58TH AOA ANNUAL RESEARCH CONFERENCE
HELD IN CONJUNCTION WITH THE AOA'S OSTEOPATHIC MEDICAL CONFERENCE & EXPOSITION (OMED)
SEATTLE, WASHINGTON
SATURDAY, OCTOBER 25TH – MONDAY, OCTOBER 27TH 2014
PRELIMINARY PROGRAM INFORMATION
SCIENCE IN SEATTLE – EMERGENT RESEARCH THEMES AND TOPICS FOR TODAY'S OSTEOPATHIC PRACTITIONER

Program Chair: Edward J. Wagner, PhD
Program Co-Chair: Beatrice Saviola, PhD

Program at a Glance
The 2014 research conference program comprises four main themes. The first of these deals with the underrepresentation of women in biomedical and clinical research, and the compelling evidence attesting to the need for more equitable male: female ratios that, in turn, will help promote the practice of a more sound, gender-based medicine. Our second theme will investigate the developmental origins, pathogenesis and potential treatment options for autism spectrum disorders. The third theme focuses on the problematic issues that our medical professionals currently face in the realm of infectious diseases. The final session endeavors to explore recent developments that serve to further our understanding of how Osteopathic Manipulative Treatment imparts therapeutic benefit to patients by improving neurological, musculoskeletal and immune function as well as body fluid dynamics. Each of these themes will be presented by preeminent basic and clinical scientists from around the world, and they will report on their latest, cutting-edge research. This comprehensive research program will offer new insight and provide a newfound appreciation for the intrinsic processes that promote normal development, determine an individual's ability to maintain well-being and respond to various types of medicinal interventions, and how this information might be translated into more gender-specific pharmaceutical and osteopathic manipulative therapies.
Program Schedule and Presentation Summaries
Room 2AB
Washington State Convention Center

Saturday, October 25
Time: 8:30 – 11:30 a.m.

Theme 1 - Gender Differences and Women’s Health: Does Sex Really Matter?  Biomedical research conducted over the last half-century has undoubtedly led to significant advances in our ability to diagnose and treat an ever-expanding number of disease states. However, the fact remains that the human and animal subjects included in this research are almost exclusively male, and as a result, comparatively little data have been generated in females. Only in recent years, has there been a burgeoning collective effort to promote research that focuses on the study of women and gender differences in the laboratory, field, and clinic. This research is beginning to reveal clear sex/gender differences in a wide range of biological processes including, but not limited to, those associated with drug abuse, energy and fluid balance, and the control and perception of pain. As such, it will have progressively greater impact on how we approach disease prevention and treatment. Six renowned experts will cover these compelling topics within the overall theme of sex/gender differences and women’s health. The following objectives will be stressed:

**Learning Objectives:**
1) To learn how sex/gender differences manifest themselves in a wide variety of biological processes and disease states,
2) To understand how gonadal steroid hormones influence the development and maintenance of these sex/gender differences,
3) To appreciate the need for finding more reliable, gender-specific biomarkers and therapeutic interventions that are appropriately tailored to men and women.

8:30-9:00 a.m.
Edward J. Wagner, PhD
Associate Professor of Physiology
Dept. of Basic Medical Sciences
College of Osteopathic Medicine of the Pacific
Western University of Health Sciences

Gonadal Steroid Modulation of Cannabinoid CB1 Receptor Function: Sex-Specific Effects in the Regulation of Energy Homeostasis

**Presentation Summary:**
The term “cannabinoid” refers to the class of 60 or so compounds found in the plant cannabis sativa, of which Δ9-tetrahydrocannabinol (THC) is the major bioactive constituent. Endogenous cannabinoids such as anandamide and 2-arachidonyl glycerol are synthesized de novo from phospholipids via the enzymatic activities of phospholipases C and D. These compounds act to varying degrees at two subtypes of cannabinoid receptors: the CB1 and CB2 receptors. It is now widely accepted that cannabinoids play an important regulatory role in processes controlled by the hypothalamus including reproduction, responses to stress, and energy homeostasis. There is also extensive precedence for sex differences in cannabinoid-regulated biology – ranging from antinociception to self-administration. This talk will focus on sex differences in the
cannabinoid regulation of energy intake, meal pattern and energy expenditure, and the
dichotomous modulatory effects of gonadal steroids on these indices of energy balance.
Activation of cannabinoid CB1 receptors stimulates appetite in humans and rodents, and
orchidectomized male guinea pigs are significantly more responsive to cannabinoid-
induced hyperphagia and hypothermia than are ovariectomized females. Estradiol per se
decreases energy consumption and expenditure, and greatly attenuates the hyperphagia,
hypothermia, and reduction in excitatory synaptic input onto anorexigenic
proopiomelanocortin (POMC) neurons in ovariectomized females that are caused by the
activation of hypothalamic cannabinoid CB1 receptors. By contrast, testosterone per se
stimulates energy intake in orchidectomized males in an endocannabinoid-dependent
fashion, and augments the cannabinoid-induced presynaptic inhibition of excitatory input
onto POMC neurons. These observations impart critical insight into the sex-specific
synaptic and hormonal determinants underlying the cannabinoid regulation of energy
homeostasis.

