

FUNCTIONAL MEDICINE UPDATE

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Dr. Bland begins this issue with his monthly interview.

Researcher of the Month

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Dr. Jan Marino (Nino) Ramirez was educated in Germany and spent many years working at the University of Chicago in the Department of Organismal Biology and Anatomy. In 2008, Dr. Ramirez relocated to Seattle to work in the Department of Neurological Surgery at the University of Washington School of Medicine and also to become Director of the Center for Integrative Brain Research at Seattle Children's Research Institute.

At Seattle Children's Research Institute, Dr. Ramirez and his research colleagues focus on understanding the neuronal basis of a variety of brain functions to find novel ways to treat neurological disorders in children, including epilepsy, Rett syndrome, brain tumors, and sudden infant death syndrome (SIDS). They are particularly interested in understanding developmental alterations of cellular properties involved in the response of the respiratory network to hypoxia. This response elicits a cascade of molecular events that are regulated by endogenously released neuromodulators.

Dr. Bland and Dr. Ramirez met by chance on a flight between Chicago and Seattle. Dr. Bland has had the opportunity to personally visit Dr. Ramirez's laboratory, and he describes the groundbreaking research he observed there. From his research, Dr. Ramirez expects to gain new insights into principal mechanisms of respiratory rhythm generation and the hypoxic response in mammals. Due to the importance of the respiratory system for the survival of any mammal, progress in this field will not only have important scientific significance, but also clinical implications.

Epigenetic Side Effects of Common Pharmaceuticals

Dr. Bland has been discussing the concept of epigenetics in *Functional Medicine Update* for some time. The term refers to DNA and chromatin modifications that persist from one cell division to the next, despite a lack of change in the underlying DNA sequence. In his interview with Dr. Ramirez, the subject of a resistance to medications that develops over time was discussed. Dr. Bland refers to a 2009 article on this subject by Dr. Antonei

Csoka and Dr. Moshe Szyf (McGill University) that was published in *Medical Hypotheses*. The authors write: “The epigenome is dynamic and responsive to environmental signals not only during development, but also throughout life; and it is becoming increasingly apparent that chemicals can cause changes in gene expression that persist long after exposure has ceased. Here we present the hypothesis that commonly-used pharmaceutical drugs can cause such persistent epigenetic changes.” They continue, “If this hypothesis is correct the consequences for modern medicine are profound, since it would imply that our current understanding of pharmacology is an oversimplification. We propose that epigenetic side-effects of pharmaceuticals may be involved in the etiology of heart disease, cancer, neurological and cognitive disorders, obesity, diabetes, infertility, and sexual dysfunction. It is suggested that a systems biology approach employing microarray analyses of gene expression and methylation patterns can lead to a better understanding of long-term side-effects of drugs, and that in the future, epigenetic assays should be incorporated into the safety assessment of all pharmaceutical drugs.”
REF #1

Early Screening Tests for Dementia and Alzheimer’s Disease: Genetic Tests Don’t Tell the Whole Story

According to an editorial published in the *British Medical Journal (BMJ)* in 2009, dementia has an expected prevalence of 13 in 1000 people aged 65-69 and 122 in 1000 in those over 80, but only about half of those affected are diagnosed. No definitive test for early diagnosis exists, but in the United Kingdom, the most commonly performed test is the mini-mental state examination, which is used in research and clinical settings.

This same issue of *BMJ* features an article titled “Self Administered Cognitive Screening Test (TYM) for Detection of Alzheimer’s Disease: Cross Sectional Study.” Developed by researchers from the Department of Neurology at Addenbrooke’s Hospital, Cambridge, the TYM (“test your memory”) test meets three requirements they identified as critical for widespread use: minimal operator time to administer, tests a reasonable range of cognitive functions, and is sensitive to mild Alzheimer’s disease. To evaluate the test, the researchers designed a cross-sectional study involving 540 control participants (aged 18-95) and 139 patients attending a memory clinic with dementia/mild cognitive impairment. After evaluating the results, they concluded that the TYM can be completed quickly and accurately by normal controls, and is a powerful and valid screening test for Alzheimer’s disease. A copy of the test accompanies the article.
REF #2-3

