Perry, PhD[2]

5. **EMERGING RISK FACTOR (ERF) PATTERNS IN PATIENTS WITH METABOLIC SYNDROME, TYPE II DIABETES, AND CONTROLS. DREAMS 2**
   Ben Willis, M.D.; Walter McConathy, Ph.D.; Sulabha Paranjape, M.S.; Michael Clearfield, D.O., Sabitha Buttreddy, MS.; Enisa Arslanagic, M.D.; Fidelita Weis, R.N; Rubina Muzina, M.D.; Mabyn Hager, RN,; Joice Carter, DE; Karan Singh, Ph.D; and Craig Spellman, Ph.D., D.O.
   Texas College of Osteopathic Medicine and School of Public Health, University of North Texas Health Science Center and Plaza Medical Center, Fort Worth, Texas 76107

6. **LOW DENSITY LIPOPROTEIN PHENOTYPE AND CORONARY CALCIUM SCORES. DREAMS 2**
   Walter McConathy, Ph.D.; Sulabha Paranjape, M.S.; Michael Clearfield, D.O.; Ben Willis, M.D.;Sabitha Buttreddy, M.S.; Karan Singh, Ph.D.; and Craig Spellman, Ph.D., D.O.
   Texas College of Osteopathic Medicine and School of Public Health, University of North Texas Health Science Center, Fort Worth, Texas 76107

7. **ETHNIC DIFFERENCES IN TRADITIONAL AND EMERGING RISK FACTORS FOR INDIVIDUALS DEVELOPING DIABETES/METABOLIC SYNDROME AND CORONARY HEART DISEASE. DREAMS 2.**
Craig Spellman, Ph.D., D.O., Michael Clearfield, D.O., Ben Willis, M.D.; Enisa Arslanagic, M.D.; Fidelita Weis, R.N; Rubina Muzina, M.D.; Mabyn Hager, RN,; Joice Carter, DE;.Sabitha Buttreddy, MS.; Karan Singh, Ph.D; and Walter McConathy, Ph.D.
Texas College of Osteopathic Medicine and School of Public Health, University of North Texas Health Science Center, Fort Worth, Texas 76107

8. ***HIGH NORMAL A1C AS A SCREEN FOR DIABETES AND PREDIABETES IN AN UNDERSERVED LATINO POPULATION***
P. Baginsky, M.D. Touro University-California, Vallejo, CA.

9. ***THE PHARMACIST SHORTAGE IN CALIFORNIA: THE AGGREGATE DEMAND INDEX BY COUNTY***
C. Canlas, C. Chiu, A. Deukmedjian,J. Dinh, S. Kaur, D. Kusior, K. Le, V. Nguyen, J. Speck, L. Valencia.
Touro University-California, Vallejo, CA.

10. **OBESITY AND CARDIOVASCULAR RISK. DREAMS 2.**
Michael Clearfield, D.O., Craig Spellman, Ph.D., D.O., Ben Willis, M.D.; Enisa Arslanagic, M.D.; Michael Clearfield, D.O., Rubina Muzina, M.D.; Mabyn Hager, RN; Joice Carter, DE; Sabitha Buttreddy, M.S.; Sulabha Parajape, M.S.; Karan Singh, Ph.D; and Walter McConathy, Ph.D.
Texas College of Osteopathic Medicine and School of Public Health, University of North Texas Health Science Center, Fort Worth, Texas 76107

11. **TRADITIONAL AND EMERGING RISK FACTORS IN INDIVIDUALS WITH ACUTE CORONARY SYNDROME**
Jonathan Matthews, D.O., Kyle Hendrix MSIV, Michael Clearfield, D.O., Craig Spellman, Ph.D., D.O., Walter McConathy, Ph.D., Ben Willis, M.D.; Enisa Arslanagic, M.D.; Fidelita Weis, R.N; Rubina Muzina, M.D.; Mabyn Hager, RN; Joice Carter, DE; Sabitha Buttreddy, MS.; Karan Singh, Ph.D
Texas College of Osteopathic Medicine and School of Public Health, University of North Texas Health Science Center and Plaza Medical Center,

12. **A CROSS-SECTIONAL SURVEY OF SCHISTOSOMIASIS INCIDENCE AND PERCEPTIONS IN MINGO TANZANIA**
Thomas M. Sichi OMS2 MPH, Justin Knebel,
Candice Carmel Blagmon OMS2 MPH

13. ***NEW PHARMACIST SUPPLY PROJECTIONS: LOWER SEPARATION RATES AND INCREASED GRADUATES BOOST SUPPLY ESTIMATES***
K.K. Knapp[1], J.M. Cultice[2]
1. Touro University-California, Vallejo, CA. 2. Operations Research Analyst, Bureau of Health Professions, Health Resources and Services Administration, USDHHS, Rockville, MD.

14. **ESTIMATING RISK FACTORS FOR DIABETES AMONG SCHIZOPHRENICS WITH EXPOSURE TO ATYPICAL ANTIPSYCHOTICS.**
Mitchell J. Barnett, PharmD, MS[1,3], Tim L. Holman, MS[2], Tami R. Argo, PharmD, MS[4], Paul J. Perry, PhD[2,3]
[1] Center for Research in the Implementation of Innovative Strategies in Practice, Iowa City VAMC
[2]Roy and Lucille Carver College of Medicine, University of Iowa
[3]Touro College of Pharmacy
[4] Texas College of Pharmacy

15. **CROSS-CULTURAL HEALTH LITERACY: EFFECTIVENESS OF A TAGALOG BROCHURE IN EDUCATING FILIPINOS ABOUT VALLEY FEVER (COCCIDIOIDOMYCOSIS)**
Gemmie S. Devera, MSPAS/MPH 2007 Candidate
Touro University-California, Vallejo, CA

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Canlas Crystal, Chiu Charlene, Deukmedjian Ani, Dinh James, Kaur Sandeep, Kusior Daria, Le Kelly, Nguyen Vinh, Speck Joshua, Valencia Laurie

ABSTRACTS

ORAL PRESENTATIONS

Keynote speaker

Chemical modifications of proteins in aging and disease

John W. Baynes, PhD
Carolina Distinguished Professor Emeritus
Dept of Biochemistry, University of South Carolina

As students are well aware, biochemists spend a lot of time studying regulatory biology – the network of reversible and irreversible biochemical communication and control systems that direct metabolism and its response to changing demands. However, often ignored, but equally important, is an underlying web of spontaneous, less tightly regulated organic reactions between the components of biological fluids. This *nonenzymatic* chemistry produces chemical modifications, adducts and crosslinks that accumulate on tissue proteins with age. Some of these compounds affect the structure, function and turnover of biomolecules; others induce signaling cascades, inflammatory responses and pathology; while others affect the activity of metabolic pathways.

The focus of this presentation will be on advanced glycoxidation and lipoxidation end-products (AGE/ALEs), which are formed by oxidative modification of proteins by carbohydrates and lipids. These products accumulate naturally on proteins with age, but accelerated accumulation of AGE/ALEs during hyperglycemia and hyperlipidemia is implicated in the development of long-term complications of diabetes – retinopathy, nephropathy, neuropathy and vascular disease. New drugs are being developed to inhibit AGE/ALE formation, and these drugs show promise for the treatment of diabetic complications.

Development of methods for control of nonenzymatic chemistry is a frontier area of research in biochemistry, and translation of the results of these studies to clinical practice should lead to longer, healthier lifespans in the 21st century.

Assessment of the Contribution of Lactate to Fatty Acid Synthesis by Mass Isotopomer Distribution Analysis (MIDA)

Dr. Karl Meszaros and Dr. Jean-Marc Schwarz

Background: Lactate has a variety of important roles in carbohydrate and fat metabolism. The relative contributions of glucose and lactate to fatty acid synthesis are not known.

Hypotheses and aims: We hypothesized that, at physiological concentrations, extracellular lactate competes with glucose as a source of acetyl-CoA, hence as a carbon source for the synthesis of fatty acids.

Methods: In the present study adipocytes were isolated from the epidydimal fat pad of rats, and incubated for 2 h with 5 mM U-^{13}C-glucose in the absence and presence of unlabeled lactate. Thereafter, lipids were extracted, the fatty acids were trans-esterified, and the distribution of ^{13}C in the carbon chain of palmitate was analyzed by gas chromatography/mass spectrometry.

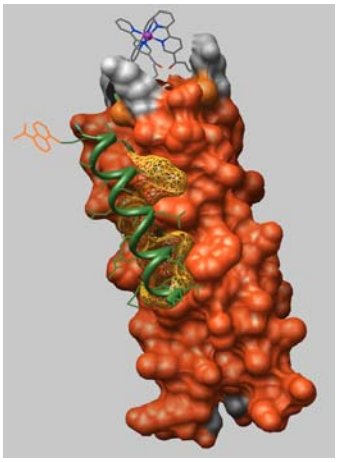
Results: The data were evaluated by an extended application of MIDA. Due to the high abundance of ^{13}C in the glucose substrate, newly synthesized palmitate was highly labeled, containing 12 to 16 atoms of ^{13}C in the carbon skeleton. Thus, palmitate was synthesized from a highly labeled acetyl-CoA precursor pool. The labeling (enrichment) of the precursor acetyl-CoA pool was derived by MIDA calculations from the enrichment pattern of the labeled species of palmitate. In the absence of lactate, the calculated enrichment of acetyl-CoA was 90%. Addition of unlabeled lactate (1, 3 or 9 mM) to the incubation medium markedly decreased the enrichment of acetyl-CoA (to 60, 40 and 20%, respectively).

Conclusion: We concluded that in the presence of physiological concentrations of glucose and lactate, the contribution of lactate to the synthesis of fatty acids was about 50%.

A Metallopeptide Mimic Of The Coiled Coil Domain Of Class 1 Viruses Is A Useful Target For Antiviral Drugs.

Lifeng Cai, Yanxia Hou and Miriam Gochin*

Touro University – California, 1310 Johnson Lane, Mare Island, CA 94592



Trimeric coiled coil (in red) anchored by a tris-bipyridyl-Fe complex. The fluorophore (orange)-labeled peptide from another domain of gp41 is shown in green, bound to the coiled coil.

Background: We have been working on a metallopeptide construct of the coiled coil domain of HIV-1 gp41, for use as a receptor to detect entry inhibitors through high throughput screening. A metal coordination complex holds together three component peptides from the trimeric coiled coil and also acts as a probe of binding to the coiled coil. Binding of a second viral domain is the process that precipitates fusion in the intact virus. Small molecules able to prevent the binding can act as fusion inhibitors. The metallopeptide has been used in a fluorescence assay, in which the role of the metal complex is to quench fluorescently labeled peptide from the second viral domain upon binding. This is the basis for a simple assay in which small molecule inhibitors are detected by an increase in fluorescence in a ternary system containing the metallopeptide, the fluorescent peptide and the small molecule inhibitor. The metallopeptide has also been used to design an electrochemical sensor, in which label free detection of small molecule inhibitors has been demonstrated using immobilized receptor on a gold surface.

Methods: We have carried out studies to confirm that the metallopeptide is representative of the intact viral protein, including the ability of the assay systems to specifically and sensitively detect know gp41 fusion inhibitors. We will demonstrate a novel class of peptidomimetic fusion inhibitors that we have detected. Although these only inhibit in the micromolar range, they are relatively small and amenable to modification, so that they may be developed into more potent fusion inhibitors, especially by taking advantage of multiple binding sites up and down the coiled coil. These alternative sites can be selected using various peptide constructs. A similar fusion process occurs with other class 1 viruses including paramyxoviruses (RSV, Mumps, Measles, Sendai Virus), orthomyxoviruses (Influenza A), coronavirus (SARS), retroviruses (HIV, HTLV) and filovirus (Ebola), so that broader application of the method is expected.

Keywords: HIV-1 fusion inhibitors, fluorescence, electrochemistry, high throughput screening

Trojan Horse Encapsidated RNA Vaccines Stimulate Specific Immunity

Alison A. McCormick [1,2], Tina A. Corbo[2], Sherri Wykoff-Clary[2], Mark L. Smith[2], Long V. Nguyen[2], Kenneth E. Palmer[2], and Gregory P. Pogue [2]

1. Touro University-California, Vallejo, CA.
2. Large Scale Biology Corporation, Vacaville, CA.

Background and Hypothesis: Therapeutic vaccines to treat cancer are designed to stimulate cytotoxic T lymphocytes (CTL) and other effector cells to recognize class I antigens in a context that minimizes anergy and maximizes T cell activation. One powerful way to stimulate CTL activity is to present antigen in the context of a particulate delivery systems that stimulates uptake by professional antigen presenting cells and augments cross priming. A second effective method is to deliver infectious RNA that can prime virus encoded intracellular delivery of a vaccine antgen. We combined these two approaches to maximize antigen delivery, by encapsidating Semliki Forest Virus RNA into a rod shaped virus using tobacco mosaic virus (TMV) coat protein. In order to drive encapsidation, we introduced a TMV origin of assembly into self replicating but defective SVF RNA encoding the model antigen b-Galactosidase (bGal). When exposed in vitro to TMV coat protien, synthetic SFV-bGal-ori RNA can then be efficiently encapsidated, and RNA is both protected from degredation and in a particulate form which stimulates antigen presenting cell uptake. We tested this composite vaccine in cellular assays for bGal expression, and in mice to evaluate vaccine efficacy.