**Learning Objectives:**

1) Recognize that there are sex differences in many facets of cannabinoid-regulated
biology
2) Understand the interplay between the organizational and activational effects of gonadal
steroid hormones in the cannabinoid regulation of energy homeostasis
3) Appreciate how gender and hormonal status might influence the decision to use
cannabinoids as pharmacotherapeutic adjuncts in the treatment of conditions such as
HIV/AIDS- and cancer-induced cachexia, as well as obesity and the metabolic
syndrome.

**References:**

1) Haney, M., Rabkin, J., Gunderson, E., Foltin, R.W.: Dronabinol and marijuana in
HIV+ marijuana smokers: acute effects on caloric intake and mood.
2) Sinchak, K., Wagner, E.J.: Estradiol signaling in the regulation of reproduction and
A reflection of differences in the endocannabinoid system? Life Sci., 92: 476-481,
2013.

9:05-9:35 a.m.
Kathleen Curtis, PhD
Assistant Professor of Physiology
Department of Pharmacology and Physiology
College of Osteopathic Medicine
Oklahoma State Center for Health Sciences

**Estrogen and Body Sodium Balance: Behavioral Responses and Central Pathways In Rats**

**Presentation Summary:**
There has been increasing focus on the role of estrogens in cardiovascular regulation and
body fluid balance, particularly with regard to body sodium homeostasis. Much research
has addressed the effects of estrogens on the release of vasopressin in response to hyperosmolality[1]. However, though often overlooked, water and sodium ingestion play an integral role in the maintenance of body sodium balance. Accordingly, we have focused on estrogen modulation of behavioral responses to sodium challenges, and on the central pathways implicated in such responses. During hypernatremia produced by slow hypertonic NaCl infusion, ovariectomized (OVX) rats given estradiol exhibited decreased latency to begin drinking water[2], along with blunted neuronal activation selective to the hindbrain sympathoexcitatory area[3]. Given that elevated blood pressure decreases stimulated drinking[4], these findings suggest that estrogens reduce cardiovascular responses to hypernatremia, thereby ‘permitting’ more rapid expression of the drinking response. In contrast, during hyponatremia produced by administration of the diuretic/natriuretic drug, furosemide, estradiol-treated OVX rats consumed similar volumes of concentrated NaCl solutions as did OVX rats without estradiol, but drank less water. Despite differences in the behavioral responses, neuronal activation in forebrain circumventricular organs increased after furosemide administration in both groups, suggesting that estrogen alters the detection of hormones or electrolytes that stimulate behavioral responses to sodium loss. Together, these findings indicate that estrogen has broad effects in body sodium balance that include behavioral responses to sodium challenges, and that these effects involve changes in central pathways associated with body fluid regulation. The direction of the behavioral effects and the specific central areas involved depend on whether the challenge entails hypo- or hyper- natremia.

**Learning Objectives:**
1) To increase understanding of estrogen effects on behavioral responses to body sodium imbalance
2) To increase understanding of signals that stimulate or inhibit behavioral responses to body sodium imbalance
3) To increase understanding of estrogen effects on central pathways that mediate behavioral responses to body sodium imbalance

**References:**
Sex Differences in Cannabinoid Analgesia

**Presentation Summary:**
Several cannabinoid drugs, including delta-9-tetrahydrocannabinol (THC, the primary psychoactive constituent of marijuana), are more potent analgesics in female rats than in males. Sex differences in THC-induced analgesia are mediated by estradiol in females: within 24 hr after estradiol peaks during the estrous cycle, females’ sensitivity to THC peaks; furthermore, in ovariectomized rats, estradiol but not progesterone enhances females’ sensitivity to THC. Sex differences in THC-induced analgesia in the rat are in part due to sex-specific metabolism of THC, with females producing more of the primary active metabolite 11-OH-THC than males. Pharmacodynamic mechanisms such as more CB2 receptors in females may also contribute to greater cannabinoid analgesia in females, particularly in cases of chronic inflammatory pain. Sex differences in cannabinoid analgesia, should they occur similarly in humans, could be important given women’s greater lifetime experience of chronic pain compared to men.

**Learning Objectives:**
To gain a preliminary understanding of:
1) Sexual differentiation of sensitivity to drug effects.
2) Gonadal hormone modulation of sensitivity to cannabinoids.
3) Pharmacokinetic and pharmacodynamic mechanisms that may underlie sex differences in cannabinoid drug sensitivity.

