



# Excelling in medical research and education

**Professor Nissar Darmani** chairs the Department of Basic Medical Sciences at the Western University of Health Sciences, a world-leading medical school. Here, he describes interdisciplinary research currently taking place and highlights the University's unique strengths



**Could you first discuss your background and how this led you to your present roles?**

I obtained my PhD in Neuropharmacology from the University of Wales Institute of Science and

Technology (UWIST) in the UK, then left to pursue a postdoctoral fellowship in the US on the neuropsychopharmacology of drug abuse. The literature on marijuana indicated that the main psychoactive component has anti-emetic activity against

vomiting caused by chemotherapeutic agents. The mechanisms of marijuana's anti-vomiting action was then unknown. My laboratory was the first to demonstrate which cannabinoid receptor is responsible for this effect.

Funding from industry and the National Institutes of Health (NIH) has supported my research and ultimately taken me towards further research and administrative duties as Chair of the Department of Basic Medical Sciences (BMS) and, subsequently, Associate Dean for Research at the College of Osteopathic Medicine of the Pacific (COMP) at the Western University of Health Sciences (WesternU).

**As one of the largest graduate schools for health professions in California, what sets WesternU apart from the rest?**

WesternU consists of nine health-related colleges that offer postgraduate professional degrees to educate tomorrow's healthcare professionals, with a compassionate approach to care. We focus on the fundamental mechanisms underlying the onset, progression and dissemination of disease in both animals and humans in an interprofessional education/research setting, in line with our presidential edict, 'Science, caring and humanism'.

**Can you give a brief synopsis of the graduate colleges within WesternU**

### and explain why COMP is of particular importance?

WesternU was originally founded as COMP at Pomona, California in 1977 by current President Dr Philip Pumerantz.

Subsequently, the following graduate colleges were established: Allied Health Professions (established to educate physician assistants and physical therapists); Nursing; Pharmacy; Veterinary Medicine; Dental Medicine; Podiatric Medicine; Optometry; Biomedical Sciences; and COMP-Northwest (an additional site for Osteopathic Medical Education in Lebanon, Oregon).

### What are the key objectives of the BMS Department?

The Department recognises the synergistic relationship between teaching and research. Thus, our faculty educates students to create, integrate and communicate biomedical knowledge and apply this, with a humanistic approach, to patient care. Our goal is to make biomedical discoveries and educate clinicians and scientists as future healthcare leaders.

### How has the Department expanded its research component and facilities in recent years and what have been the implications?

Prior to 2005, COMP was mainly a teaching institution. Since then, the Department of BMS at our Pomona (COMP-Pomona, California) and Lebanon (COMP-Northwest, Oregon) campuses has significantly expanded its faculty and research facilities, by 300 per cent and 642 per cent respectively.

The BMS faculty and core equipment facilities have been supported not only through intramural support from WesternU, but also via extramural funding from the NIH, diverse research foundations, industry and private donations. This has led to substantial increases in our peer-reviewed manuscripts, book and abstract publications, which have increased the reputation of the Department as a key research institution in Southern California.

### Can you discuss the systems-based medical science curriculum adopted by the Department?

Here at COMP, we implement a systems-based curriculum in the first and second years of our medical school teaching. Initially, students participate in a number of foundational basic science courses, detailing anatomy, biochemistry, molecular and cell biology, genetics, histology, embryology, microbiology and immunology. After these disciplines, the systems-based curriculum begins, which is designed around the 10 body systems (cardiovascular, renal, respiratory, endocrine etc.). By delivering the content in a systems-based approach, students are introduced to both the basic science and the clinical aspects

of each of the body systems. Therefore, they learn the healthy state, as well as the disease states associated with these systems.

### How does this generate success?

Past analyses of student learning and advances in medical education have demonstrated that teaching, practising and assessing knowledge and skills in the context of how they will be used in the future leads to better retention and application of the knowledge. By assessing performance on in-class exams, national board exams and with preceptor feedback, we have found our students to be better at retaining the basic and clinical sciences taught in the first and second year of medical school when they transition to the clinical educational portion of the curriculum.