Methods: SFVbGal-ori RNA was synthesized in vitro and mixed for assembly at a 1:1.25molar excess of RNAse free TMV coat protein at room temperature for 16 hours. Product was recovered by PEG precipitation and characterized by protein concentration, electrophoretic mobility and electron microscopy. The ability of the pseudovirus to express bGal protein was determined by exposing BHK-21 cells with 2ug pseudovirus, and then stained for bGal enzyme after 20 hours using X-Gal substrate. The ability of the pseudo virus to stimulate appropriate immunity was measured after C57B/6 mice were given 20-25ug pseudovirus vaccine s.c. without adjuvant. Antibody mediated immune responses to bGal were measured in serum by ELISA and cellular mediated immune responses against bGal were measure by ELISPOT after bGal peptide stimulation of 10^5 spleen cells.

Results: Cell analysis of pseudovirus enzyme expression indicated that after cellular uptake, RNA was uncoated and translated to produce functional bGal protein. Immune response analysis showed antibodies, and more importantly, cellular responses were induced after intracellular expression and antigen presentation of bGal-derived peptides.

Conclusions and future directions: TMV encapsidated RNA has advantages as a vaccine delivery method, including targeting particulate antigen uptake in antigen presenting cells, RNA uncoating and expression, stimulation of antibodies and cellular responses. Future experiments will test the efficacy of TMV encapsidated BGal SFV-ori RNA to protect mice after lethal challeng of a bGal expressing tumor line. Analysis of other important tumor genes or co delivery of cytokines are also planned.

Permeation is a Much Larger Determinant of Block of HERG By Quinidine and Cisapride Than Inactivation.

Cheung K., Stratton, M.J., Pham N., and Miller A.

Touro University College of Osteopathic Medicine, Vallejo, CA.

Background and Hypothesis: The human ether-a-go-go-related gene (HERG) encodes a voltage-gated potassium channel involved in terminating the ventricular action potential. Block of HERG can result in the lethal arrhythmia Torsade de Pointes, characterized by severely compromised cardiac output. A large number of pharmaceutical compounds still in use have been shown to block HERG. However, the mechanisms by which drugs block HERG are still poorly understood. Previously published data has shown that HERG block by quinidine and cisapride is reduced with elevated extracellular potassium. This reduction in block could be explained by two general mechanisms: a "knockoff" effect of the permeant ion or an indirect effect in which extracellular potassium slows HERG inactivation and the drugs preferentially block the inactivated state. It should be possible to distinguish between these two mechanisms by using extracellular electrolytes that alter HERG inactivation and also show different permeabilities through HERG channels.

Methods: Block of HERG by quinidine and cisapride was tested using two electrode voltage clamping of *Xenopus* oocytes in extracellular solutions of potassium (K) rubidium (Rb), cesium (Cs) and tetraethylammonium (TEA). The permeability of HERG follows the sequence $P_K=P_{Rb}>P_{Cs}>>>P_{TEA}$. Extracellular K, Rb, Cs, and TEA all slow HERG inactivation.

Results: Changing the extracellular solution from 0 mM to 20 mM potassium reduced HERG block of cisapride 8-fold and HERG block of quinidine 10-fold. A similar reduction was also seen when changing the extracellular solution from 0 mM potassium to 0 mM potassium with 20 mM rubidium. Changing the extracellular solution from 0 mM potassium to 0 mM potassium with 20 mM cesium only reduced HERG block by cisapride 2-fold and HERG block by quinidine 2.5-fold. Changing the extracellular solution from 0 mM potassium to 0 mM potassium with 40 mM TEA did not alter HERG block by cisapride or quinidine.

Conclusions: Since 20 mM potassium, 20 mM rubidium, 20 mM cesium, and 40 mM TEA slow HERG inactivation by approximately equal amounts and the rank order of HERG permeability is $P_K=P_{Rb}>P_{Cs}>>>P_{TEA}$, these results suggest that cisapride and quinidine do not preferentially block inactivated HERG channels, and that permeation through HERG channels is a larger determinant of HERG block by quinidine and cisapride than is inactivation.

Acrolein inhibits paraoxonase-1 activity : effect of hemodialysis and putative role in atherogenesis

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Background: Patients with chronic renal failure have an increased risk for death from cardiovascular disease, especially those patients in end-stage renal disease and undergoing hemodialysis, that is due in part to deficit in paraoxonase (PON-1). Putative causes for reduced PON-1 activity in chronic renal failure patients are reduced HDL levels, altered HDL subfraction distribution, reduced PON1 concentration and different paraoxonase phenotype distributions. In a previous study we had shown that hemodialyis increases PON-1 activity by up to 40%. Acrolein is a very reactive dicarbonyl, one of the most concentrated substances in tobacco smoke and a terminal product of lipoperoxidation. Acrolein readily forms adducts with lysine and oxidizes cysteine. Recently, acrolein has been postulated as a uremic toxin, due to demonstrated increase in serum via an altered catabolism of polyamines in this condition. No study had been performed as to the efficacy of the removal of acrolein by hemodialysis. In a preparatory *in vitro* study presented as a poster here, we demonstrate inactivation of PON-1 in HDL by acrolein.

Hypothesis and aims: We hypothesized that acrolein may be in part responsible for paraoxonase activity inhibition in the uremic milieu. Our first aim was to confirm that acrolein levels are high in ESRD, determine the rate of clearance by hemodialysis and finally, whether there is a correlation with PON-1 changes.

Methods: We conducted a study with 44 end-stage renal disease (ESRD) patients undergoing hemodialysis in whom paired pre and post-dialysis samples were studied along with 30 age-matched control subjects. We measured PON-1 activities, as well acrolein and AGE products, lipid peroxidation, apoA, lipid profiles, HDL-subclasses, in each of the patients and evaluated the correlations of uremia-associated substances (urea, creatinine) with paraoxonase activity and acrolein levels.

Results: Dialysis produces a 5-40% increment in PON-1 activity (average 20 ± 8%) while no significant changes in either apoA-I or HDL subclasses distribution was observed. Serum acrolein levels were 312 ± 76 μmol/ml for control subjects; 914 ± 210 μmol/ml for CRF patients. Acrolein levels correlate poorly with BUN or creatinine ($r = 0.3$, $p < 0.01$). Dialysis produced a 30 ± 5 % decrease in acrolein levels. This change correlates ($r = 0.5$, $p < 0.001$) with the efficiency of dialysis as determined by either creatinine or urea rate of change. A correlation ($r = 0.35$, $p < 0.01$) was observed between changes in PON-1 activity and changes in acrolein concentration.

Conclusions: Our data give both in vitro and in vivo support to the contention that high serum levels of acrolein in ESRD patients are partly responsible for inhibition of PON-1. We show that acrolein is partially removed by dialysis (similar efficacy than creatinine). Our results confirm previous data suggesting acrolein is a uremic toxin and suggest another mechanism for renal failure induced atherogenesis, which would act synergistically with HDL and LDL as well as hemodynamic changes in this disease. If acrolein is in part responsible for loss of PON-1 activity, this information suggests that other sources (tobacco, infection, inflammation) have to be especially addressed in CRF patients. The potential use of cysteine of N-Ac-cysteine to counteract acrolein action on PON-1 warrants further study as well.

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Health-Related Quality Of Life (Hrqol) In Primary Care Patients With Type 2 Diabetes Mellitus And Depression

Bijal M. Shah and Katherine K. Knapp

Hypotheses and aims: To (1) determine the prevalence of depression in primary care patients with type 2 diabetes mellitus (T2DM) and (2) compare HRQoL in diabetic patients based on the severity of depressive symptoms.

Methods: Primary care patients with T2DM were recruited during their scheduled clinic appointments. Self-reported data on demographic characteristics were collected via a survey. Data on Hemoglobin A1C values and comorbid conditions were collected from patient charts. The Zung self-rating depression scale was used to measure depressive symptoms and the SF-8 was used to measure HRQoL. Analysis of variance (ANOVA) was used to compare HRQoL summary scores and domain scores for general health (GH), physical functioning (PF), role physical (RP), bodily pain (BP), vitality (VI), social functioning (SF), mental health (MH) and role emotional (RE) in diabetic patients based on the severity of symptoms.

Results: A total of 217 surveys were collected with a usable response rate of 93%. The mean age of the overall sample was 57.3 years (SD = 11.9), 62.2% were female and 61% were Hispanic. The Zung self-rating depression scale indicated that 72.1% of patients met criteria for depression. Scores for the domains of GH, PF, RP, BP, VI, SF, MH and RE decreased significantly ($p<0.001$) as the severity of depressive symptoms increased. Similarly, ANOVA results showed that summary scores for PCS-8 ($F=24.16$, $p<0.001$) and MCS-8 ($F=40.00$, $p<0.001$) decreased significantly as depressive symptom severity increased. Post-hoc analyses revealed significant differences between groups.

Conclusions: Patients with T2DM were found to have a high prevalence of depressive symptoms, including symptoms of severe depression. Mental as well as physical HRQoL decreased significantly as the severity of depressive symptoms increased. Detection and treatment of depression may help to improve HRQoL in patients with type 2 diabetes mellitus.

Effects Of Oxidized Low Density Lipoprotein On Hsp 70 Expression In The Cerebral Cortex Of Huntington's Disease Transgenic Mice

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Background and Hypothesis: Huntington's Disease (HD) is a progressive, autosomal dominant neurodegenerative disorder characterized by choreiform movements and changes in behavior and cognition. Huntingtin protein aggregates, due to polyglutamine tract expansion, form intracellular and intranuclear inclusions, which are hallmarks of HD cellular pathology. These inclusions co-localize with heat shock proteins (HSP) and both intracellular and extracellular HSP may play a role in HD pathogenicity. HSP are expressed by cells in response to environmental stressors and are well known for their role as molecular chaperones in a variety of intracellular protein processing. To test the hypothesis that HSP production and transport across cortical cell membranes is altered in Huntington's Disease, we examined HSP levels in R6/2 transgenic mouse model of HD. We measured intracellular Hsc70/Hsp70 (iHSP) and extracellular Hsp70 (eHSP) in response to an oxidative stressor in HD mutants at asymptomatic (18-25 days, young) and symptomatic (>80days, old) ages and compared them with age matched littermate controls (WT).

Methods: Cerebral cortex from young and old HD and WT was microdissected and incubated in artificial cerebrospinal fluid with low-density lipoprotein (LDL, control) or oxidized-LDL (ox-LDL, stressor) for 24h. Samples were analyzed for iHSP (immunoblots) and eHSP (ELISA).

Results: Compared to the LDL treated control, ox-LDL decreased iHSP to 63±7% and increased eHSP by 5±1μg/mg tissue in young WT. In young HD, ox-LDL had no effect on iHSP (100±6%) but decreased eHSP by 2.4±3μg/mg tissue. Thus, ox-LDL treated HD tissue retained relatively more iHSP than WT ($p=0.002$) while the eHsp70 was decreased compared to WT ($p=0.01$). In old WT, ox-LDL decreased iHSP to 81.0±8.94% and increased eHSP by 3.25±2.24μg/mg tissue. In old HD, ox-LDL also decreased iHSP to 68.6±9.90% and increased eHsp70 by 4.63±2.4μg/mg tissue; iHSP and eHSP were not significantly different between HD and WT ($p=0.37$ and $p=0.868$, respectively). As the WT mice age, there is no significant difference in ox-LDL effect on iHSP or eHSP ($p=0.162$ and $p=0.964$, respectively). However, as HD mice age, ox-LDL effect on iHSP levels was significantly decreased while eHSP was significantly increased when compared to WT controls ($p=0.017$ and $p=0.002$, respectively).

Conclusions: Asymptomatic HD cortical cells have decreased ability to transport HSP following exposure to an oxidative stressor but are able to transport more HSP as they age. Because Hsp70 production is thought to be cytoprotective, this may indicate a compensatory mechanism to retain Hsp70 in HD animals as disease symptoms progress. Furthermore, the abnormal response to stressors at asymptomatic ages may contribute to the aggregation of inclusions and the pathogenesis of HD.

Acknowledgment: AAN Medical Summer Student fellowship and AMA Seed Grand (DHL).

Cardiovascular Disease Prevention through Active Education

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Background and Hypothesis: The Stanford Medical Youth Science program (SMYSP) provides a school-based intervention to teach high school students from under-resourced schools to conduct survey research about cardiovascular disease risk factors or a health issue that interests them. The goal of this intervention is to develop health knowledge and involvement based on educational outreach. The objectives were to 1) Develop a school-based curriculum in partnership with 4 underserved high schools; 2) Teach students research methods and how to create a scientific poster on a cardiovascular disease risk factor or health topic that interests them; 3) To give students the opportunity to present their work to fellow students, teachers, school personnel, family members and their local community; 4) At the end of the intervention assess change in student self-confidence regarding researching healthcare issues relevant to them.

Methods: Trained 4 high school biology teachers at schools serving predominantly native American, rural Latino, urban Latino or urban African American students at a 1 day one on one training session. Teachers were trained to use visual images, statistics, web-based activities, and worksheets developed in this project to increase awareness of cardiovascular disease risk factors and to teach the scientific method to the students. The students were administered pre and post baseline questionnaires to measure their self-confidence in dealing with the healthcare issues applicable to themselves and their community. SMYSP provided 1 support staff member at each school site to help carry out the intervention. Pre and Post baseline questionnaires measured change in student self-confidence over the course of the school year.

Results: +13.2% increase in students who responded that they know how to locate health information on the internet (p value .004); + 12.5% increase in students who responded that they know how to write a scientific question (p value .02); +16.4% increase in students who responded that they know how to approach a health agency person to gather information (p value .001); +30.9% increase in students who responded that they know how to design a health survey (p value <. 001), + 35.6 % increase in students who responded that they know how to choose a sample population to study a health issue (p value < .0001); +27.8% increase in students who responded that they know how to collect health data (p value <.0001); +22.4% increase in students who responded that they know how to use a computer program to enter and analyze data (p value <.0001). +23.1% increase in students who responded that they know how to create graphs and tables on health data collected (p value <.0001), and a +15.8% increase in students who responded that they know how to talk with others about their health study (p value .0004).