**References:**

**10:10-10:20 BREAK**

**10:25-10:55 a.m.**
**Jill Becker, PhD**
Patricia Y. Gurin Collegiate Professor of Psychology
Research Professor Molecular & Behavioral Neuroscience Institute
University of Michigan

Sex Differences in Cocaine Self Administration: Neurochemistry and Behavior
**Presentation Summary:**
Cocaine dependence is characterized by compulsive drug taking that supersedes other recreational, occupational or social pursuits. Furthermore, there are sex differences in the motivation to take drugs of abuse including cocaine. Using the rat as an animal model, we find that in females there are rapid effects of estradiol on the ascending dopamine system that enhance the female's motivation to engage in these behaviors. Female rats exhibit greater behavioral sensitization to cocaine, acquire cocaine self-administration more rapidly, and work harder to receive cocaine than males, and estradiol enhances these sex differences. In a behavioral paradigm, rats vulnerable to addiction can be identified within the larger population based on their preference for cocaine over palatable food rewards. We find that cocaine-preferring rats increased their drug intake at the expense of pellets, displayed increased motivation for cocaine, attenuated motivation for pellets and an attenuated cocaine-induced dopamine release in dialysate, compared with animals that preferred palatable food pellets. Females are more likely to develop a cocaine preferences than are males.

Funding: R21-DA-032856, R21-DA-032747-02 and R01-DA-012677 to JBB

**Learning Objectives:**
1) Advance the understanding of the effect of estradiol to enhance motivation through its effects on the reward system.
2) Advise regarding the importance of valid animal models for addiction to determine factors contributing to individual differences in addiction vulnerability.
3) Promote consideration of the role of social factors in limiting addiction liability in females.

**References:**
Sex Influences on Brain and Memory: The Burden of Proof Has Shifted

Presentation Summary:
The past decade witnessed tremendous growth in the evidence for potent sex influences on the brain at all levels of its function, down to the molecular level. The domain of emotional memory is no exception. This talk will highlight these developments, with a focus on sex influences on amygdala/stress hormone interactions in long-term memory formation. The general conclusion is that the burden of proof on the sex influence issue, both for those studying emotional memory and for neuroscience in general, has shifted: From those pursuing the issue generally having to justify why, to those not doing so having to justify why not.

Learning Objectives:
1) Understand why sex influences are so important for brain science
2) Understand some of the sources of resistance to the issue
3) Have specific examples of how lack of attention to sex influences can lead to false conclusions.

Time: 1:30 – 4:15 p.m.
Theme 2 - Autism Spectrum Disorders: How close are we to tearing down the wall?
Autism spectrum disorders (ASD) are currently believed to affect 3-4 out of every 1,000 children between the ages of 3-10. It is more prevalent in males; affecting three boys for every girl diagnosed with the condition. Children afflicted with ASD demonstrate deficits, to varying degrees, in 1) social interaction, 2) verbal and nonverbal communication, and 3) repetitive behaviors or interests. While in some individuals the problems in communication and social skills become more apparent as the child lags further behind other, “normal” conspecifics of the same age, others may start developing on a normal trajectory and then, somewhere between 12-36 months of age, begin to regress and lose the language and social skills they had previously acquired. The staggering increase in the incidence and prevalence of ASD has outpaced our ability to fully grasp its etiologies and pathogenesis, and to devise appropriate and reliable treatment options. Five experts will explore recent developments that serve to further our understanding of the underlying causes and complex manifestations of ASD, and provide insight into potential therapeutic strategies for treating it. The following objectives will be stressed:

Learning Objectives:
1) To learn the various manifestations of ASD, and how they can differentially impact social interaction and communication,
2) To understand how ASD arises from a combination of genetic, immunologic and environmental factors,
To appreciate the need for developing new animal models that more closely mimic the symptomatology of ASD so that we can better understand its various etiologies and, as a result, develop more promising strategies and targets for treatment.

1:30-2:00 p.m.
Veronica Miller, PhD
Research Scientist
Research Assistant Professor
School of Public Health at Albany
Wadsworth Center for Laboratories and Research
NY State Dept. of Health
Albany, New York.

Sex Differences in the Effects of Prenatal Toxicant and Viral Exposures on Brain Growth and Behavior in Offspring

Presentation Summary:
Autism spectrum disorders (ASDs) are estimated to affect 1/62 children and males are three times more likely to be affected with the disorders than females. The etiology of ASDs is complex, but known to involve genetic and environmental factors. In this presentation we will demonstrate that exposures to two factors associated with developmental abnormalities have sex-specific effects on brain development and behavior in offspring. Firstly we will show that there are innate sex-differences in the growth of the brain. Secondly, exposure to endocrine disrupters has sex-specific effects on the growth of white matter in rodent offspring. Finally we illustrate that neuroendocrine disrupters are not the only factors which have sex-specific effects on the growth of the brain. Gestational exposure to the flu virus also induces both sex and dose-dependent effects on neurochemicals, neuroinflammation, oxytocin, testosterone and induces sex-specific ASD-like behaviors in offspring. This talk highlights the importance of including both male and female offspring in developmental studies. We also provide strong evidence that there may be different mechanisms associated with the precipitation of ASD-like behaviors in male and females, associated with innate differences in neuro-immune responses to ASD-risk factors.