### On a personal level, can you introduce your own research and explain why it is so significant?

In 1998, I introduced and subsequently validated the smallest vomit-competent animal (the least shrew, *Cryptotis parva*) for laboratory use. The cost of a large vomit-capable laboratory-used animal such as the ferret, monkey, dog or cat can approach US \$2,000. Furthermore, such large animals are considered as household pets and so their use for research has been frowned upon by the general public. Although the ferret has been used in the laboratory as the gold standard for vomiting studies since the mid-1970s, and its use has led to the introduction of major classes of anti-emetics, use of the least shrew may surpass the ferret, since the latter species does not consistently vomit in response to the peripheral administration of some specific emetogens.

In the 16 years since introducing the least shrew as a vomiting animal model, major discoveries have been made by my group regarding new emetogens, such as leukotrienes C and D; the additive interaction of serotonin 5-HT<sub>3</sub> receptors with substance P neurokinin 1 (NK1) receptors in causing emesis; and the potential of new classes of antiemetics, such as the L-type calcium channel blockers (nifedipine and amlodipine). Furthermore, this species has been used in my laboratory to identify unknown intracellular signalling pathways of vomiting caused by diverse emetogens.

### How do you hope the Department will continue to evolve in the coming years?

The Department will further expand its research capacity in terms of additional research space, funding, publications and reputation as a major centre for innovative teaching and biomedical research. We plan to open a new research avenue on lifestyle medicine and wellness as a new strategic research pillar both at our Pomona and Oregon campuses.

## Reaching out

The BMS faculty collaborates within their Department, with other researchers at WesternU and with external research institutions worldwide. Here, **Professor Darmani** outlines some of the collaborative, interdisciplinary and translational research programmes underway

**Dr Xiaoning Bi** collaborates with **Dr Gary Lynch** (University of California at Irvine) and **Dr Michel Baudry** (Graduate College of Biomedical Sciences, WesternU) on understanding mechanisms of learning and memory. They have found that the protease calpain plays important roles in long-lasting modulation of synaptic transmission.

**Dr Edward Wagner** collaborates with **Dr Kevin Sinchak** (California State University) to study how gonadal steroid hormones influence nociceptin-mediated regulation of sex behaviour and neurotransmission at proopiomelanocortin (POMC) synapses.

**Dr Mihai Covasa** collaborates with researchers at the AgroParisTech in France, where he also supervises PhD students.

**Dr Raj Kandpal** collaborates with NIH and Temple University researchers to validate the altered transcriptome during diabetic retinopathy and investigate the role of Cadherins and Eph receptors in cancer.

**Dr Li Zhong** maintains his research collaborations on cancer with investigators at Hebei University in China and the City of Hope National Medical Centre and Beckman Institute.

**Dr Robert Pechnick** collaborates with researchers from the University of Texas at Galveston and Cedars-Sinai Medical Center to study, respectively, disorders caused by hallucinogens and mechanisms of neurogenesis.

# Stopping sickness

Professor Nissar Darmani has achieved several world firsts in emesis research and developed innovative new treatments

**IN ADDITION TO** his other roles, Nissar Darmani is Professor of Pharmacology at the College of Osteopathic Medicine of the Pacific (COMP). He is a world-leader in the field of emesis (vomiting) research, having published over 40 papers in this area alone. Emesis is a debilitating condition caused by a range of factors including diseases such as gastritis and drugs such as chemotherapeutics and toxins. Existing anti-emetics can suppress nausea and vomiting, but often do not completely prevent the condition. There is therefore an urgent need for more effective treatments.

One of Darmani's most important contributions to the field was the proposal of a new animal model. Since he introduced the least shrew into the lab, Darmani's lab has characterised the majority of existing emetic neurotransmitter systems, as well as many new ones.

## Timeline of achievements

2001

Although scientists had known of marijuana's ability to suppress vomiting caused by anti-cancer drugs for 30 years, Darmani was the first to identify the underlying mechanism for this: stimulation of the cannabinoid CB1 receptor by the psychoactive component ( $\Delta$ -9-THC) of the plant.

2009

In a seminal review, Darmani challenged a well-established dogma surrounding the neurotransmitter basis of chemotherapy-induced vomiting, instead proposing a more involved, multitransmitter-mediated system.