Conclusions: Teachers successfully implemented curriculum with support from SMYSP staff. Students learned about cardiovascular disease risk factors through hands-on methods, teacher presentations, and support from SMYSP staff. The pre and post questionnaire results suggest that the intervention resulted in significant increase in student self-confidence in exploring and presenting healthcare issues by the end of the academic year which in turn will encourage them to get involved in their own health and that of their community. Tracking the students over the course of several years and offering readily available resources to enter the health prevention or learn about health issues over a more extended period might further increase the effectiveness of this intervention

New Pharmacist Supply Projections: Lower Separation Rates and Increased Graduates Boost Supply Estimates

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Background and Hypothesis: The Bureau of Health Professions (BHPr) maintains an active U.S. pharmacist workforce model that is periodically updated as new data about new workforce entrants, international graduates and separation rates are available. This paper revises the 2000 BHPr model and includes estimates of the full-time-equivalent workforce. The model is important because the last national pharmacist census occurred in 1989-1991 making the model the most reliable source of pharmacist workforce data.

Methods: Total pharmacist headcounts are drawn from 2004 BLS data. The total count is distributed into 50 age groups by gender using data from a national survey. The model projects these numbers forward in time by (i) adding, each year, the projected number of new entrants and (ii) subtracting, each year, the projected number of both base-year pharmacists and new entrants who will die or retire. The composite of base-year pharmacists and new entrants who have neither died nor retired constitutes the active pharmacist supply for a given year. The FTE workforce is based on 2004 data showing men working 91% and women 81% of a 40 hour workweek. We applied these factors to estimate the projected FTE pharmacist supply.

Results: Substantial increases in the estimated U.S. pharmacist supply were noted: 19,157 (2004) to 65,080 (2020). Primary factors were longer persistence in the workforce (59%) and increased U.S. graduates (35%). Increases from international pharmacy graduates achieving U.S. licensure were <6%. More pharmacists working part-time reduced the full-time equivalent (FTE) supply by about 15%. Pharmacists' mean age declined from 47 to 43 by 2020. Due to unequal distribution across age groups, large pharmacist cohorts approaching retirement ages will find fewer pharmacists available to replace them. Pharmacists-to-over-65-population ratios decrease after 2011 and continue falling beyond 2020 reflecting baby boomers passing through older age cohorts.

Conclusions: Pharmacists working longer and educational expansion caused an unpredicted increase in supply estimates and a three-year reduction in mean age by 2020. More part-time work resulting in about 15% FTE workforce reduction counterbalances these trends. Reductions in pharmacist-to-over-65-population ratios from 2011 onward, despite supply increases, illustrate the impending healthcare challenge as baby boomers move through their senior years. Historical fluctuations in graduates could create a shortfall of experienced, senior pharmacists during the early phases of the baby boomer retirement era. Coincident demands for more physicians and nurses over the same period and shortages in all three professions argue for proactive steps, important among them continued monitoring of work trends among pharmacists and other health professionals.

Simple Spectroscopic Monitoring Of Liquid Surface Curvature Changes In Thin Wells

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Background and Hypotheses: The boundary between liquid and solid is often characterized by a curved liquid surface in thin tubes or in small liquid drops on a solid surface. The surface curvature is a manifestation of the equilibrium between solid surface tension, liquid surface tension, solid-liquid interface tension and gravity.

Methods: Knowledge of these forces is important in many technological processes, including surfactant development in drug delivery formulation and physiology, micro- or nano-manufacturing, microfluidics and surface fabrication. Classical liquid surface tension measurements are very precise, but require complex preparation and expertise in sample handling. Few simple and high-throughput (HT) methods are currently available to study liquid-solid-surface interactions. Here we report a simple fluorescence method to study liquid surface curvature changes in thin-well plates, with a dynamic range of 60% and a relative sensitivity of 2%.

Results: It exploits the effect of total internal reflection on fluorescence emission through a curved liquid surface. Application of the effect is demonstrated by a method for rapid and universal determination of surfactant critical micelle concentration (CMC) and by a simple assay for promiscuous inhibitors resulting from micelle formation. Plate-based measurement of surface curvature is an efficient method for investigating systems where colloidal properties, surface tension or interfacial tension are paramount.

Genetic and biochemical analysis of human caspase 12

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Background the Hypotheses: *Casp12* encodes the protein caspase 12 (casp12), which has a downregulatory effect upon interleukin-1 (IL1) activation and subsequent inflammatory immune reactions. *Casp12* is primarily a pseudogene (*Casp12p1*) in most humans, but ~20% of people of African ancestry have a functional, intact form of *Casp12*. This allele is increased in African-American individuals with severe sepsis. We examined *Casp12* allele distribution in populations of Indians and Central Asians and in a pilot screen found that a small number of Tamils (2 of 10; 20%) possess the intact *Casp12* allele. Gujratis, Punjabis and other Central Asians (Baluchi, Iranian, Pakistani or Afghani) were all homozygous for *Casp12p1,* as were nearly all other Indians (18/19; 95%). Thus, small but distinct populations outside of Africa still harbor *Casp12*.

Methods: To examine the biochemical properties of the protein, we expressed recombinant human casp12. In order to better characterize the role of casp12 in the inflammatory process, we generated a rabbit polyclonal antiserum to casp12 and used it to determine if the protein interacted directly with components of the inflammasome. The inflammasome is a cytosolic protein complex that allows activation of precursors of proinflammatory caspases, which then cleave the precursor of IL1 into its active form.

Results and Conclusions: Immunoprecipitation of casp12 with our antisera revealed that the protein did not interact with the inflammasome components ASC, Cardinal, or Caspase 5. Casp12 may thus exert its downregulatory effects by direct interaction with IL1.

Mutation of the Phospholipase Catalytic Domain of the *Pseudomonas aeruginosa* Cytotoxin ExoU Abolishes Colonization Promoting Activity and Reduces Corneal Disease Severity

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Backgrounds and Hypotheses: We have shown that ExoU, a type III secreted cytotoxin of *Pseudomonas aeruginosa*, contributes to corneal disease pathology and ocular colonization in the murine scarification model of microbial keratitis. Subsequently, we showed that this is associated with ExoU-mediated repression of phagocyte infiltration of infected corneas *in vivo*. ExoU has patatin-like phospholipase activity which is required for its cytotoxic activity (injury and cell death) towards mammalian cells *in vitro* and disease in a murine model of acute pneumonia. We hypothesized that phospholipase activity was required for ExoU-mediated colonization and disease in the cornea.

Methods: The murine scarification model was used to examine corneal disease pathology and bacterial colonization (viability) at 24 and 48 h after inoculation with ~10^6 cfu in 5 μl of a double effector mutant of *P. aeruginosa* strain PA103 (PA103Δ*exoUexoT*::Tc) complemented with *exoU*, phospholipase-inactive *exoU* (*exoU*D344A) or plasmid control (pUCP18). Eyes were photographed and disease severity scored. Colonization of the complemented mutants was also assessed at 6 h post-inoculation which is prior to significant phagocyte infiltration of the cornea. Complementation of the double effector mutant was used to avoid confounding effects of ExoT which also contributes to corneal disease and colonization.

Results: Complementation with *exoU* caused significantly more disease pathology (increased disease severity scores) and ~1000-fold greater ocular colonization at 48 h post-infection than the phospholipase-inactive *exoU* which did not differ significantly from the effector mutant complemented with control plasmid. Surprisingly, neither *exoU,* nor its inactive phospholipase form, contributed significantly to early (6 h) ocular colonization.

Conclusion: The phospholipase catalytic domain of ExoU is required for its contribution to ocular colonization *in vivo* and its contribution to corneal pathology at 48 h post-infection. The data suggest, however, that early cytotoxic effects on epithelial cells are not important for these *in vivo* effects at least in this model. The phospholipase-mediated colonization and disease promoting activity of ExoU at 48 h may be associated with repression of phagocyte infiltration of infected corneas associated with this toxin.

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POSTER PRESENTATIONS

BASIC SCIENCES

1. *Separation of L- and D-Lactate enantiomers: a method to detect endogenous glycation*

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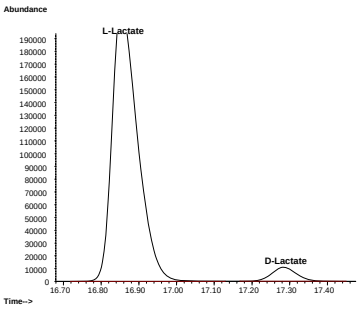
Background and Hypothesis: L-lactate is the normal end product of anaerobic glycolysis. However, in the presence of increased metabolic fluxes, trioses from glycolysis can lead to the endogenous formation of advanced glycation endproducts (AGE), through the very reactive dicarbonyl methylglyoxal (MG). Glycation is thought to contribute to disease processes such as diabetic complications, macrovascular disease, Alzheimer's disease, cirrhosis, uraemia, arthritis, ageing and others. [1] Methylglyoxal may be converted to D-lactate, a stereoisomer of L-lactate. D-lactate is the end product of the glyoxalase pathway, its major detoxification mechanism. D-lactate levels may therefore be surrogate markers of increased MG flux and hence potential markers that could be used for dynamic monitoring of AGE formation. We developed a new Gas Chromatography/Mass Spectrometry (GC/MS) method to separate L and D-lactate enantiomers and to quantify their relative concentrations.



Methods: GC/MS analyses were performed with HP 6890 equipped with MSD 5973 using both electron ionization (EI) and chemical ionization (CI) sources. Various lactate derivatization methods and GC columns have been tested. Separation by an achiral Stabiliwax column (60m, 0.32mm ID, 1µm df, Restek) using 2-butanol/HCL and (S)-(+)-2-phenylbutyric chloride (PBC) resulted in high degree of racemization and poor yield. [2] The method was further modified by using enantiomerically pure (S)-(+)-3-methyl-2-butanol/HCL and trifluoroacetic anhydride (TFAA) but did not produce acceptable resolution or yield. [3] Derivatizing lactate as n-propylamide heptafluorobutyrate using an HP-5MS capillary column (60m, 0.25mm ID, 0.25µm df, J&W) did not result in separation but produced a high yield. [4] We used this method with a chiral Rt-BDEXcst column (30m, 0.25 ID, 0.25µm df, Restek) to achieve high resolution, high yield and racemization free separation of lactate to measure concentration of its enantiomers from diabetic and non-diabetic subjects. Internal standards of sodium L- and D-lactate were purchased from Fluka. Isolation of lactate from plasma was performed using ion-exchange chromatography. [4]

Results: Plasma D-lactate represents 1 to 8% of L-lactate for healthy subjects and 8-15% for diabetic subjects. The highest D-lactate concentrations were found in the diabetic subjects with higher glycemia levels.

Conclusions: Our preliminary results suggest D-lactate can be assessed by GC/MS and that D-lactate concentration is present in both healthy and diabetic subjects. This method may be used to monitor changes of AGE precursor formation associated with diet or pharmacological treatment. Future studies monitoring the kinetics of D-lactate formation and its relation to AGE production may help to develop an acute test of AGE metabolism and screening of best therapeutic agent to prevent AGE formation.

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2. Free Serum Acrolein Levels In Several Disease States Associated With Oxidative Stress Or Inflammation.

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Background: Acrolein is a highly reactive air pollutant of human health concern, chiefly as it is a component of cigarette smoke. Lipid peroxidation and threonine oxidation by myeloperoxidase are potential sources of endogenous acrolein during inflammation. Another source is altered polyamine metabolism in renal failure. Acrolein can be metabolized in the liver by enzymes including the aldo-keto reductase family of enzymes. Acrolein oxidizes cysteine and forms adducts with lysine through the Maillard reaction, with deleterious consequences on protein function. There exist several reports on acrolein-adducts in renal failure, stroke and other conditions, but scarce data is available on free acrolein levels in conditions associated with increased oxidative stress.

Hypothesis: We tested the hypothesis that free serum acrolein levels are increased in conditions associated with increased oxidative stress and inflammation: renal failure, stroke, infection and diabetes, as well as in liver disease by impaired metabolism.

Design and Methods: We performed a nested case-control study with 35 chronic liver disease patients (aged 45-73 years, 20 alcohol-related; 8 terminal cirrhosis, 2 fatty livers 5 hepatocellular carcinomas); 40 chronic renal failure (CRF) patients undergoing dialysis (20 diabetes, 10 chronic glomerulonephritis, 10 other); 22 type 2 diabetic patients (mean HbA1c 10%); 15 stroke (CVA) patients (12 ischemic, 3 hemorrhagic); 10 acute pneumonia patients and 40 age-matched controls. Fasting blood samples were analyzed for acrolein using a fluorometric method through the reaction of m-aminophenol in acidic media.

Results: Serum acrolein levels were 312 ± 76 μmol/ml for control subjects; 914 ± 210 μmol/ml for CRF patients; 340 ± 96 for diabetic patients; 300 ± 89 for chronic liver disease patients; 330 ± 91 for CVA patients and 1212 ± 210 for pneumonia patients. The differences between controls and CRF, or pneumonia patients are significant with a $p < 0.001$. In diabetic patients, acrolein correlates with fasting glycemia and HbA1c ($r=0.5$ and 0.41 respectively, $p < 0.05$). In renal patients, acrolein does not correlate with creatinine or BUN.