Learning Objectives:
1) The first learning objective is that there are innate sex differences in the development of immune cells (oligodendrocytes, astrocytes and microglia) in the brain.
2) The second objective is the concept that exposure to neuroendocrine disrupters such as Polychlorinated Biphenyls (PCBs) induce sex-specific changes in brain development in addition to hypothyroxinemia, which are associated with ASD-behaviors.
3) The third learning objective is that exposures to immune challenges such as the influenza virus during pregnancy, can lead to lasting sex-specific changes in neurochemical metabolism, oxytocin levels, neuroinflammation, contributing to ASD-like behaviors in offspring.
Presentation Summary:
Progress in gaining an understanding of the autism spectrum disorders (ASD) is slowed by the relative lack of ecologically relevant animal models in which to study potential causes of the disorders. An animal model that is intended as a platform on which to base studies of autism must, at minimum, address the broad aspects and symptoms of autism: social dysfunction, restricted or repetitive behaviors and/or perseveration, language impairments, and the sex differences in the incidence of autism. Unfortunately, many of the typical laboratory animals are limited in their ability to address the broader aspects of autism. Consequently, rather than modeling autism as a disorder, many animal studies focus on specific symptoms of autism.

Although there often are cognitive deficits associated with the disorders, at their core ASD may best be described as a socialization disorder and the social impairments may persist throughout life. Further, among the various symptoms of ASD, deficits in social behaviors are least likely to improve with age. Thus, studying social behavior may be an effective route to understanding ASD. Over the past two decades, prairie voles have been the predominant animal model in which to study the formation and maintenance of social affiliation. In contrast to more traditional laboratory animals, prairie voles display social behaviors, and even autonomic responses, that are remarkably similar to those of humans. These parallels have led to the wide-spread use of voles to study the neural and physiological bases of social attachment. More recently, prairie voles have been suggested as animal model in which to study autism Prairie vole social behavior has been well-characterized. Sexually naïve animals are highly social and avoid isolation to the point that they appear to actively seek out contact with other voles. However, after forming a bond with a mate, a remarkable transformation occurs: previously very social animals begin to display strong aversions to contact with strangers. Rather than seeking out companions, they actively avoid contact with strangers. This switch from social to asocial behavior is unlike that seen in any other laboratory animal, but is remarkably similar to the behavioral changes that occur during autistic regression. The parallels between vole social behavior and the development of autism are of great significance since previous research has provided a good understanding of the neural mechanisms underlying the behavioral change in voles. Studies using voles have examined reciprocal interactions between neurochemistry and social bonding (especially for dopamine, oxytocin, and vasopressin; all of which have been linked to ASD).

We recently have been able to produce behaviors in voles that appear to address at least two of the core criteria outlined above: prairie voles that ingest heavy metals in their drinking water subsequently exhibit sex-specific deficits in social behavior. Male, but not
female, prairie voles that receive metals treatment significantly reduce social contact when confronted with an unfamiliar individual. Importantly, the social avoidance is not displayed when a familiar sibling rather than a stranger is used as the stimulus animal. We are using a two-pronged approach to further probe this phenomenon – examining potential neurochemical bases that underlie the behavioral change, and studying the intestinal microbiota to gain insights into the basis for the sex difference.

**Learning Objectives:**
1. Appreciate the utility of animal models for studying ASD
2. Understand potential for links between environmental factors and ASD
3. Appreciate the importance of studying social behavior as a route to understanding ASD

**References:**

2:40-3:10 p.m.
Xiaoning Bi, PhD
Associate Professor of Physiology
Dept. of Basic Medical Sciences
College of Osteopathic Medicine of the Pacific
Western University of Health Sciences