2010

Darmani identified a new class of endogenous chemicals that can cause profound vomiting – the leukotrienes. He also found these can specifically be blocked by an anti-asthmatic called pranlukast.

2011

The team demonstrated that two antagonists of the major emetic transmitters in chemotherapy-induced emesis prevent vomiting when administered by themselves, and their efficacy is even greater when combined.

2014

The Darmani laboratory introduced the already-used two anti-hypertension drugs as new broad-spectrum anti-vomiting agents.

## Cannabinoid influence

**Dr Edward Wagner** is investigating cannabinoids, a class of around 60 chemical compounds, found in the plant *Cannabis sativa*. He has revealed the gender-specific effects of these compounds



**CANNABINOIDS ACT** ON two types of receptors: CB1, found mainly in the nervous system and reproductive tract, and CB2, found primarily in the cells and tissues of the immune system. A growing body of evidence suggests they

regulate a diverse range of processes, including learning, memory, reproduction, energy balance and stress. Furthermore, many of these functions are sexually differentiated and/or controlled by hormones.

Using cutting-edge equipment housed at the College of Osteopathic Medicine of the Pacific (COMP), Associate Professor of Physiology Edward Wagner assesses cannabinoid-induced changes in food intake; meal size, frequency and duration; core body temperature; and body weight. He also works to understand how these changes correlate with changes in the release of neurotransmitter and cell excitability at anorexigenic proopiomelanocortin (POMC) synapses – an important component of the hypothalamic circuits responsible for regulating energy homeostasis and reproduction. POMC neurons can be activated by positive energy

balance to suppress appetite and accelerate metabolism. Conversely, under conditions of fasting, their activity is inhibited. A further subpopulation of these neurons secretes a neuropeptide which inhibits gonadotropin-releasing hormone (GnRH) neurons, aiding control of the reproductive axis.

### GENDER SENSITIVITY

Through his National Institutes of Health (NIH)-funded research, Wagner has shown that the ability of cannabinoids to elicit CB1 receptor-mediated increases in appetite and decreases in energy expenditure are indeed dependent on gender, with males being more sensitive to the effects. Furthermore, he has resolved these actions to the level of POMC neurons.

Wagner found that in males, activation of the CB1 receptor inhibits POMC neurons by activating a different type of channel than in females. Activation of this channel causes a more complete termination of neuronal firing – explaining why cannabinoids are more effective at inhibiting POMC neuronal activity in males.

### THERAPEUTIC IMPLICATIONS

Wagner's discovery that males are more sensitive to the appetite-modulating properties

of cannabinoids correlates with marked gender differences in their pre- and post-synaptic actions at POMC synapses. These findings advance fundamental pharmacological understanding and have great clinical ramifications. Cannabinoid ligands are used to treat cachexia (wasting syndrome) and control appetite, and the finding that gender and hormonal state affects their efficacy could change how cannabinoids are used to treat a range of conditions, including HIV/AIDS, cancer-related cachexia and obesity.

# Neuronal health and disease

Dr Xiaoning Bi's investigations into changes in connectivity between neurons that underlie learning and memory could lead to new treatments for a range of nervous system disorders



**XIAONING BI, PROFESSOR** of Physiology at the College of Osteopathic Medicine of the Pacific (COMP)-Pomona, has been studying synaptic plasticity for over 20 years. Now, her laboratory is working to understand how neurons develop, mature and function. She also investigates what happens at the end of neuronal life: how neurons die in the ageing process, by genetic defects or by damaging insults. By understanding the mechanisms that mediate these processes, she hopes to develop preventive strategies and treatments for central nervous system (CNS) disorders.

## THE PROTEIN BALANCE

One of Bi's major research projects is focused on the role of protein homeostasis in the modification of neuronal connectivity strength. Protein synthesis and degradation in dendritic spines – small extensions from the dendrites of a neuron – has a crucial role in learning and memory and is regulated by a number of factors. This project specifically focuses on neurotrophic factor- and positive AMPAR modulator-induced dendritic protein synthesis. Bi hopes the results of the investigations will lead to a better understanding of complex neurodevelopmental disorders, such as autism spectrum disorder (ASD).