Conclusions: Free acrolein levels are increased by more than 100% in CRF, confirming data from other authors. In another study presented at this meeting, we explore the effect of hemodialysis on these levels. We failed to see a difference in acrolein levels in liver disease, suggesting that liver metabolism is not a major player in the circulating acrolein pool. Data from other authors had shown increased acrolein adducts in stroke, we did not find an increase in free acrolein in this small n study. Acrolein levels are extremely high in pneumonia (almost 4-fold), suggesting it as a potential marker of infection and/or damage by inflammation. This new finding also lends mechanistic support to the synthesis of acrolein from threonine by phagocytes MPO as a major source of acrolein in vivo. Free acrolein levels in diabetes correlate with glycemic control, suggesting a link with hyperglycemia and oxidative stress.

3. Prophage Induction in Salmonella enterica serovar Typhimurium

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Background and Hypothesis: The chromosome of *Salmonella enterica* serovar Typhimurium contains four active prophages: Fels-1, Fels-2, Gifsy-1 and Gifgy-2. They encode fitness factors as well as Type III effector proteins which both strengthen bacterial virulence. Under environmental stress, the prophages can escape by entering a lytic cycle and searching for a new host and better chances of survival. In the present study, we investigate environmental factors that can trigger phage escape from the Salmonella genome.

Methods: We quantified phage escape using quantitative Real-Time PCR. The copy number of a Fels-1 gene (STM916) was normalized to the copy number of *ansP*, a reference gene localized near the terminus of replication on the Salmonella chromosome. The copy number of *ilvG*, a bacterial gene localized close to the origin of replication was also quantified to distinguish phage escape from chromosome replication. Phage escape was first tested in exponential phase (3h growth), stationary phase (24h growth), and after treatment with hydrogen peroxide (H_2O_2, 2 mM).

Results: The relative changes in *ilvG* and STM916 copy numbers between 3h and 24h, were a normal representation of loci copy numbers in actively growing cells compared to slow growing stationary phase cells. On another hand, H_2O_2 treatment induced a strong phage response with a 35 fold increase in STM916 copies, as well as a 8 fold increase in a neighboring bacterial gene (dps), suggesting a non-specific amplification of the prophage region.

Conclusions: Our preliminary data show the expected phage induction in response to H_2O_2-induced DNA damage and therefore validate our assay for the investigation of prophage escape. We can now study all four prophages and their response to environmental stress such as heat, starvation and/or antibiotic treatment. Many questions remained to be answered: Are the Gifsy phages more likely to escape than the Fels phages? Which one can induce bacterial gene transfer? And which virulent genes are more frequently transferred?

4. *Tamm Horsfall Protein (Uromodulin) Is Resistant To Carbonyl And Nitrosative Stress: A Comparative Study With Model Abundant Serum Proteins.*

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Background. Tamm Horsfall protein (THP) or uromodulin is the most abundant urinary protein. Produced by the epithelial cells of the ascending loop of Henle, it is believed to be implicated in immunomodulation and protection from urinary tract infection, cast formation and urinary lithiasis protection. As an extracellular protein it could be submitted to carbonyl or oxidative attack, especially in conditions such as diabetes, where glucose, and free AGE adducts concentrations in urine can reach very high levels, much higher than those encountered by serum proteins. These modifications could result in altered function.

Hypothesis: We tested the hypothesis that THP evolved to become resistant to carbonyl and nitrosative modifications as compared to serum proteins.

Design and Methods: THP was isolated from human urine by salting out, extensively dialyzed against water and its purity confirmed by SDS-PAGE and silver staining. THP (.2 mg/ml), HDL (.2 mg/ml) and albumin (.2 mg/ml) were incubated under sterile conditions in PBS, pH, 7.4, containing increasing concentrations of acrolein (0-10 mM), methylglyoxal (MG, 0-10 mM) and SIN-1 (0-100 mM), at 37º C for 0-24 h. Acrolein is a carbonyl compound produced in lipid peroxidation and pollution smoke, MG is a key dicarbonyl in Maillard chemistry in humans and SIN-1 is a peroxynitrite generator. After extensive dialysis, the samples were screened for fragmentation and polymerization by SDS-PAGE and for tryptophane fluorescence and AGE fluorescence by spectrofluorometry.

Results: At carbonyl concentrations of 1 mM, which are much higher than those encountered in plasma or urine in pathological conditions, HDL and albumin exhibit dimerization and polymerization as well as quenching of tryptophane fluorescence and increased AGE fluorescence whereas these changes are minimal for THP. SIN-1 produces extensive fragmentation of HDL apolipoproteins and albumin at 10 mM whereas these changes are minimal for THP.

Conclusions: This is the first study to focus on in vitro Maillard and nitrosative modifications of THP. We show that THP is more resistant to these modifications, even under very stringent conditions, than 2 abundant serum proteins. Its high glycan content (more than 30%) as well as its particular primary and spatial structure should play a role in this resistance. The results suggest that, under physiological and pathological conditions, THP may be impervious to the excess of reactive substances in urine and its function may not be altered by those.

5. Possibilities of a Periapical Granuloma

Robert B. Howe, DDS and David J. Eliot PhD

Background and Hypotheses: The maxillary sinus continues to expand throughout adult life, and as the sinus grows inferiorly, the bone surrounding the upper molar tooth roots often thins to less than 1 mm. Modern surgical procedures involving the upper molar teeth such as dental implants and periapical endodontic surgery may therefore involve intentional or inadvertent direct access to the maxillary sinus.

Methods: To begin to understand the developmental trajectory of maxillary sinus expansion and its clinical consequences, the authors undertook an anatomical study of the relationships of the roots of upper molar teeth to the floor of the maxillary sinus in a cadaveric sample representing the geriatric population. The cystic bony lesion presented here was found during the course of that study. It demonstrates the effects of a periapical granuloma presumed to have resulted from a molar tooth abscess.

Results: The cyst developed at the apices of the roots of the upper right first molar in a cadaver with evidence of scrupulous dental care that was followed by very extensive decay, occurring perhaps in a period of extended illness before death. The tooth in question had a three-quarter gold crown and gross buccal decay, strongly suggesting endodontic pathogenesis of a periapical abscess leading to formation of a granuloma and, ultimately, a bony periapical cyst. The outer dimensions of the cyst were 9 mm (mediolateral) by 7 mm (anteroposterior); its bony walls were approximately 2 mm thick and rose 7 mm above the floor of the sinus. A lumen as wide as the cyst cavity opened to the maxillary sinus superiorly; the cyst cavity was 11 mm deep. Apices of all three tooth roots were exposed to the cyst cavity, and therefore to the sinus, covered only by the soft tissue lining of the cyst. Removal of the soft tissue revealed shelf-like erosion of the hard tissue of the two buccal roots.

Conclusions: Inflammatory pathological processes may either erode hard tissues or stimulate osteogenesis. The lesion reported here shows how both processes can occur together, with lysis of bone and tooth within the cyst cavity and osteogenesis (or prevention of "normal" osteolytic expansion of the maxillary sinus) forming the steep-sided walls that were found to be protruding from the floor of the maxillary sinus.

Acknowledgement: Research supported by a Dean's Creativity Fund grant, UCSF School of Dentistry, 2001.

6. *Ilex Paraguariensis* "Mate" Protects HDL Paraoxonase activity.
Mate Drinking Increases Paraoxonase-1 Activity in Normal Subjects: a Pilot Study

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Background: The antioxidant activity of high-density lipoprotein is largely due to its paraoxonase-1 (PON-1) content. Experiments with transgenic knock-out mice indicate the potential for this enzyme to protect against atherogenesis. This relationship has been further strengthened by the publication of the first prospective study showing that low serum PON-1 activity is an independent predictor of new CHD events. Studies from our laboratory, which have since been confirmed by others, have demonstrated the antioxidant properties of *Ilex paraguariensis* "mate" with regard to human LDL oxidation in vivo. This beverage has gained popularity in the United States in the last few years. It is used as a very popular folk beverage dating from pre-Columbian times, in large regions of South America.

Hypotheses and aims: The first aim of the present study was to address the hypothesis that polyphenol-rich IP extracts are capable of protecting HDL from in vitro oxidative stress, preserving PON-1 activity. Recent studies have shown that high polyphenol-containing beverages such as pomegranate juice can increase PON-1 activity in serum. A second aim of this study was to test the hypothesis that IP drinking increases PON-1 activity in a small sample of healthy human subjects. We based our idea on the recent observation that dietary antioxidants can affect PON1 levels and activities by reducing oxidative stress (which inactivates PON-1), and also directly by affecting paraoxonase gene expression.

Methods: **Protection of PON-1 activity when HDL is oxidized: in vitro study**
HDL preparation. HDL (d= 1.063-1.210 g/ml) was isolated from pooled fresh human serum by sequential flotation ultracentrifugation.HDL was incubated in sterile conditions in the absence or presence of AAPH (1-10 mmol/l final concentration) or CUSO4 (10 umol/l at 37 8C for a period of 0–16 h. Samples were incubated in the presence or absence of extracts of IP (2–20 Al/ml). PON-1 activity, lipoperoxides and SDS-PAGE was performed. **Increase in PON-1 in serum after mate drinking**. Capillary blood was obtained from healthy human volunteers (n=4) when fasting and sampled again at 1 h after drinking 1/2 liter of mate or water or coffee and milk in a 60 min period. PON-1 activity was determined from the initial velocity of p-nitrophenol production at 37C and recorded at 405 nm in a VERSAmax (Tunable) Microplate Reader.

Results: Molecular changes induced by APPH on apoA-I are blocked by Ilex paraguariensis as shown by SDS-PAGE. Ilex paraguariensis protects PON-1 activity on HDL during oxidative stress in a concentration dependent manner. PON-1 activity increased significantly after mate drinking in all subjects, averaging a 10 % ± 1% vs 0 ± 1 % for control breakfast or water ($P \pm 0.05$).

Conclusions: Mate protects HDL from the loss of PON-1 activity and changes on apoA-I structure caused by oxidative stress in a time and concentration dependent manner. Our data give in vivo proof of principle for a positive effect of *Ilex paraguariensis* on PON-1 activity in vivo. PON1 activity could be a target for dietary modulation or pharmacological intervention. The magnitude of the effect, though modest, is similar to that found for several studies with statins. A larger study with kinetic data and evaluation of HDL composition and PON-1 mass is warranted. If proven in this projected study, our preliminary results would suggest another way to increase PON-1 activity and thus HDL protection of LDL oxidation.

Acknowledgment: Supported by Touro University.

7. Toward the mechanism of anesthetic-induced amnesia: Anesthetics shut down memory consolidation by inhibiting hippocampal *Arc*-protein synthesis in the rat.

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Introduction: The amygdala plays a role in the memory consolidation effects of anesthesia [1]. Recently, the mechanism by which the amygdala influences memory consolidation has been linked to hippocampal synaptic plasticity changes involving the immediate-early gene *Arc* (activity-regulated cytoskeletal associated protein) [2]. Post-learning amygdala manipulations that enhance memory also enhance hippocampal *Arc* and conversely manipulations that impair memory decrease *Arc*. Here we determine whether the memory consolidation effects of anesthesia might also be mediated via an *Arc-protein*-related hippocampal mechanism.
Methods: Following IACUC approval, 27 well-handled rats learned the inhibitory avoidance (IA) paradigm during exposure either to air, 0.3% sevoflurane or 1.4% desflurane. Hippocampal *Arc*-protein was measured using immunohistochemistry at 60-min following the learning experience in a subset of animals. In the remaining rats, memory was assessed at 24 h. *Arc*-protein was imaged at the cellular level with a Typhoon Trio+ Variable Mode Imager (Amersham Biosciences). Hippocampal *Arc*-protein was quantified using ImageQuant TL (Amersham Biosciences). Signal intensity changes were compared using ANOVA with post-hoc t-tests. $P < 0.05$ was considered significant.
Results: Memory at 24 hours was significantly suppressed by both anesthetics, see figure. Representative hippocampal *Arc*-protein signal is also shown in the figure. Quantitative *Arc*-protein analysis revealed that mean (SD) *Arc*-protein levels in the hippocampal CA1 region were significantly enhanced with learning, as expected. However, *Arc*-protein in anesthetic exposed rats was not significantly different from the levels found in caged-controls and was significantly reduced compared with levels found in the air-trained rats ($P < 0.05$ for sevoflurane and $P < 0.05$ for desflurane, but one-tailed only).
Conclusions: Hippocampal *Arc*-protein synthesis is suppressed by low amnesic doses of volatile anesthetics that block long-term memory consolidation. Taken together with other results demonstrating that hippocampal *Arc*-mRNA is not suppressed by anesthesia, these findings offer strong pin-point evidence that anesthetics block long-term memory consolidation through a mechanism localized to the direct (translation inhibition) or the indirect (amygdala mediated) suppression of *Arc*-protein synthesis.
References:
[1] Anesthesiology 2005, 102:754-60.
[2] PNAS 2005, 102:10718-23.
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8. *M*echanism of action of N-terminal domain of β-catenin on optic axon branching

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Background and Hypothesis: Cadherin and Wnt signaling are key molecular pathways involved in the establishment of axonal connectivity in the developing visual system. β–catenin, a cytoplasmic adaptor protein, is a component of both Cadherin and Wnt signaling pathways. The N-terminal domain of β-catenin contains interaction sites for both α-catenin (required for Cad adhesion) and for GSK-3β (required for Wnt signaling). Previous work showed that overexpression of NTERM in optic axons in live *Xenopus* tadpoles reduces their number of terminal branches (Edalat et al., 2006). Here we address the cellular and molecular mechanisms of action of NTERM on branching in optic axons.

Methods:

1. We used timelapse confocal imaging at 1 hr intervals to examine branching (extension and retraction) dynamics in NTERM and control optic axonal arbors *in vivo*.
2. We examined whether a truncated N-terminal domain of β-catenin that contains only the GSK3β binding domain also inhibits branching in optic axonal arbors.