**Understanding Autism Spectrum Disorder: Insight from Research on Genetically-Linked Syndromes**

**Presentation Summary:**
According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the core features of autism spectrum disorder (ASD) are deficits in social cognition and communication, and restricted interests and repetitive behaviors. The newly defined ASDs encompass autism, Asperger syndrome, and pervasive developmental disorder not otherwise specified. The most recent survey indicates that the prevalence of ASD is 1 in 68 children in the US and the male to female ratio is about 4~5:1. While ASD is among the most inheritable neuropsychiatric disorders, recent studies have shown that genetic contributions to ASD are highly heterogeneous. Furthermore, the core deficits in children emerge at different developmental stages and evolve with distinct time-courses, which create a challenge for ASD research. On the other hand, the presence of ASD in syndromes with identified genetic etiologies presents a unique opportunity to study the links between alterations of specific behaviors and genetic mutations. Accumulating evidence from human and animal studies has indicated that disruption of synaptogenesis and synaptic plasticity may constitute a common mechanism for ASD. For instance,
Impairment in hippocampal long-term potentiation (LTP) in a mouse model of Fragile X syndrome is caused by deficits in spine stabilization, due to dysregulation of the actin network in dendritic spines. Hippocampal LTP consolidation is also impaired in mice with maternal deletion of ube3a, a mouse model for Angelman’s syndrome, another neurodevelopmental disorder with close ties to ASD. Our recent results indicated that LTP impairment in this mouse model is associated with changes in the regulation of a potassium channel and with deficits in spine stability. Tuberous sclerosis also exhibits ASD co-occurrence and recent research has shown that TSC proteins control axon formation in cultured hippocampal neurons. These results suggest that several developmental neuropsychiatric disorders might be the results of alterations of a common set of mechanisms involved in synaptogenesis and synaptic plasticity.

**Learning Objectives:**
1. Recognize the symptoms of ASD
2. Know the prevalence of ASD
3. Know the genetic and environmental risk factors of ASD

**References:**
1. Current Diagnosis & Treatment: Psychiatry, 2e >Chapter 34. Autism and the Pervasive Developmental Disorders
3. Harrison's Principles of Internal Medicine, 18e >Chapter 390. Biology of Psychiatric Disorders

3:15-3:45 p.m.
Judy Van De Water, PhD
Professor
Division of Rheumatology/Allergy and Clinical Immunology
UC Davis

**Immune Dysfunction in ASD: Thinking Outside the Brain**

**Presentation Summary:**
Maternal immune dysregulation during gestation has been described as a risk factor for neurodevelopmental disorders such as autism and schizophrenia. Such dysregulation can be manifest as inflammation or cytokine dysregulation, as well as maternal autoantibodies that recognize proteins in the developing. We have identified fetal-brain reactive maternal IgG antibodies in 23% subset of mothers of children with autism spectrum disorder (ASD), and an association between presence of these antibodies and severe behavioral manifestations. Fetal exposure during gestation to brain-reactive maternal IgG may be the underlying cause of the behavioral symptoms noted in some ASD cases and unraveling the molecular interactions between these antibodies and their targets may open new avenues for treatment and prevention. This presentation will address the maternal immune system as it relates to neurodevelopment, maternal autoantibodies to fetal brain proteins and their potential role in ASD, and how these factors might be used as early biomarkers to detect autism risk.
Learning Objectives:
1) Understanding the role of the maternal immune system during gestation and its contribution to altered neurodevelopment.
2) Understanding the relationship between maternal autoantibodies to fetal brain proteins and the development of ASD in the child.
3) Defining the potential use of maternal immune biomarkers for autism risk determination.

References:

4:30 – 6:30 p.m.
Ravenna
Sheraton Hotel
Research Directors Meeting
Room 2AB
Washington State Convention Center

Sunday, October 26th
Time: 9:30 – 11:45 p.m.

**Theme 3 - Host-Pathogen Interactions.** Human infectious pathogens create an immense global burden in terms of human morbidity and mortality. It is estimated that infectious agents are the cause of the majority of deaths in children and young adults accounting for 13 million deaths per year. In developing countries one in two deaths is caused by infectious agents. These human pathogens use a variety of means to evade and resist human host defenses which include genetic regulation of virulence factors. In addition, host defenses can be up regulated to combat invading infectious agents, hopefully ridding them from the body. It will be important to understand the interplay between host and pathogen so that new methodologies can be developed which can potentially combat these infectious agents. Four experts will describe recent research developments in host pathogen-interactions including bacterial mechanisms to evade host defenses and host mechanisms to control invading pathogens. The following learning objectives will be covered in this session.

**Learning Objectives:**
1) To appreciate how bacteria invade human host cells and resist the host immune system.
2) To understand how host defenses combat invading microbes by compartmentalizing pathogens in spaces that contain reactive oxygen intermediates, lowered acidity, lowered oxygen tension, and toxic peptides.
3) To appreciate the development of engineered host products that can fight bacterial pathogens to resist their colonization and growth.

9:30-10:00 a.m.
**Hector Morbidoni, PhD**
Catedra de Microbiologia
Universidad Nacional de Rosario
Argentina

**Non-Essential but Critically Important: The Role of Mycolic Acid Composition in Mycobacterial Cell Permeability and Virulence**