## UNIFYING FEATURES

Niemann-Pick Type C disease (NPC) is a rare genetic disorder. This life-threatening condition causes severe and progressive symptoms and is currently without an effective treatment. It is caused by mutations in the NCP1 and NPC2 genes, which cause accumulation of cholesterol, and other lipids, in the cellular transport system.

Neurodegeneration is a hallmark of the condition and in most cases the cause of death, but the underlying mechanisms are as yet unknown. However, a growing body of evidence suggests mechanisms are shared with Alzheimer's disease (AD). Indeed, both diseases are characterised by neurofibrillary tangles and inflammation and Bi recently showed the presence of abnormal autophagy and lysosomal function in both diseases. Bi aims to better understand how interruption of cholesterol maintenance generates neuronal death, with a view to developing therapeutic strategies to stimulate neuronal survival.

# Research highlights

*International Innovation* showcases some of the exciting research currently underway within the Department of Basic Medical Sciences

## BIOCHEMISTRY

Professor Raj Kandpal is leading efforts to understand the mechanisms underlying disease processes and identify therapeutic targets. Diabetic retinopathy is a common complication of diabetes. It occurs when high blood sugar levels damage the back of the eye and if left untreated, can cause blindness. To tackle this problem, in partnership with the National Eye Institute, his team is investigating the mRNA, proteomics and mitochondrial bioenergetics profiles of normal and diabetic retina. The researchers hope this will reveal the molecular level impact of diabetes in photoreceptor cells. Using cell biological, molecular biological and genetic approaches, his team has also made advances in breast cancer and human deafness.

Central to Dr Thomas Squier's research goals is the development and application of molecular probes to enable *in situ* measurements of protein function in both self-assembled biomaterials and within living cells. Currently, he is using such molecular probes in high-throughput screens that permit the creation of new self-assembled biomaterials that take advantage of synthetic biology approaches to create low-cost and biocompatible functionalised materials. He envisages these new materials as providing a means to link binding to material responses that will have a range of diagnostic and therapeutic applications.

Dr Katherine Mitsouras' research is focused on the mechanisms underlying papilloma virus (uuPV-1) infection, persistence, progression and development of uuPV-1 induced disease. She is identifying host genetic variants that affect the susceptibility of snow leopards to uuPV-1 infection and to the development of uuPV-1 induced disease, which includes oral papillomatous lesions that can in turn progress to oral squamous cell carcinoma.

## PHARMACOLOGY

Dr Robert Pechnick leads the pharmacology discipline in the Department of BMS and his research is focused on neuropsychopharmacology. He uses *in vivo* and *in vitro* approaches to understand the causes of and to develop new treatments for various forms of mental illnesses including drug addiction.

Dr Sebastien Fuchs is studying the biochemistry and physiology of Angiotensin-Converting Enzyme (ACE) *in vivo* in genetically modified animals. Beside blood pressure, ACE is involved in many other function including peptide presentation (immunology), extracellular matrix control (end-organ damages), male fertility and Alzheimer's disease (AD).

Dr Glen Kisby's research involves DNA damage, DNA repair, neurodegenerative diseases (AD, Parkinson's, amyotrophic lateral sclerosis), and neurodevelopmental disorders (eg. schizophrenia).

Dr John Mata is involved with natural product research involving role of dietary constituents on cancer prevention and identification of active compounds from natural products.

## MICROBIOLOGY/IMMUNOLOGY

The bacterium that causes tuberculosis, *Mycobacterium tuberculosis* (MTB), can sense environmental stresses and resist them in order to survive in the body. Creating an acidic environment is one way the body controls bacterial infection. Bacteria can respond to this defence by altering the activity of many of their genes. Dr Beatrice Saviola's group has identified a gene, lipF, that is turned on in response to acid. Saviola is further interested in studying MTB virulence and microbial pathogenesis. Moreover, Dr Vishwanath Venketaraman's laboratory is actively involved in understanding the host immune response against MTB infection and is characterising the beneficial effects of glutathione in augmenting the immune responses against MTB infection in individuals with HIV infection and Type 2 diabetes.