Results: Analysis of preliminary timelapse confocal data shows that NTERM reduces branch number in optic axonal arbors by inhibiting extension of new branches. Overexpression of a truncated NTERM that contains only the GSK3β binding domain does not reduce branch number in optic axonal arbors.

Conclusions: These data demonstrate that the α-catenin binding domain of β-catenin promotes branching in optic axonal arbors by controlling the extension of new branches. This suggests that β-catenin and α-catenin interact with other factors involved in nucleation of new branches in optic axonal arbors.

9. *Acrolein Decreases Paraoxonase 1 (PON-1) Activity In HDL: Protection By Cysteine.*

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Background: Paraoxonase 1 is an esterase carried by HDL particles with antiatherogenic functions, mainly through protection of LDL from oxidation as well as through its homocysteine-thiolactonase activity. Acrolein is a very reactive dicarbonyl that is a terminal product of lipoperoxidation and one of the most concentrated substances in tobacco smoke. Acrolein readily forms adducts with lysine and oxidizes cysteine. Conditions in which serum or tissue acrolein levels are high (renal failure, heavy smoking, oxidative stress etc) are also characterized for low circulating PON-1 levels or activity. Cigarette smoke extracts have shown deleterious effect on PON-1.

Hypothesis: We tested the hypothesis that acrolein acts on HDL to decrease PON-1 activity in a time and concentration dependent fashion. By using different kinds of inhibitors we also explored whether the effect was due to cysteine or lysine/arginine modifications or to both.

Design and Methods: HDL (d= 1.063-1.210 g/ml) was isolated from pooled fresh human serum by sequential flotation ultracentrifugation, extensively dialyzed against PBS at pH 7.4 and its purity confirmed by SDS-PAGE. HDL (1 mg/ml) was incubated under sterile conditions in PBS, pH 7.4, containing increasing concentrations of acrolein (0-10 mM), at 37º C for 0-4 h. Some of the incubations included acrolein at 0.5 mM and carnosine or aminoguanidine (glycation inhibitors) or cysteine (all at 0.25-1 mM). After extensive dialysis PON-1 activity toward paraoxon was measured after the reaction of paraoxon hydrolysis into p-nitrophenol and diethylphosphate catalyzed by the enzyme. PON-1 activity was determined from the initial velocity of p-nitrophenol production (subtracting the spontaneous paraoxon hydrolysis) at 37°C and recorded at 405 nm in a Versa Max microplate reader. Samples were also screened for fragmentation and polymerization by SDS-PAGE.

Results: Acrolein produces a time and concentration dependent decrease in PON-1 activity in HDL, (IC 50= 1 mM) at only 2 h of incubation. At 0.5 mM, an activity loss of 40% is already accompanied by detectable dimerization of apoA-I. At the same concentration carnosine and aminoguanidine do not significantly protect the activity whereas cysteine affords 95% protection ($p < 0.001$).

Conclusions: Acrolein inhibits PON-1 activity in HDL at sub-mM concentrations and this inhibition is cancelled by cysteine. PON-1 has 2 critical cysteine residues in its catalytic hydrophobic pocket. The results suggest that in conditions where circulating acrolein levels are high, or where local acrolein concentrations are high (atheroma plaque, sites of lipoperoxidation), acrolein-mediated loss of PON-1 activity could be a plausible phenomenon. This could offer new insights contributing to explain low PON-1 activities in smokers and renal failure subjects as well as pointing at thiol-conserving reducing compounds as putative therapeutic palliatives

10. Structure-Activity Relationships of Flexible Heteroarotinoids as Potential Anticancer Agents

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Background and Hypotheses: One of the most promising classes of cancer chemoprevention agents designated by the Chemoprevention Working Group to the American Association for Cancer Research (AACR) is retinoids. The anti-cancer activities and toxicities of retinoic acid (RA) and synthetic retinoids are mediated through nuclear RA receptors (RARs) and retinoid X receptors (RXRs) that act as transcription factors.

Methods: Heteroarotinoids (Hets), which contain a heteroatom in the cyclic ring of an arotinoid structure, exhibit similar anti-cancer activities, but reduced toxicity in vivo, in comparison to parent retinoids and RA. A new class of Flexible Hets (Flex-Hets), which contain 3-atom urea or thiourea linkers, regulate growth and differentiation similar to RA, but do not activate RARs or RXRs. In addition, Flex-Hets induce potent apoptosis in ovarian cancer and in head and neck cancer cell lines through the intrinsic mitochondrial pathway. 4 cervical cancer cell lines were growth inhibited by micromolar concentrations of Flex-Hets to greater extents than RAR/RXR active retinoids. The most potent Flex-Het (SHetA2) inhibited each cell line of the National Cancer Institute's human tumor cell line panel at micromolar concentrations. Oral administration of Flex-Hets (SHetA2 and SHetA4) inhibited growth of OVCAR-3 ovarian cancer xenografts to similar extents as administration of a RAR/RXR-panagonist (SHet50) and Fenretinide (4-HPR) in vivo. None of these compounds induced evidence of skin, bone or liver toxicity.

Results: Structure-Activity Relationships show that generally, five membered Hets are potent than sex membered Hets. Sulfur Hets are more potent than oxygen or nitrogen Hets. SHetA2 with *p*-nitro group are more potent than SHetA3 with *p*-$COOCH_3$ group. SHetA3 with thiourea group are more potent than SHetA4 with urea group. SHetA4 with urea group is more potent with SHetA50 with amide group.

11. Hippocampal mRNA levels of the plasticity related immediate-early gene *Arc* are not suppressed by an amnesic dose of sevoflurane in the rat.

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Background: The amygdala plays a role in the memory consolidation effects of anesthesia [1]. Recently, the mechanism by which the amygdala influences memory consolidation has been linked to hippocampal synaptic plasticity changes involving the immediate-early gene *Arc* (activity-regulated cytoskeletal associated protein) [2]. Post-learning amygdala manipulations that enhance memory also enhance hippocampal *Arc* and conversely manipulations that impair memory decrease *Arc*. Here we determine whether the memory consolidation effects of anesthesia might also be mediated via an *Arc*-related hippocampal mechanism.

Methods: Following IACUC approval, 27 well-handled rats learned the inhibitory avoidance (IA) paradigm during exposure either to air, 0.1 or 0.3% sevoflurane. Hippocampal *Arc* mRNA (as a potential marker for *Arc* protein) was determined using *in situ* hybridization at 15-min following the learning experience in a subset of animals. In the remaining rats, memory was assessed at 24 h. *Arc* mRNA signal was imaged at the cellular level with a Typhoon Trio+ Variable Mode Imager (Amersham Biosciences). Hippocampal *Arc* mRNA was quantified using ImageQuant TL (Amersham Biosciences). Signal intensity changes were compared using ANOVA with post-hoc t-tests. $P < 0.05$ was considered significant.

Results: Memory at 24 hours showed a dose-dependent reduction, reaching significance for animals trained in the presence of 0.3% sevoflurane. Memory enhancement was not seen, nor expected with the 0.1% dose because of the learning parameters used. Representative hippocampal *Arc* mRNA signal is shown in the figure. Quantitative *Arc* mRNA analysis revealed that mean (SD) *Arc* mRNA was induced with learning mainly in the CA1 region, as expected. However, *Arc* mRNA did not significantly differ between the Air-trained and the sevoflurane exposed animals.

Conclusions: Hippocampal *Arc* mRNA levels did not differ between amnesic and non-amnesic doses of sevoflurane. This establishes that the amnesic effect of low dose sevoflurane is NOT primarily due to an anesthetic-induced failure of encoding. Rather, sevoflurane-induced amnesia must occur through the disruption of memory consolidation at a mechanistic site downstream from hippocampal *Arc* mRNA induction. The next plausible target now becomes *Arc* protein synthesis, itself. *Arc* mRNA cannot serve as a marker for sevoflurane-induced amnesia. Alternatively, the possibility is raised that *Arc* may not be a key protein in the memory consolidation effects of anesthetics.

References:

[1] Anesthesiology 2005, 102:754-60.
[2] PNAS 2005, 102:10718-23.

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12. Transdermal Delivery Of Penbutolol: In Vitro Characterization

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Background and Hypothesis: Penbutolol, [1-*t*-butylamino-3-(2-cyclopentylphenoxy) propan-2-ol] is a non-cardioselective β-adrenoreceptor blocking agent and used for the treatment of hypertension. The conventional dosage form for penbutolol is tablet which has limitations including hepatic first-pass metabolism, high incidence of adverse effects due to variable absorption profile and poor patient compliance.
In this project, we investigated the feasibility of delivering penbutolol sulfate transdermally across porcine ear skin.

Methods: A High-performance liquid chromatographic technique was developed for the quantitation of penbutolol sulfate using Waters HPLC system equipped with ultraviolet (Waters 2487 dual absorbance) and fluorescence (Waters 2475 multi wavelength) detectors. Penbutolol was assayed at 271 nm with water: acetonitrile (70: 30) as the mobile phase. The flow rate was 1ml/ml and a reversed phase (Sunfire, Waters C_{18} 5µm 4.6x 100 mm) column was used.Transdermal delivery was determined in vitro using Permegear automated flow-through diffusion system. Porcine ear skin, a representative permeation model for human skin, was used for the experiments. The skin pieces were secured into Permegear diffusion cells and each donor cell was caped for the duration of the experiment. The donor compartment was charged with 1ml of the saturated drug solution. The receiver solution (phosphate buffered saline) was pumped (Ismatec pump, IPC ISM 933) through the diffusion cells at a flow rate of 0.2 ml/h for 12 hours. The samples were collected with a Retriever IV fraction collector at 2 h intervals and analyzed by HPLC. The permeation data were plotted as the cumulative amount of the drug collected in the receiver compartment as a function of time. The fluxes of penbutolol were calculated from the slope of the plot of the cumulative amount of the drug permeated at steady state versus time using linear regression analysis.

Results: The present investigation was carried out in order to assess transdermal permeation of penbutolol across porcine ear skin. An HPLC method was developed for the quantitation of penbutolol.Transdermal flux of penbutolol across porcine ear skin into PBS was 0.56ng/cm^2/h.

Conclusions: In vitro diffusion studies of penbutolol across porcine ear skin showed that the drug could be a potential candidate for transdermal delivery. Passive penbutolol diffusion across porcine ear skin was found to be low. Future studies in our laboratory will examine the feasibility of transdermal iontophoretic flux enhancement for penbutolol.

13. *Effects of Exercise Intensity on Glycemia Control After a Dietary Glucose Challenge*

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Background and Hypothesis: Excessive post-meal hyperglycemia is a major risk factor for Type 2 diabetes. Exercise is an effective clinical intervention for diabetic hyperglycemia management with current guidelines recommending 150 min/wk of moderate intensity (exertion) aerobic exercise. However, moderate intensity exercise (e.g. brisk jogging) can be too rigorous for many obese and debilitated diabetics. Although lower intensity exercise (e.g. leisurely walking) may be more practical, its effectiveness for glycemia control is unclear. The purpose of this study is to investigate the importance of exercise intensity on glycemia control by comparing the ability of low vs. moderate intensity exercise to normalize glycemia in non-diabetics during a dietary glucose challenge. The HYPOTHESIS is that an acute bout of low intensity cycling exercise performed shortly after ingesting a glucose load reduces hyperglycemia exposure at least as effectively as an isocalorie expending moderate intensity bout in non-diabetic human subjects. Data may support re-evaluation of diabetes exercise guidelines and provide further insight into exercise mediated glycemic control mechanisms.

Methods: Using a blood glucose home metering system (Lifescan® One Touch Ultra), fingertip blood samples were assayed in a 49 year-old non-diabetic male at 5-10 min. intervals before, during, and after consuming 56 gms (14 x 4 gm tablets; 1 tablet per 30 sec.) of glucose (Walgreens® brand Glucose Tablets). Data were collected under three experimental conditions (1) while subject remained sedentary (S) and as subject performed (2) low (L) intensity (45-50% VO2max; HR = 80-85 bpm) and (3) moderate (M) intensity (65-70% VO2max; HR = 110-120 bpm) recumbent cycling exercise. VO2max was estimated using a CardioCoach®-PLUS Fitness Assessment Instrument (Korr®). Cycling durations (low intensity = 42 min.; moderate intensity = 86 min.) were adjusted to achieve isocaloric (equal) energy expenditure (311 C consumed) during each exercise bout. Glycemia data from each condition were plotted to form a glycemic profile and parameters related to glycemic exposure were evaluated for (1) time to glycemic normalization, (2) glycemic peak and (3) total glycemic exposure. Data are presented as preliminary results from this pilot study.

Results: Glycemia was normalized within 2 hrs under all conditions with no apparent difference. However, performing low or moderate intensity cycling resulted in a lower peak glycemic response compared to the sedentary profile over the testing period (S = 174 mg/dL; M = 154 mg/dL; L = 132 mg/dL). Furthermore, both exercise regimens reduced total hyperglycemic exposure to the glucose challenge based on the relative area under glycemic curves (S = 111 units; M = 70 units; S = 64 units).

Conclusions: Consistent with existing studies, results indicate that exercise is effective for reducing postprandial glycemic exposure when performed after a dietary glucose challenge. In support of the specific hypothesis, data also revealed that low intensity exercise is equally effective and may even be more effective than moderate intensity exercise in minimizing glycemic exposure. However, additional data are necessary to support these limited results.