**Presentation Summary:**
Mycobacterium tuberculosis is a human infectious pathogen responsible for two million deaths worldwide; treatment of tuberculosis requires several drugs and due to the appearance of drug resistant strains is also calling for the development of novel more effective compounds. Infections caused by Non Tuberculous Mycobacteria (NTM), even when of lesser importance- are very hard to treat and a cause of growing concern. Mycolic acids (MAs) are very long modified fatty acids that are both essential structural components of the mycobacterial cell wall as well as diffusible regulators of host immune response. Importantly, MAs and other components are responsible for the low permeability of mycobacteria that restricts entrance of drugs to the cell. Synthesis of these cell components is targeted by several drugs in clinical use; moreover, research groups are developing novel anti-tubercular
agents targeting enzymes of the MAs pathway. At the same time, it is of note to mention that composition of MAs varies within different species; in addition, the content of MAs in each species is made up of different sub-families with differences in subtle but important chemical modifications. Our research, as well as results from other groups, demonstrated that regardless of the quantitative importance of each sub-family, all of them are required for proper maintenance of cell wall permeability, cell growth, and in the case of pathogenic mycobacteria, of their virulence. Our research on non essential gene products such as Mycolic Acid Methyl Transferases (MMTs) and in NTM showed that these enzymes are involved in the mechanisms of action of the drugs Isoxyl and Thiacetazone. Surprisingly, enzymes of the pathways leading to unsaturated fatty acid (UFA) synthesis were also found to play a role in the action of the mentioned drugs. Overall, our research and the results from other groups reveal the intricacies and importance of fatty acid and MAs synthesis in mycobacteria, validating even non-essential components as targets for the development of drugs that may become useful helpers if combined with drugs currently in use that have limited access to the mycobacterial cytoplasm.

**Learning Objectives:**
1) To understand the basis of the cell wall composition in mycobacteria, with emphasis on the role of mycolic acids.
2) To appreciate why the synthesis of mycolic acids is a useful source of targets for drug development.
3) To appreciate how by inhibition of non essential mycobacterial cell wall components can be exploited to increase drug potency.

**References:**

10:00-10:30 a.m.
**Michael R. Yeaman, MSc, PhD**
Professor of Medicine
David Geffen School of Medicine at UCLA
Chief, Division of Molecular Medicine
Harbor-UCLA Medical Center

**Host Defense Peptides: Immunology to Innovation**

**Presentation Summary:**
Host Defense Peptides: Immunology to Innovation. Host defense peptides (HDPs) are evolutionarily ancient immune effector molecules that have potent antimicrobial activity even against organisms which have become resistant to the most contemporary antibiotics. HDPs are diverse in structure and mechanism, and are induced in response to infection or
host tissue injury. Different structural classes of HDPs are expressed by specific human tissues, and have relative efficacy spectra favoring specific pathogens. Structural and mechanistic insights into HDPs have allowed molecular engineering of non-natural peptides that may advance novel anti-infectives to address the growing threat of antibiotic resistance. The discussion will highlight advances in understanding the immunology of HDPs, and recent examples of how these advances are translated to anti-infective candidates.

**Learning Objectives:**
1) To understand the basic immunology and antimicrobial mechanisms of host defense peptides from humans.
2) To consider the structure-activity relationships associated with pathogen-specific activities of human HDPs.
3) To appreciate the advancing efforts to leverage HDPs as templates for development of novel anti-infectives.

**References:**

**10:35 – 11:05 a.m.**
**Joseph Bianco, PhD**
Cleveland Clinic
Room 608/609

**Cleveland Clinic Session: Empathy in Osteopathic Medicine: What are the Data?**

**Note:** Part of the morning schedule will take place in Room 608/609 so participants can take part in Cleveland Clinic Presentation from 10:35 a.m.-11:05 a.m.—Empathy in Osteopathic Medicine: What are the Data? The Research Conference will then continue in Room 2 AB for the rest of the morning.

**11:10-11:40 a.m.**
**Beatrice Saviola, PhD**
Associate Professor of Microbiology
Dept. of Basic Medical Sciences
College of Osteopathic Medicine of the Pacific
Western University of Health Sciences

**Surviving a Stressful Situation: Stress and Mycobacteria**

**Presentation Summary:**
Tuberculosis is estimated to infect a third of the world’s population and continues to be a fatal illness for many. The microbe causing tuberculosis, Mycobacterium tuberculosis, is capable of causing a latent infection which can reactivate upon immunosuppression. There
are antibiotic treatments available, however Mycobacterium tuberculosis has evolved single and multi-drug resistance and many drugs that were effective previously now have decreased reliability. Mycobacterium tuberculosis typically survives in phagosomes in macrophages which is a location where pH can drop to pH 5.5 or lower, and there may be reactive oxygen intermediates as well. This mycobacterium has evolved mechanisms to survive environmental stresses in vivo which help it persist during latency and possibly reactivate after a prolonged quiescence. Salicylic has been shown to be an antmycobacterial compound and recently I have shown that at lower concentrations it induces transcriptionally the DNA region 5’ to the Rv3488 gene of M. tuberculosis. Rv3488 is a DNA binding protein and has been shown to bind DNA sequences between the Rv3488 and lipF genes of M. tuberculosis. Salicylic acid has been proposed to behave as a signaling molecule to modulate mycobacterial responses. Possibly salicylic acid binds to Rv3488 or another transcriptional regulator to modulate promoter binding and upregulation of transcription of the Rv3488 promoter region. Alternatively as salicylic acid is an inhibitory molecule for M. smegmatis, its toxic effects may induce Rv3488 promoter regulation. In addition, the divergently transcribed upstream gene of Rv3488 is lipF which is induced by acidic stress as high as pH 6.4, which indicates it is indeed induced in vivo. Interestingly there seems to be a lower minimum of pH induction which may indicate something of the mechanism by which this gene is induced.