## PHYSIOLOGY

The early detection of cancer is paramount, and Dr Li Zhong is using autoantibody profiles as biomarkers to achieve this. His team has already developed a novel screening technology for the early detection of lung cancer. Using five combined biomarkers, they achieved a sensitivity and specificity of over 90 per cent for stage I non-small cell lung cancer detection. Their test is much more sensitive and specific than biomarkers traditionally used for lung cancer.

Obesity and diabetes are major causes of morbidity and mortality worldwide. Using a combination of molecular, neuroanatomical, behavioral, biochemical and physiological approaches, Dr Mihai Covasa and his team are investigating satiation signals that control eating and regulation of body weight including the role of gut microbiota in intestinal chemosensation.

# Tomorrow's healthcare leaders

The **College of Osteopathic Medicine of the Pacific** supports the Western University of Health Sciences in its drive to provide caring and well-educated physicians in all medical specialities. In an environment that nurtures respect for humanity, students are provided with classroom and clinical experiences that emphasise the osteopathic philosophy

**THE WESTERN UNIVERSITY** of Health Sciences (WesternU) is one of the largest graduate schools for health professions in California. It was established in 1977 as a response to a shortage of primary care physicians in the western US. Originally formed as the College of Osteopathic Medicine of the Pacific (COMP), today it comprises nine graduate colleges.

In the US currently, a college graduate can take two paths in order to become a medical doctor; the allopathic medical schools (MD programmes) or the osteopathic medical schools (DO programmes). Even though both medical graduate programmes teach identical basic science and clinical curricula, the

osteopathic students receive further specialised training in bone, joint and tissue manipulation. Furthermore, osteopathy takes a more holistic view of health and disease, treating not only the sickness but the entire patient.

## THE DEPARTMENT

The Department of Basic Medical Sciences (BMS) at COMP, chaired by Professor Nissar Darmani, comprises four key disciplines: biochemistry, microbiology/immunology, pharmacology, and physiology. Each is taught by experts in their field, as Darmani explains: "Our faculty are highly qualified individuals with either a PhD, or dual DO/PhD or MD/PhD degrees. We give preference to those faculty who are outstanding educators with a record of excellence in teaching, significant scholarly activity and strong potential for independent grant-supported research".

One of the Department's major responsibilities is providing preclinical biomedical education to first and second-year medical students at WesternU. It has a robust, systems-based medical science curriculum that integrates both basic and clinical sciences. It provides a strong scientific foundation for students and introduces them to the clinical world early on through interactions with physicians.

Indeed, supporting the career development of its students is an important aspect of the Department's work. Junior faculty members are mentored by senior faculty, helping them to become the next generation of successful and well-funded scientists. "Many BMS faculty are funded to train postdoctoral fellows, graduate research students and medical students in research methodology to solve challenging biological problems. This helps to support the career development of the next generation of scientists, physician investigators and educators," Darmani comments.

## RESEARCH MISSION

The Department aims to make significant contributions to understanding the mechanisms underlying the onset, progression and spread of disease. The faculty of internationally renowned investigators shares ideas by identifying scientific synergy, using cutting-edge concepts and experimental approaches.

A large number of faculty members are engaged in collaborative, interdisciplinary research programmes, focused on one or more of the three longstanding research clusters at WesternU. The integrative neurobiology cluster has diverse research foci, ranging from the triggers of neurodegenerative disease, to how the central nervous system controls energy balance. The immunology and infectious diseases cluster studies pathogens and how the body defends itself against them; while the molecular and metabolic disease cluster uses cellular, biochemical and molecular approaches to study cancer and identify biomarkers for detection.

## FUTURE PERSPECTIVES

Looking ahead, the Department's research will focus on investigator-initiated grants, the funding for which will depend on collaborative, multiple-principal investigator (PI) proposals. This work will include studies on neurodegenerative disease, cancer and substance abuse. The BMS Department's current involvement in a number of joint research projects puts it in a good position to initiate such projects.

The high quality training and world-leading research of COMP makes it well-placed to produce informed, compassionate physicians, who will become highly skilled future healthcare practitioners and innovators – not only delivering effective healthcare, but leading the field of medicine.

## INTELLIGENCE

DEPARTMENT OF BASIC MEDICAL SCIENCES (BMS)

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