14. Developing New Treatments For Alcoholism: Potential Role Of The Neurokinin-1 Receptor.

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Background and Hypothesis: There are few effective medications currently available for the treatment of alcoholism despite ethanol's devastating impact on individuals addicted to ethanol as well as on the society. Furthermore, the medications currently approved for alcoholism are limited by severe side effects and compliance issues. The neurokinin-1 (NK1) receptor is the preferred receptor for substance P, which previously has been studied for its role in depression and anxiety. Recently, the NK1 receptor has been shown to have a role in addiction. In the present study we examined a possible role for the NK1 receptor antagonist LY303870 in treatment of alcoholism.

Methods: The consumption of ethanol after LY303870 treatment (1-20 mg/kg) was measured in two different paradigms. 1) Continuous-access-two-bottle-choice, when the rats were given unlimited access to ethanol and water. Consumption of ethanol (g/kg) and water (ml) was recorded 16 and 24 hrs after administration of the drug. 2) Operant self-administration of ethanol, when consumption (g/kg) and the number of lever presses for ethanol was recorded during a 30-minute session. Each rat was given four consecutive i.p. injections of vehicle or 1, 10 or 20 mg/kg of LY303870 respectively in random order. LY303870 was given as an acute dose 30 minutes before ethanol and water bottles were presented or before the rats were placed in the operant self-administration chambers.

Results: We showed that a single injection of LY303870 reduced ethanol intake using both the continuous-access-two-bottle choice and the operant ethanol self-administration paradigm. Water consumption was not affected in the two-bottle-choice paradigm. Furthermore, LY303870 did not affect the locomotor activity in an open filed chamber compared to controls. This rule out the possibility that the decreased response in the self-administration chamber after LY303870 treatment would be due to decreased mobility.

Conclusions: The present study confirms that the NK1 receptor may be involved in addiction and that the NK1 receptor antagonist LY303870 could be a candidate for a novel treatment of alcoholism.

16. Are Tamm-Horsfall protein (uromodulin) levels in Caucasian than in Asian populations? A pilot study

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Background. Tamm Horsfall protein (THP) or uromodulin is the most abundant urinary protein. Produced by the epithelial cells of the ascending loop of Henle, it is believed to be implicated in immunomodulation and protection from urinary tract infection, cast formation and urinary lithiasis protection. During one of our summer 2006 research projects (urine proteome), to set up the technique, several urine samples from lab members were run. This led to a serendipitous finding. THP appeared consistently lower in Asian subjects. This fact aroused our curiosity and led to this pilot study to confirm or reject the following hypothesis.

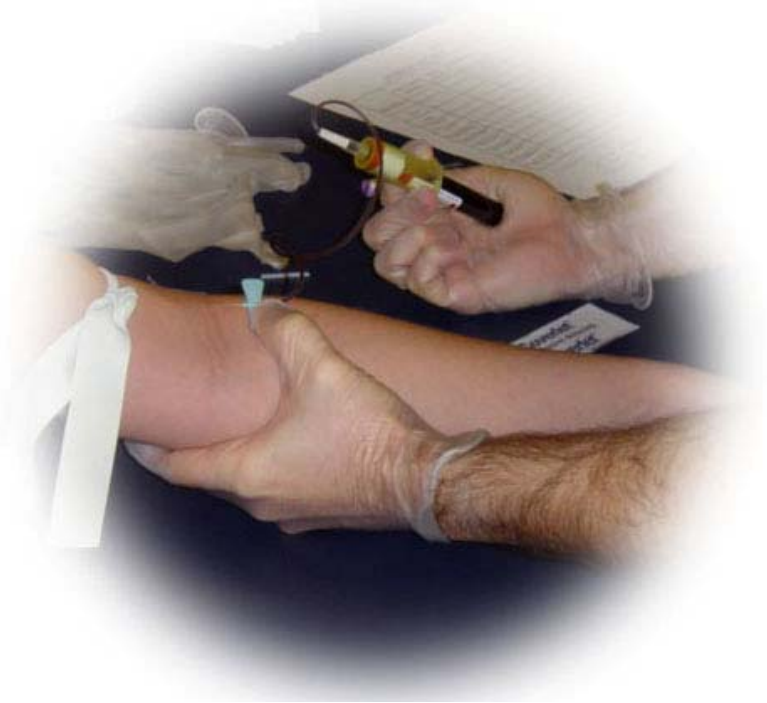
Hypothesis: We tested the hypothesis that urine THP levels are different in Japanese than in Caucasian populations.

Design and Methods: This is a small, cross-sectional study. Urine (first void) was collected from Caucasian student volunteers (n=10, 5 females, 5 males, mean age=26) and from 10 age and sex matched healthy Japanese subjects (staff from Showa University Northern Yokohama Hospital, Yokohama, Japan). The fresh samples urinalysis was negative for all abnormals. After centrifugation, urine was kept at – 80 C and thawed once for analysis. Urine samples were concentrated and loaded (5 ug protein) on SDS-PAGE (10%). Bands were stained with Coomassie and Silver Staining. Densitometry was performed with Image J after digital capture of the gels.

Results: Densitometric analysis of our samples showed no significant difference between the 2 populations studied. It became clear that the range of THP urinary excretion is rather large, therefore explaining the chance findings that motivated the study. Polymeric forms of THP show a clear trend to be more concentrated in Caucasians than in Japanese subjects

Conclusions: Although small, to our knowledge this is the first study to focus on in putative differences in THP levels in different human populations. No significant differences in total THP excretion in Japanese vs Caucasian subjects was found, but our data suggest there are qualitative differences in the polymerization of the protein. This issue warrants further investigation.

POSTER PRESENTATIONS



CLINICAL SCIENCES

1. Long Term Use of Beta Blockers in White and Black Patients after Acute Myocardial Infarction

Mitchell Barnett, PharmD, MS[1,2], Mary Vaughn-Sarazin, PhD[1], Gary Rosenthal, MD[1]

Objectives: While quality improvement efforts have focused on increasing the use of beta blockers in hospitalized patients with acute myocardial infarction (AMI), less is known about longer term use post discharge. The objectives of this study were to determine: 1) changes in the use of beta blockers over time; and 2) differences in long term use in black and white patients.

Methods: The VA Patient Treatment File (PTF) was used to identify 1038 consecutive white (n=895) and black (n=143) patients admitted with a principle diagnosis of AMI in FY 2002 in VISNs 10, 15, & 23 and who were discharged alive. DSS pharmacy files were used to identify all outpatient prescriptions for beta-blockers during the 720 days after hospital discharge. Patients were considered to have "consistent beta-blocker use" during consecutive 180-day follow-up intervals if they received prescriptions for a 90 day or greater supply during the interval. Analyses within each interval only included patients who survived to the end of the interval.

Results: Beta blockers were consistently used in 73.6% of patients during the first 180 day interval after discharge. Consistent use was relatively well maintained at 360, 540, and 720 days with rates of 70.5, 68.6%, and 67.1%, respectively. Rates of consistent beta blocker use during the first 180 day interval were similar for blacks and whites (69.7% vs. 74.1%, P=.31), but were lower for blacks between 180-360 days (60.2% vs. 72.1%, P=.01), 360-540 days (58.7% vs. 70.1%; P=.02), and 540-720 days (54.6% vs. 69.1%; P<.01).

Conclusion: Beta-blockers were consistently prescribed for nearly three-quarters of patients during the first 180 days after hospitalization for AMI. While use was similar in black and white patients during the first 180 days after discharge, rates of use were consistently lower in blacks thereafter. Such variation may be responsible, in part, for the differential long-term death rates between blacks and whites after AMI observed in other studies.

Impact: While recent interventions have been successful in increasing the use of beta blockers immediately after discharge, new efforts may be needed to identify and overcome barriers to the long-term use in black patients.

2. Ischemia-modified albumin levels are higher during the first week after an acute ischemic stroke: a pilot study.

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Background: Ischemia modified albumin (IMA) measured by the cobalt binding test could become a triage tool in acute coronary syndrome patients. It does not appear to be very tissue or clinically specific and might also find utility in stroke. A recent article suggests that IMA levels may be a biomarker for early identification of acute stroke, showing elevations in the first day.

Objective: In this pilot study we set out to confirm this contention and to test the hypothesis that IMA levels raise even more in subsequent days after the acute episode.

Materials and Methods: We studied 12 consecutive patients presenting within 6 h of the onset of an acute neurological deficit 8 cerebral infarctions, 4 cerebellar infarctions, as well as 40 age-matched controls. Serum samples were obtained for all patients at initial presentation and repeated only in patients with stroke at 2, 4 and 6 days. In some cases samples were also taken 2 weeks after the episode. IMA was measured by the albumin-cobalt-binding test and expressed as absorbance arbitrary units. To rule out bias generated by changes in total albumin concentration, serum albumin was measured in all samples. Samples were kept at -80 ºC before analysis and all tests were run concurrently on the same plate in a Versa Max microplate reader. The intra-assay CV was 5%.

Results: The initial IMA was 0.57 ± 0.08 AU for stroke patients vs 0.55 ± 0.09 AU for control subjects, showing no significant differences ($p < 0.2$). At 2-4 days IMA levels raised to 0.69 ± 0.1 AU ($p < 0.001$ vs day 0). IMA levels not only do not return to control levels in 2 or 4 days but continue to rise and, in some cases, remain elevated for more than a week (0.7 ± 0.03, n =3). No significant differences in total serum albumin levels were detected among the samples.

Conclusion: Even with the limitations of small sample numbers, this is the first study to serially measure IMA levels in stroke patients after 24h post-episode, and the data are consistent with a persistent elevation of IMA levels beyond the first day, suggesting this marker is sensitive to changes in brain tissue resulting from ischemic injury and its oxidative stress consequences. Since the IMA assay is inexpensive and could become a point-of-care option, it could become a useful marker for assessing degree of cerebral damage. More studies in parallel with brain CT scanning may provide more information during treatment, however, CT does not necessarily show significant findings in cerebral infarction, especially in the acute phase and for small lesions. Also CT has radiation hazards and is more expensive than chemical assays. Further studies are needed to better delineate the response curve of IMA to acute ischemic stroke, its diagnostic yield and its potential as a marker in this condition.

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3. Coping Strategies, Metabolic Control And Depressive Symptoms In Patients With Type 2 Diabetes Mellitus: Is There A Relationship?

Bijal M. Shah and Katherine K. Knapp

Hypotheses and aims: To determine the relationship between coping strategy, metabolic control and depressive symptoms in patients with type 2 diabetes mellitus (T2DM).

Methods: Primary care patients with T2DM were recruited during their scheduled clinic appointments. Self-report data on demographic characteristics were collected via a survey. The Zung self-rating depression scale was used measure depressive symptoms. The Diabetes Coping Measure (DCM) was used to measure coping strategies (tackling spirit, avoidance, passive resignation and diabetes integration). Data on Hemoglobin A1C (HbA1C) values and comorbid conditions were collected from patient charts. Pearson's correlation coefficients were used to determine the relationship between HbA1C values and coping strategy. A hierarchical regression model was used to identify the coping strategies associated with depressive symptoms. Age, gender, body mass index and Charlson comorbidity score were entered as control variables in the regression model.

Results: A total of 217 surveys were collected with a usable response rate of 93%. The mean age of the overall sample was 57.3 years (SD = 11.9), 62.2% were female and 61% were Hispanic. The Zung self-rating depression scale indicated that 72.1% of patients met criteria for depression. The regression model for depressive symptoms was significant ($F=7.66$, $p<0.001$). Greater use of tackling spirit (a measure of problem-focused coping) was associated with decreased depressive symptoms ($\beta= -0.18$, $p<0.005$). Passive resignation coping ($\beta=0.27$, $p<0.006$) and poor diabetes integration were associated with higher depressive symptom scores ($\beta=0.17$, $p<0.044$). A significant relationship was also seen between high HbA1C values and avoidance coping ($r=0.27$, $p<0.001$), passive resignation coping ($r=0.30$, $p<0.001$) and poor diabetes integration ($r=0.26$, $p<0.001$).

Conclusions: Increased use of passive resignation and diabetes integration (emotion-focused coping strategies) was associated with increased depressive symptoms whereas tackling spirit (problem-focused coping) was associated with decreased depressive symptoms in patients with type 2 diabetes mellitus. Emotion-focused coping and avoidance coping were also associated with poor metabolic control in patients with T2DM.

4. Risk of Cerebrovascular Events in Elderly VA Dementia Patients: Comparison Between Antipsychotic and Non-Antipsychotic Users.

Mitchell Barnett, PharmD, MS[1,2], Heidi Wehring, PharmD[2], and Paul Perry, PhD[2]

Objectives: Second generation antipsychotics (2nd GAPs) are often used to control behavioral problems associated with dementia because of lower side effects than first generation antipsychotics (1st GAPs). However, concerns have surfaced about the increased risk for cerebrovascular events (CVEs) of 2nd GAPs. This study determined the risk of CVEs associated with 1st and 2nd GAPs in veterans with dementia.

Methods: The Patient Treatment and Outpatient Care files for FY 2001 identified veterans 65 years and older with Alzheimer's or vascular dementia. 1st and 2nd GAP use during an 18 month observation period (4/02-9/03) were determined using DSS Pharmacy files. Hospitalizations for CVEs in VHA or private sector hospitals were identified from the Patient Treatment File and Medicare Part A files. Cox regression was used to model the time to first CVE, censoring for death and adjusting for demographics, comorbidity, and use of specific medications (e.g., anticoagulants, anti-hypertensives, diabetic medications).