Learning Objectives:
1) To understand how host defenses combat invading mycobacteria by compartmentalizing pathogens in spaces that contain reactive oxygen intermediates, and lowered acidity.
2) To appreciate how mycobacteria invade human host cells and resist host stresses.
3) To appreciate how the targeting of certain mycobacterial gene products can inhibit mycobacterial growth in vivo.

References:
- http://www.who.int/topics/tuberculosis/en/

1:30 – 4:30 p.m.
Student Poster Competition
Exhibit Hall 4
Washington State Convention Center

6:00 – 7:00 p.m.
Research Conference Reception
Ravenna
Sheraton Hotel
Room 2AB
Washington State Convention Center

Monday, October 27th
Time: 9:30 – 11:45 a.m.

**Theme 4 – Emergent Insights into the Therapeutic Utility of Osteopathic Manipulative Medicine:** In keeping with one of the basic tenets of the annual AOA Research Conference, this session explores how Osteopathic Manipulative Treatment can best be integrated into the four basic principles of the Osteopathic Medical Philosophy and impart therapeutic benefit to patients by improving the structure and function of the neurological, musculoskeletal, and immune systems, as well as tissue perfusion and body fluid dynamics. Five experts will explore recent developments that serve to heighten our appreciation for the mechanisms underlying the therapeutic potential of Osteopathic Manipulative Medicine. The following objectives will be stressed:

**Learning Objectives:**
1) To understand the four basic principles of the Osteopathic Medical Philosophy,
2) To learn how Osteopathic Manipulative Treatment can improve health through improved functioning of neurological, muscular and immune systems.
3) To appreciate new animal models and how they have aided in the elucidation of therapeutic mechanisms through which Osteopathic Manipulative Treatment restores structure and function of various body systems.

9:30-10:00 a.m.
Paul Standley, PhD
Assistant Dean - Curricular Affairs
Professor
Departments of Basic Medical Sciences and Physiology
The University of Arizona
College of Medicine-Phoenix

**Modeled Myofascial Release: A Vehicle for In Vitro Fibroblast-Directed Skeletal Myoblast Differentiation and Myotube Functionality**

**Presentation Summary:**
Skeletal muscle functionality is governed by multiple stimuli including cytokines and mechanical strain. Fibroblasts embedded within intramuscular connective tissue respond to mechanical strain by secreting cytokines that induce myoblast differentiation, and we hypothesize regulates myotube function. A coculture was established to allow crosstalk between paracrine molecules secreted by fibroblasts in Bioflex wells, and myoblasts on non-deformable coverslips situated above Bioflex wells. Cyclic-short duration strain (CSDS) modeling overuse injury, acyclic long-duration strain (ALDS) modeling manual therapy, and combined strain paradigm (CSDS+ALDS) were applied to fibroblasts. Non-strained myoblasts in uniculture and coculture served as controls. 96hrs post-strain myotube contraction was induced by perfusion of ACh[10-11-10-3M], and KCl[10-2M]. CSDS-fibroblasts increased ACh-induced contractile sensitivity vs. uniculture (P<0.05). As
contraction is dependent upon ACh binding, expression and clustering of nicotinic receptors (nAChRs) were measured. CSDS-fibroblasts increased nAChR expression (P<0.05) which correlated with myotube contraction. ALDS-fibroblast did not significantly affect contraction or nAChR expression. Agrin-treated myotubes were then used to design a computer program to identify αBGT-stained nAChR clusters. Similar to agrin-treatment, ALDS-fibroblasts increased macroclustering (P<0.05); while CSDS-fibroblasts disrupted macroclusters from forming. CSDS-fibroblasts produced nAChRs preferentially located in microclustered regions (P<0.05). Fibroblast mediate myotube differentiation with multiple functional phenotypes. Similar to muscle injury, CSDS-fibroblasts disrupted nAChR clusters and hypersensitized myotube contraction, while ALDS-fibroblasts persevered nAChRs in large macroclusters which may have important clinical implications for neuromuscular disorders. Cellular strategies targeting the stability of neuromuscular junctions and aimed at improving muscle functionality, such as through the use of strained and non-strained fibroblasts should be further explored.

**Learning Objectives:**
1) Identify laboratory-based methods to model osteopathic manipulative treatments in vitro.
2) Describe changes in myoblast differentiation parameters and the role of fibroblasts in MFR scenarios in vitro.
3) Describe changes in myotube function and the role of fibroblasts in MFR scenarios in vitro.