Homocysteine Metabolism Linked with Tau and Amyloid Protein Regulation

Tau hyperphosphorylation is a central event in the development of Alzheimer’s disease, as is the accumulation of amyloid- β peptides derived from the amyloid precursor protein (APP). It has been reported that epidemiological evidence indicates that elevated plasma homocysteine is an independent risk factor for Alzheimer’s disease. Homocysteine is a key intermediate in the methyl cycle and elevated plasma homocysteine results in a global decrease in cellular methylation. Research has been published proposing that the protein phosphatase 2A (PP2A) methylation system is the link relating elevated plasma homocysteine to Alzheimer’s disease. REF #4-5

Insulin Dysfunction, Inflammatory Signaling, and Oxidative Chemistry

In the January 2010 issue of *Functional Medicine Update*, Dr. Bland profiled the work of Dr. Suzanne Craft, a researcher who focuses on the connections between insulin and Alzheimer's disease and cognitive impairment. This month Dr. Bland further discusses a 2007 article that was published in the *Journal of Neuroscience* titled "Insulin Dysfunction Induces *In Vivo* Tau Hyperphosphorylation through Distinct Mechanisms." Data collected for this article indicate that insulin dysfunction induced abnormal tau hyperphosphorylation through two distinct mechanisms: one was consequent to hypothermia; the other was temperature-independent, inherent to insulin depletion, and probably caused by inhibition of phosphatase activity. REF #6

Dr. Bland next discusses an animal study published in *The FASEB Journal* in 2009. In this study, a group of researchers from the University of Oxford, UK, tested the hypothesis that short-term ingestion of a high-fat diet (55% kcal from fat) would impair exercise capacity and cognitive function in rats, compared with a control chow diet (7.5% kcal from fat) via mitochondrial uncoupling and energy deprivation. They found that rats ran 35% less far on a treadmill and showed cognitive impairment in a maze test with 9 days of high-fat feeding, with respiratory uncoupling in skeletal muscle mitochondria, associated with increased uncoupling protein (UCP3) levels. The results suggest that high-fat feeding, even over short periods of time, alters skeletal muscle UCP3 expression, affecting energy production and physical performance. REF # 7

Diet and Cognitive Function in Humans

A group of researchers from Columbia University has published a number of articles on the topic of the Mediterranean diet and risk of cognitive impairment, dementia, and Alzheimer's disease. After collecting data from large-scale, community-based studies, this group has consistently concluded that adherence to a Mediterranean diet is associated with longer survival, reduced risk of cardiovascular or cancer mortality, and reduced risk of neurodegenerative disease. In addition, a Mediterranean diet might also have protective effects against cognitive decline in older individuals, because it combines several foods and nutrients potentially protective against cognitive dysfunction or dementia, such as fish, monounsaturated fatty acids, vitamins B12 and folate, antioxidants (vitamin E, carotenoids, flavonoids), and moderate amounts of alcohol. REF #8-10

A Short-Term Overeating Study in Human Subjects

Numerous prospective studies have reported on weight gain, insulin resistance, and insulin signaling in experimental animals, but not in humans. In 2009, a group of researchers from Sweden examined insulin signaling in adipocytes from lean volunteers, before and at the end of a 4-week period of consuming a fast-food, high-calorie diet that led to weight gain. Dr. Bland discusses the findings from this study. REF #11

Nutritional Programming and Metabolic Syndrome

Dr. Bland discusses a 2009 review article published in *Nature Reviews Endocrinology* that addresses the concept of nutritional programming. The authors write, "As will be

outlined in this Review, the metabolic syndrome can be considered a developmental process that can be accelerated by changes in the nutritional environment in early life. The metabolic syndrome considered in this light could provide a potential explanation for the fact that not all individuals with obesity are insulin resistant or at high risk of developing cardiovascular disease.” REF #12

Telomere Length and Vascular Dementia

Human telomeres shorten with each cell division *in vitro* and with donor age *in vivo*. A number of studies have been published showing results supporting the hypotheses that telomere attrition may be related to diseases of aging through mechanisms involving oxidative stress, inflammation, and progression to cardiovascular disease. Dr. Bland addresses this subject as part of his ongoing discussion of altered insulin signaling and risk to Alzheimer’s disease. REF #13-15

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