Results: The mean age of patients (n=21,304) was 78.2 (SD, 5.5) years; 97% were male and 24% and 76% were categorized as having Alzheimer's and vascular dementias, respectively. 2% and 15% of patients received prescriptions for a 1st or 2nd GAP during the observation period. Relative to patients who received no antipsychotics, the risk of a CVE was similar for patients receiving 1st GAPs (hazard ratio [HR], 1.27; 95% CI, 0.79-2.02) or 2nd (HR, 1.01; 95% CI, 0.84-1.20) GAPs. These results were similar in separate analyses of patients with Alzheimer's or vascular dementia. In analyses of patients receiving antipsychotics, no increased risk of a CVE was found for individual 2nd GAPs (olanzapine [HR, 0.88; 95% CI, 0.50-1.55], risperidone [HR, 0.62; 95% CI, 0.37-1.06], or quetiapine [HR, 0.82; 95% CI, 0.46-1.44], relative to haloperidol (1st GAP).

Conclusion: In contrast to a recent FDA warning, this study found no increase in the risk of CVEs in veterans with dementia who received 2nd GAPs, relative to veterans receiving 1st GAPs or without anti-psychotic use.

Impact: While 2nd GAPs are more expensive, the current study suggests that clinicians should weigh the benefits of 1st and 2nd GAPs in controlling behavioral symptoms in dementia, independent of concerns about the risk of CVEs.

5. Emerging Risk Factor (Erf) Patterns In Patients With Metabolic Syndrome, Type Ii Diabetes, And Controls. Dreams 2

Ben Willis, M.D.; Walter McConathy, Ph.D.; Sulabha Paranjape, M.S.; Michael Clearfield, D.O., Sabitha Buttreddy, MS.; Enisa Arslanagic, M.D.; Fidelita Weis, R.N; Rubina Muzina, M.D.; Mabyn Hager, RN,; Joice Carter, DE; Karan Singh, Ph.D; and Craig Spellman, Ph.D., D.O.

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Hypotheses and aims: Three subsets of patients identified with Diabetes Type II (DM), Metabolic Syndrome without diabetes (MS) and Control (C) were evaluated regarding emerging risk factors (ERF) in coronary heart disease (CHD). These groups were evaluated to better understand ERF pattern distinctions between diabetic patients and metabolic syndrome patients at risk.

Methods: ERF assessed include: apolipoproteins B and A-I; lipoprotein (a); hsCRP; homocysteine; PAI-1; myeloperoxidase; resistin, IL-6, TNF-alpha, and leptin. Low-density lipoprotein size was assessed by gradient gel electrophoresis with LDL characterized by relative mobility (Rf) or phenotyped as large low-density lipoprotein (LDL) particles (LLDL, pattern A phenotype) or small, dense low-density lipoprotein (sLDL) particles (pattern B phenotype). Electron beam computed tomography (EBCT) for coronary calcium (Ca) quantification was used as the assessment of CHD risk.

Results: Both the DM group and MS group differed from C in regard to standard anthropomorphic and biochemical metrics for the metabolic syndrome and a number of traditional CHD risk factors. Systolic blood pressure (SBP), BMI, waist circumference, hip circumference, insulin levels, and triglycerides were greater in both MS and DM groups compared to control ($p < 0.001$) but did not differ significantly between MS and DM. The MS group did show significantly higher diastolic blood pressure than DM ($p=0.01$). Glucose and hemoglobin A1c (HbA1c) were significantly higher in DM than MS and Control ($p < 0.001$) as expected. The ERF evaluation showed significantly higher hsCRP in MS and DM compared to C ($p =. 001$). Apolipoprotein AI and B differed between MS, DM and C, but only Apolipoprotein-B was significantly greater in MS compared to DM ($p < 0.001$). TNF-α was significantly lower in MS than in C ($p=0.024$), but no other group differences were significant. LDL phenotype comparisons showed significantly higher proportion of DM and MS exhibiting sLDL compared to C ($p =0.002$) but no significant differences between MS and DM. Ca quantification showed significantly greater Ca score in DM than in C ($p=0.006$), or MS ($p=0.003$) while MS and C did not differ significantly.

Conclusions: These findings suggest that while metabolic syndrome and Type II diabetes share a number of increased traditional and ERF for CHD, the development of diabetes predicts a higher risk of CHD. Subtle differences in apolipoprotein patterns and the interaction of TNF-α in insulin resistance syndrome may help explain this risk profile.

6. Low Density Lipoprotein Phenotype And Coronary Calcium Scores. Dreams 2

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Hypotheses and aims: An increase in plasma triglycerides and a decrease in high-density lipoprotein (HDL) are associated with the prevalence of small, dense low-density lipoprotein (LDL) particles. The present study investigated the clinical significance of LDL size as related to the accumulation of calcium in the coronary arteries as part of the DREAMS study program.

Methods: To explore the role of emerging risk factors (ERF) in CHD, we studied groups of subjects (n = 218) free of evidence of CHD who were at the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) goals (study groups: Hispanic diabetic/MS [HD], nonHispanic diabetic/MS [nonHD], and candidates for bariatric surgery [Ba] controls [C]). A fifth group with CHD was also included, acute coronary syndrome patients (ACS). ERF assessed include: apolipoproteins A-I and B; Lp(a); hsCRP; homocysteine; PAI-1; myeloperoxidase; resistin, IL-6, and leptin. LDL size was assessed by gradient gel electrophoresis with LDL characterized by relative mobility (Rf) or phenotyped as high molecular weight LDL particles (HMW LDL), pattern A phenotype) or small, dense low molecular weight LDL (LMW LDL) particles (pattern B phenotype). Electron beam computed tomography (EBCT) for coronary calcium (Ca) quantification was used as the assessment of CHD risk and Ca scores were log transformed or grouped as categories.

Results: When comparing the subjects grouped by LDL phenotype (LMW LDL vs HMW LDL), both waist/hip circumference and BMI were significantly higher in subjects with the LMW LDL phenotype ($p<0.05$). Consistent with this finding, TG levels were higher and HDL-C was lower in LMW LDL subjects. ApoA-I was lower and apoB higher in the LMW LDL group as well as the Rf of LMW LDL. Of the other biochemical markers tested, PAI-1 was higher in LMW LDL while adiponectin was lower ($p<0.05$). The % LMW LDL in each of the 5 groupings of subjects increased ($p=0.004$) from C (24.2 %) to BA (37.5%) to HD(51.4%) to nonHD (54%) to ACS (62.5). In exploring the relationship of LDL phenotype to Ca scores, the transformed Ca scores were increased in LMW LDL when contrasted to HMW LDL ($p<0.001$) and the LMW LDL phenotype was more prevalent in subjects with Ca scores >100 ($p<0.009$).

Conclusions: These findings support the relationship of small, dense LDL (LMW LDL) with metabolic diseases like diabetes and metabolic syndrome. The relationship of Ca scores and LMW LDL demonstrated an association of the LDL phenotype with CHD. These studies are consistent with a reduced LDL particle diameter being a significant predictor of CHD.

7. Ethnic Differences In Traditional And Emerging Risk Factors For Individuals Developing Diabetes/Metabolic Syndrome And Coronary Heart Disease. Dreams 2.

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Hypotheses and aims: The goal of this substudy of DREAMS is to determine the prevalence in ethnic groups of traditional and emerging risk factors (ERF) for individuals developing diabetes/metabolic syndrome (MS). Our objective is to examine the frequency of ERF in those at risk for developing coronary heart disease (CHD).

Methods: To explore the role of ERF in CHD, we studied three groups of subjects free of evidence of CHD who are at National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) goals (study groups: Hispanic diabetic/MS [HD], nonHispanic diabetic/MS [nonHD], and controls [C]). ERF assessed include: apolipoproteins B and A-I; lipoprotein (a); hsCRP; homocysteine; PAI-1; myeloperoxidase; resistin, IL-6, and leptin. Electron beam computed tomography (EBCT) for coronary calcium (Ca) quantification was used as the assessment of CHD risk. Comparing the three groups revealed several differences with respect to risk factors.

Results: As expected a number of the anthropomorphic parameters including blood pressure for the diabetic groups differed ($p<0.01$) from the controls as well as lipoprotein related factors (TC, HDL-C, TG). Interestingly, Lp(a) was lowest in the HD group ($p<0.001$); other traditional and ERF showed significant differences (CRP, leptin), between the diabetic groups and controls while adiponectin and IL6 were both significantly lower in the nonHD than either HD or C. Comparisons of HD with nonHD showed only a significant difference ($p<0.05$) with Lp(a). The total Ca score was lowest in HD, C intermediate, and highest in nonHD; the distribution of Ca score categories (0-400) between HD and controls was not significant ($p<0.20$) while nonHD was ($p<0.031$).

Conclusions: These findings support the primary expectation that ERF will assist in identifying individuals at risk for CHD (via EBCT), who are currently at their stated LDL-C level by ATP III guidelines. Some of our secondary expectations supported by these preliminary findings include: Hispanic vs Caucasian diabetic patients have a different pattern of ERF and the pattern of ERF between controls and those at risk will be different. If new markers for CHD risk in diabetics are identified, this will assist in identifying individuals without currently recognized risk factors still experiencing CHD events. Identification of these factors will serve as a basis for the application of primary prevention strategies in populations previously not considered at risk relative to their LDL-C

8. *High Normal A1C as a Screen for Diabetes and Prediabetes in an Underserved Latino Population.*

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Background and Hypothesis: Individuals with prediabetes have substantial risk of developing diabetes (DM) and cardiovascular disease. Moreover, DM can be delayed or prevented in many of these individuals with medications and/or lifestyle changes. Yet many of those at high risk are never screened for prediabetes, often as a result of socioeconomic barriers. A simple and inexpensive screening tool is in great need. As previously reported, we conducted a small pilot study in a high-risk population, to evaluate several simple approximations of the oral glucose tolerance test (OGTT). We now report the use of a lower cutpoint for the HbA1C, 5.8%, as a screen for prediabetes or diabetes in these subjects. Subjects were recruited from underserved Latino communities in California.

Methods: After an overnight fast, a standard 75-gram OGTT was performed. In addition to venous sample for plasma glucose, Hemoglobin A1C was determined. Data was collected on 73 subjects, age range 19-67. 91.8% had body mass index (BMI) $\geq$25.

Results: 12.3% of subjects had abnormal glucose on OGTT: 5.5% previously undiagnosed DM, 6.8% impaired fasting glucose and/or impaired glucose tolerance. Of the 73 subjects, 13 (17.8%) had an A1C $\geq$ 5.8%. As a method of screening for prediabetes or diabetes, A1C of $\geq$5.8% had sensitivity of 89%, specificity of 92%, positive predictive value 62%, and negative predictive value 98%.

Conclusions: This appears to be an extremely useful screening tool. Using portable kits, A1C could be used to screen large groups of people without access to a laboratory, and identify individuals with prediabetes, who may be candidates for further screening. Thus, the high normal A1C may offer significant advantages for this population over a laboratory-based OGTT. A larger-scale study of this test should be performed, to confirm its validity.

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9. *The Pharmacist Shortage in California: The Aggregate Demand Index by County*

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Background and Hypothesis: It has been evidenced that the shortage of pharmacists first emanated nearly 20 years ago in 1988 (Manasse, 1988). It then appeared to have subsided to some extent by 1994. However, the Department of Health and Human Services re-identified a pharmacist shortage in 2000 when the number of unfilled vacancies at many community pharmacies, across the nation rose from 2,700 in 1998 to 7,000 in 2000. Based on the perceived shortage, our group chose to examine the demand for pharmacists on a more local level in relation to the different counties in California. Efforts were made to determine where the greatest shortage lies and how it correlates with changes in population. Even with seven pharmacy schools in California and an increase in the number of new pharmacists graduating, the shortage for pharmacists is not likely to be resolved for quite some time.

Methods: Randomly selected community pharmacies were contacted by telephone in July 2006. Pharmacist in Charge (PIC) respondents were asked to rate the demand level for open positions in their pharmacies using a 5-point scale where 5= high demand: difficult to fill open positions, 4= moderate demand: some difficulty in filling open positions, 3= balance between supply and demand, 2= demand is less than available supply and 1= demand is much less than available supply. The resulting data were adjusted for each county population using 2005 Census Bureau data. The result was an aggregate county-based demand index for California which was analyzed.

Results: There were 794 completed calls where responses per county ranged from 1-22 (mean=13.53). The top 5 counties in population had a significantly lower mean demand index than the bottom five least populous counties excluding Alpine County (2-tailed t-test, $p=0.008$). The population-adjusted aggregate demand index (ADI) for the state of California was 3.75. The greatest unmet demand was found in Tehama, Lassen, Plumas, Mariposa and Mono county, whereas the lowest unmet demand was found in Colusa, Sutter, Yolo, Lake and San Mateo county. There was not a significant difference between North and South counties ($p=0.70$).

Conclusions: The unmet demand for pharmacists in California was greater in counties with lower populations.

10. Obesity And Cardiovascular Risk. Dreams 2.

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Hypotheses and aims: Centrally distributed visceral fat represents a major health issue. It is frequently associated with Type 2 diabetes (DM) and cardiovascular disease (CVD) and has become a major public health challenge around the world. Our objective was to assess the impact of varying degrees of obesity on parameters related to CVD.

Methods: Based on the DREAMS protocol, we compared three groups with central obesity: subjects with metabolic syndrome (MS, n=51), Type 2 diabetics (DM, n=61) and bariatric surgery candidates without DM (BA, n=26). The three groups of subjects were free of evidence of CHD and are at National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) goals. In these three groups we determined the prevalence of traditional and emerging risk factors (ERF) for obese individuals. ERF assessed included: apolipoproteins B and A-I; Lp(a); hsCRP; homocysteine; PAI-1; myeloperoxidase; resistin, IL-6, and leptin. Electron beam computed tomography (EBCT) was used for coronary calcium (Ca) quantification as an assessment of CHD risk.