**References:**
Lymphatic Pump Treatment as an Adjunctive Therapy for the Treatment of Pneumonia

Presentation Summary:
The osteopathic medical profession has designed a set of body-based manipulative medicine techniques called lymphatic pump techniques (LPT) that target the musculoskeletal system and enhance the flow of lymph through the lymphatic system. Clinical studies support the use of LPT as an adjunctive therapy for the treatment of pneumonia; however, the mechanisms by which LPT protects against pneumonia are unclear. Animal studies from our lab demonstrate that LPT significantly enhances thoracic and mesenteric lymph flow, mobilizes leukocytes from the gastrointestinal lymphoid tissues (GALT) into lymph circulation, and significantly increases the lymphatic flux of leukocytes, cytokines, and other inflammatory mediators in lymph. In addition, LPT inhibits bacterial growth in the lungs of rats with acute pneumonia. Collectively, these studies suggest that LPT can stimulate the lymphatic and immune systems, which may accelerate the clearance of pneumonia. Understanding the physiological changes that result from manual therapies, such as LPT, will help support their clinical use. The purpose of this lecture is to illustrate the importance of the lymphatic immune system during infection and edema and discuss current research that supports the use of osteopathic manipulative treatments, including LPT, to enhance the lymphatic and immune systems and protect against infectious disease.

Learning Objectives:
1) Review the basic physiology of the lymphatic system.
2) Understand current research models to study the effect of OMT on the lymphatic and immune systems.
3) Discuss research for the clinical support of OMT as an adjunctive therapy for the treatment of pneumonia.

References:
The OSTEOPATHic Health Outcomes In Chronic Low Back Pain (OSTEOPATHIC) Trial

Presentation Summary
The OSTEOPATHic Health outcomes In Chronic low back pain (OSTEOPATHIC) Trial is the largest and most rigorously designed randomized controlled trial of osteopathic manual treatment (OMT) to date (ClinicalTrial.gov identifier, NCT00315120). It is the first such trial to definitively show the efficacy of OMT by reporting statistically significant and clinically relevant outcomes. This presentation will focus on describing patient patterns of clinical response to OMT over 12 weeks, including factors associated with such response and biomedical mechanisms that may help explain OMT effects.

Learning Objectives:
1) Describe methodological aspects and results of the OSTEOPATHIC Trial.
2) Present patient clinical response and relapse profiles over 12 weeks for OMT.
3) Present patient characteristics and biomedical findings that are associated with short-term clinical response to OMT.

References:

OMT to Improve the Quality of Life in Patients

Presentation Summary:
One of the central osteopathic tenets promotes a considered study of our patients’ triune (body-mind-spirit) well-being. While this tenet underlies overall patient Quality-of-Life (QoL), his or her definition of QoL varies depending upon individual values and even on the particular disorder affecting that person. For these reasons, studying QoL issues may
involve measuring pain versus comfort levels; physical versus non-physical perceptions; and functional capacity vs limitations – some being more difficult to study than others. Recently data related indirectly to QoL has been mined from patient satisfaction data as have measures of empathy as previously discussed at this conference.

Despite being a bit more difficult to measure, the evidence-base needed to understand QoL issues is increasing. Fueled by – and powering – both bedside-to-bench and bench-to-bedside observations, osteopathic practitioners are increasingly assessing outcomes (including QoL) by studying the physiology and outcomes associated with the application of one or more of the 5 Models of Osteopathic Health. Considering the biopsychosocial, neurological-autonomic, respiratory-circulatory, metabolic-bioenergetic, or postural-biomechanical models has inspired new hypotheses which can in turn be tested.

This lecture will attempt to look at improvement in QoL from this vantage point. It will offer recent examples of the use of OMT to improve the QoL as related to measures associated with their application to various models and their physiological impact. It will also consider the recent investigation of OMT to modify homeostatic mechanisms postulated to upregulate endothelial nitric oxide synthase (eNOS) or enhance cranial hemodynamics. Based upon a second central osteopathic tenet, applying OMT to enhance homeostatic mechanisms to prevent loss of QoL in certain neurodegenerative disorders would be yet another interesting hypothesis to test.

**Learning Objectives:**

1) Name the five models of approaching osteopathic healthcare and at least one example of each where enhancement (using OMT) could impact a patient’s quality of life (QoL).
2) State the value of integrating objective measures of physical, psychocognitive and physiological parameters to better interpret QoL in the context of “body-unity”, homeostasis and functional capabilities.
3) State physiological connections including enhancement of lymphatic flow, upregulation of endothelial nitric oxide synthase (eNOS), and enhancement of vascular perfusion/drainage when considering interventions such as exercise, OMT to the cranial base, and/or lymphatic pump OMT. Recognize potential links to immediate as well as preventive care related to quality-of-life.