Results: With respect to anthropomorphic parameters, the BA group was younger than the DM and MS groups ($p<0.01$) and had significantly higher waist and hip circumference as well as BMI ($p<0.03$). Diastolic blood pressure was lower in DM in comparison to BA and MS ($p<0.03$) as well as lipoprotein related parameters (TC, LDL-C and apoB, $p< 0.02$) while Lp(a) was higher in BA ($p<0.03$). CRP was highest in the BA group while both glucose and HbA1c were higher in DM than the other groups. Leptin and TNFα were the high in BA while IL6 was highest in DM ($p<0.03$). The assessment of CHD risk by EBCT showed that the Ca score for DM was higher than MS ($p<0.003$) and the BA group had intermediate values not very dissimilar to MS scores.

Conclusions: These studies demonstrate that DM with the highest Ca score had the most normal lipoprotein pattern of the 3 groups while carbohydrate metabolism was the most deranged. The variation in cytokines between these groups is consistent with the degree of variation in obesity of these 3 groups. These studies point to the need to identify new markers for CHD risk in obese subjects since individuals at risk without currently recognized risk factors still experience CHD events. Identification of these factors will serve as a basis for the application of more stringent primary prevention strategies in populations previously not considered at risk relative to their LDL-C.

11. Traditional And Emerging Risk Factors In Individuals With Acute Coronary Syndrome

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Hypotheses and aims: Current LDL-C goals as stated by the Nat.1 Cholesteroi Ed Program Adult Treatment PanelIII (NCEP-ATP III) recommend an LDL-C< 100 mg/dl for high risk individuals. However, many patients still present with acute coronary and LDL< 100 mg/dl. In DREAMS-ACS, 19 subjects who presented with both ACS and a baseline LDL-C<100 mg/dl were evaluated for risk factors to determine whether a risk pattern could be detected to predict an acute CHD event.

Methods: To explore the role of traditional and emerging risk factors, ACS subjects were evaluated at one month after stabilization from their acute events and at baseline in controls who were non-overweight, non-diabetic, non-CVD subjects at NCEP-ATP III goals. ACS is defined as individuals with ischemic EKG changes including ST segment elevation or depression, elevated troponin levels, or unstable angina with a coronary lesion of> 70% stenosis. Exclusion criteria included patients with prior percutaneous intervention procedure within the last year or cardiogenic shock. Traditional risk factors included a history of hypertension, diabetes, smoking, family history of premature CHD, or and HDL-C< 40 mg/dl. Emerging risk factors assessed included: LDL particle size; apolipoproteins B and A-I; lipoprotein (a); hsCRP; homocysteine; PAI-1; myeloperoxidase; resistin, IL-6, and leptin.

Results: Mean LDL-C levels in ACS subjects was 83.2 mg/dl compared to 106 mg/dl in the control group(p=0.112). Those subjects with ACS had significantly higher levels of TG and lower levels of TC and HDL-C. ACS subjects also were noted to have significantly increased BMI, waist circumference, waist/hip ratio, history of smoking and family history of premature CHD. In the ACS group 40% had DM and 52% had metabolic syndrome (METS). Of the non-traditional risk factors, only elevated levels of hs-CRP, homocysteine, interleukin 6 and myeloperoxidase reached significance. 89.5% ACS patients had either a CRP > 3 mg/L, DM or METS.

Conclusions: The prevalence of ACS in individuals at their stated LDL-C goal is not a rare occurrence. In DREAMS-ACS 19 subjects with a LDL-C<100 mg/dl presented with ACS and the prevalence of having METS or CRP > 3 was 89.5%. The addition of the emerging risk factor homocysteine did not add to the ability to predict ACS risk. Therefore, in individuals presenting with LDL-C at goal, the presence of METS, DM or an elevated CRP > 3 mg/L predicted 90% of those who went on to an acute coronary event.

12. A Cross-Sectional Survey of Schistosomiasis: Incidence and Perceptions in Mingo Tanzania

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Background: Schistosomiasis is a major cause of morbidity and mortality in a large part of the tropical world; an estimated 207 million people have the disease, 120 million symptomatic. This cross-sectional study examines the incidence, perceptions of, and ability to self-diagnose schistosomiasis in Mingo, Tanzania.

Methods: The study was carried out in a single day where a sample of 50 people was simultaneously interviewed for perceptions of schistosomiasis and tested via stool and urine sample for the presence of schistosome eggs. The perceptions prior to the study were that the fishermen (male) were the primary risk group and that the locals had an adequate ability to self-diagnose schistosomiasis infection.

Results: The results showed that while 96% of those interviewed felt they had schistosomiasis; only 42% had a positive schistosome egg sample. The rate of infection was not significantly different between genders (41.6% schistosomiasis infection in females (n=24) and 42.3% infection in males (N=26)). Interestingly, the rate of infection for those 13 years and under was 33% (N=6). By occupation, the rate of schistosomiasis infection among fishermen was 47%, farmers 41%, and other occupations 25%. There were two types of schistosomiasis observed: 57% *Schistosoma mansoni,* and *43% Schistosoma haematobium.* The most important implication of this data is that women and children are equally at risk and must be included in any schistosomiasis reduction campaign. Fortunately, reducing their risk factors in Mingo is a simpler process than addressing the men's occupational exposure.

Conclusions: The lack of accuracy of self-diagnosis coupled with the potentially lethal complications of both the prevalent Schistosoma mansoni infection and the main medication (praziquantel) present a challenge to health officials that can best be addressed by consistent monitoring and treatment of schistosomiasis infection.

13. *New Pharmacist Supply Projections: Lower Separation Rates and Increased Graduates Boost Supply Estimates*

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Background and Hypothesis: The Bureau of Health Professions (BHPr) maintains an active U.S. pharmacist workforce model that is periodically updated as new data about new workforce entrants, international graduates and separation rates are available. This paper revises the 2000 BHPr model and includes estimates of the full-time-equivalent workforce. The model is important because the last national pharmacist census occurred in 1989-1991 making the model the most reliable source of pharmacist workforce data.

Methods: Total pharmacist headcounts are drawn from 2004 BLS data. The total count is distributed into 50 age groups by gender using data from a national survey. The model projects these numbers forward in time by (i) adding, each year, the projected number of new entrants and (ii) subtracting, each year, the projected number of both base-year pharmacists and new entrants who will die or retire. The composite of base-year pharmacists and new entrants who have neither died nor retired constitutes the active pharmacist supply for a given year. The FTE workforce is based on 2004 data showing men working 91% and women 81% of a 40 hour workweek. We applied these factors to estimate the projected FTE pharmacist supply.

Results: Substantial increases in the estimated U.S. pharmacist supply were noted: 19,157 (2004) to 65,080 (2020). Primary factors were longer persistence in the workforce (59%) and increased U.S. graduates (35%). Increases from international pharmacy graduates achieving U.S. licensure were <6%. More pharmacists working part-time reduced the full-time equivalent (FTE) supply by about 15%. Pharmacists' mean age declined from 47 to 43 by 2020. Due to unequal distribution across age groups, large pharmacist cohorts approaching retirement ages will find fewer pharmacists available to replace them. Pharmacists-to-over-65-population ratios decrease after 2011 and continue falling beyond 2020 reflecting baby boomers passing through older age cohorts.

Conclusions: Pharmacists working longer and educational expansion caused an unpredicted increase in supply estimates and a three-year reduction in mean age by 2020. More part-time work resulting in about 15% FTE workforce reduction counterbalances these trends. Reductions in pharmacist-to-over-65-population ratios from 2011 onward, despite supply increases, illustrate the impending healthcare challenge as baby boomers move through their senior years. Historical fluctuations in graduates could create a shortfall of experienced, senior pharmacists during the early phases of the baby boomer retirement era. Coincident demands for more physicians and nurses over the same period and shortages in all three professions argue for proactive steps, important among them continued monitoring of work trends among pharmacists and other health professionals.

14. Estimating Risk Factors for Diabetes Among Schizophrenics with Exposure to Atypical Antipsychotics.

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Hypotheses and aims: Recent ADA guidelines have identified age $\geq$45, BMI $\geq$25kg/m^2, positive family history, gestational diabetes, physical inactivity, smoking, elevated blood pressure and lipids, and being non-white as risk factors for developing diabetes type II (DM-II). In addition, atypical antipsychotic(AAP) exposure has been shown to be a risk factor for DM-II. The exact relationship between AAP exposure and DM-II remains unclear however, because schizophrenia itself is related to DMII risk factors, including inactivity, smoking, and increased BMI. This study estimates the risk of ADA factors and AAP exposure for DM-II among schizophrenics.

Methods: Data was collected via structured interview for 107 schizophrenic outpatients at a tertiary care center in Iowa City, IA. Data collected included: age, height, weight, waist circumference, blood pressure, lipid level, and random capillary glucose; along with smoking history, level of physical activity, months of typical and atypical antipsychotic exposure, and if previously diagnosed with DMII. Patients not previously diagnosed with DMII who had a random glucose >120mg/dl were followed up with a fasting plasma glucose. Adjusted odds for DM-II were estimated for ADA risk factors and AAP exposure using a multivariate logistic regression model.

Results: Fourteen schizophrenics met criteria for a DM-II diagnosis. Compared to non-DM-II schizophrenics (N=93), DM-II schizophrenics (N=14) had higher BMIs (35.7 $\pm$ 7.6 vs. 29.6 $\pm$ 8.2, P<.01), were more likely to be inactive (86% vs. 58%, P<.01) and were on AAP for more months (83.8 $\pm$ 70.7 vs. 47.9 $\pm$ 43.9, P<.01). The sample did not differ in age, gender, smoking history (pack years), family history of DM-II, or elevated hypertension and/or lipids. In multivariate analyses, no risk factors were found to be significant (P<.05).

Conclusions: Analyzing a recent sample of schizophrenic outpatients, BMI, physical inactivity, and exposure to AAP were all found to be positively related to DM-II; however in multivariate analyses, none of these risk factors remained significant. These results indicate that AAP exposure may not play as large a role in the development of DM-II among schizophrenics patients as previously thought

15. Cross-Cultural Health Literacy: Effectiveness of a Tagalog Brochure in Educating Filipinos about Valley Fever (Coccidioidomycosis)

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Background and Hypothesis: Valley Fever, also known as Coccidioidomycosis, is a fungal lung infection that is endemic in parts of the Southwestern United States and northern Mexico. A fungus, *Coccidioides immitis*, is found in the soil and is inhaled by affected individuals. Valley Fever disproportionately affects individuals of Filipino descent with disseminated disease. It is unclear whether a gene or some other confounding factor predisposes them to disseminated disease. In Fall 2006, I translated a brochure describing the etiology, signs, symptoms, diagnosis, and treatment of Valley Fever into Tagalog, the national language of the Philippines. Because this translation was the first of its kind in Kern County, community leaders were consulted to ensure that the language of the brochure would reflect the community it would serve. I hypothesize that the availability of a brochure in Tagalog will help raise awareness of Valley Fever in the Filipino-American Community and help teach ways of avoiding exposure to fungal spores.

Methods: Pre-intervention and post-intervention studies were conducted in interview format of 30 Filipino-Americans in a pilot study to test the brochure for its understandability. Participants were interviewed in person, by email, and over the phone. All spoke Tagalog or another Filipino dialect, and all had completed at least a high school education. Prior to reading the brochure, participants were asked about their knowledge of Valley Fever. After reading the brochure, they were asked what they learned from the brochure, whether or not it was helpful to have the information available in Tagalog, and whether or not they had any questions. Selected participants were asked, "Based on the information in the brochure, would you wear a mask and counsel others to wear masks if they were to go dusty areas?"

Results: Of the thirty participants, twenty (67%) spoke Tagalog. The other ten (33%) spoke other Filipino dialects. Fifteen (50%) did not have a health care background, while the other 50% did. All had varying knowledge of Valley Fever. Twenty-nine (97%) felt that it was useful to have Valley Fever information available in Tagalog. Twenty-nine (97%) felt that they learned useful information, especially about the signs and symptoms of Valley Fever. Participants also had several questions for the researcher, generating further dissemination of information about Valley Fever. Of the 10 participants asked about wearing a mask, eight (80%) replied, "Yes."

Conclusions: Overall, the language of the brochure was understandable regardless of what dialect Filipinos spoke or what occupation they held. Because participants felt it was helpful to have a brochure describing Valley Fever in Tagalog and because participants sought more information about Valley Fever after reading the brochure, a larger public awareness campaign is needed to further educate Filipinos about Valley Fever.

16. The Pharmacist Shortage In California: The Aggregate Demand Index By County.

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Hypotheses and aims: To evaluate the unmet demand for pharmacists in California from 57 of 58 counties.

Methods: Randomly selected community pharmacies were contacted by telephone in July 2006. Pharmacist in Charge (PIC) respondents were asked to rate the demand level for open positions in their pharmacies using a 5-point scale where 5= high demand: difficult to fill open positions, 4= moderate demand: some difficulty in filling open positions, 3= balance between supply and demand, 2= demand is less than available supply and 1= demand is much less than available supply. The resulting data were adjusted for each county population using 2005 Census Bureau data. The result was an aggregate county-based demand index for California which was analyzed.

Results: There were 794 completed calls where responses per county ranged from 1-22 (mean=13.53). The top 5 counties in population had a significantly lower mean demand index than the bottom five least populous counties excluding Alpine County (2-tailed t-test, p=0.008). The population-adjusted aggregate demand index (ADI) for the state of California was 3.75. The greatest unmet demand was found in Tehama, Lassen, Plumas, Mariposa and Mono county, whereas the lowest unmet demand was found in Colusa, Sutter, Yolo, Lake and San Mateo county. There was not a significant difference between North and South counties (p=0.70).

Conclusion: The unmet demand for pharmacists in California was greater in counties with lower populations.