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A New Year and New Opportunities for Ideas, Research, and Therapies

Is network pharmacology the next paradigm in drug discovery? This is the subject of an article by Dr. Andrew Hopkins published in *Nature Chemical Biology* that Dr. Bland discusses. Dr. Hopkins writes: "Many effective drugs act via modulation of multiple proteins rather than single targets. Advances in systems biology are revealing a phenotypic robustness and a network structure that strongly suggests that exquisitely selective compounds, compared with multi-target drugs, may exhibit lower than desired clinical efficacy. This new appreciation of the role of polypharmacy has significant implications for tackling the two major sources of attrition in drug development—efficacy and toxicity." Dr. Bland also explored this subject in a 2008 guest editorial he wrote for *Alternative Therapies in Health and Medicine* called "The Future of Nutritional Pharmacology." REF 1-2

Kinases have different signal transduction roles in different cellular contexts. A group of researchers from Rice University surveyed approaches to control the therapeutic impact of cross-reactive kinase inhibitors and published their work in *Trends in Biotechnology* under the title "Turning Promiscuous Kinase Inhibitors into Safer Drugs." This team advocates for the application of a novel selectivity filter and evaluates the possibility of turning multi-target kinase inhibitors into clinical opportunities through judicious chemical modifications. REF #3

What role will botanical drugs play in network pharmacology? Dr. Bland discusses an article titled "New Therapies from Old Medicines" that was published in *Nature Biotechnology*. The authors—from the Division of Dermatological and Dental Products at the Food and Drug Administration Center for Drug Evaluation and Research—state: "We hope the introduction of the first botanical new drug in the modern era of FDA regulation will stimulate more clinical testing of potentially useful botanical products and eventually lead to new therapies derived from complex natural mixtures that will satisfy unmet medical needs." REF #4

Introductory Remarks about Alzheimer's Disease and Current Research

As a prelude to this month's interview with Dr. Suzanne Craft, a noted researcher focusing on Alzheimer's disease and cognitive impairment, Dr. Bland discusses a series of articles to provide context. A group of researchers from Columbia University has published studies on the Mediterranean Diet and its association with both Alzheimer's disease (AD) and mild cognitive impairment (MCI). These were both community-based studies involving a large number of participants. Based on the data collected and the analyses performed, the researchers concluded that higher adherence to the Mediterranean diet is associated with a trend for reduced risk of developing mild

cognitive impairment and with reduced risk of MCI conversion to Alzheimer's disease. REF #5-6

As the interview this month will focus largely on research about the role of insulin in the development of Alzheimer's disease, Dr. Bland discusses a 2009 article published in the *Journal of Alzheimer's Disease* titled "The Alzheimer's Disease-Diabetes Angle: Inevitable Fate of Aging or Metabolic Imbalance Limiting Successful Aging." The focus of this brief article is on observations made of mammalian hibernators such as ground squirrels and hamsters. The authors, who are with the University of Heidelberg in Germany, indicate that these animals demonstrate comparable and annual recurrent periods of obesity with concomitant insulin resistance and key features of AD such as tau phosphorylation. They state: "These pathologies, however, are reversed by a time-dependent metabolic shift between carbohydrate- and fat-based metabolism, a delicate balance of kinases and phosphatases and changes in gene expression. While massive fat depots serve as the main source of metabolic fuel throughout the winter, phosphorylation of tau during obligate hibernation seems to be a reversible consequence of hypothermia. These changes gradually decrease over a period of months until the animals emerge from hibernation each spring. Thus, fat storage and tau phosphorylation occur predictably on an annual basis, but subsequent fasting depletes fat during the course of winter and ensures that each spring the obese hibernator emerges lean." REF #7

Also as part of the discussion, Dr. Bland discusses two articles that provide background on the role of foods and dietary phytochemicals in insulin signaling. One article was authored by Dr. Bland and Dr. Deanna Minich and is titled "Dietary Management of the Metabolic Syndrome Beyond Macronutrients," and the other (authored by a group of Chinese researchers and just recently published in 2009) focuses on the reported hypoglycemic and insulin-sensitizing activities of berberine, a naturally occurring alkaloid phytochemical from the Chinese botanical *Coptis chinesis*. REF #8-9

Finally, an article titled "Insulin Dysfunction Induces *In Vivo* Tau Hyperphosphorylation through Distinct Mechanisms" is discussed. Tau phosphorylation is thought to be a critical event in the pathogenesis of AD. Hyperphosphorylated tau is the major component of paired helical filaments in neurofibrillary tangles found in AD brains. This study (using an animal model) investigates the possibility that insulin dysfunction might promote tau pathology. REF #10

Researcher of the Month

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Dr. Suzanne Craft received her PhD in Neuropsychology at the University of Texas at Austin, and then completed fellowships at Boston University and Harvard Medical School specializing in Behavioral Neuroscience. She is currently Professor of Psychiatry and Behavioral Sciences at the University of Washington School of Medicine and Associate Director of the Geriatric Research, Education, and Clinical Center of the VA Puget Sound. Her research team has investigated the relationship between insulin resistance and the development of cognitive impairment and dementia in older adults. The importance of this topic is underscored by the pandemic of conditions associated with insulin resistance, which include obesity, diabetes, impaired glucose tolerance, hypertension, and cardiovascular disease.

Dr. Craft's team has identified several mechanisms through which insulin resistance may increase the risk of dementia, such as increased inflammation in the brain, reduced brain glucose metabolism, and abnormal amyloid accumulation. Building on mechanistic studies, her work has now expanded to include therapeutic strategies for reducing the risk of dementia and ameliorating cognitive impairment. Dr Craft's research team is now conducting clinical trials of insulin-sensitizing compounds, intranasal insulin, exercise, and dietary intervention. Thus, her work is poised to answer critical questions about the effects of prevention and treatment of insulin resistance on the development of Alzheimer's disease and other dementing conditions.

Dr. Craft is the recipient of a prestigious MERIT award for excellence in aging research from the National Institutes of Health. Her research was recently featured in HBO's award-winning documentary "The Alzheimer's Project." REF #11-19

References

1. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol*. 2008;4(11):682-690. Review.
2. Bland J. The future of nutritional pharmacology. *Altern Ther Health Med*. 2008;14(5):12-14.
3. Zhang X, Crespo A, Fernández A. Turning promiscuous kinase inhibitors into safer drugs. *Trends Biotechnol*. 2008;26(6):295-301.
4. Chen ST, Dou J, Temple R, Agarwal R, Wu KM, Walker S. New therapies from old medicines. *Nat Biotechnol*. 2008;26(10):1077-1083.
5. Scarmeas N, Stern Y, Tan MX, Mayeux R, Luchsinger JA. Mediterranean Diet and Risk for Alzheimer's Disease. *Ann Neurol*. 2006;59:912-921.
6. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. *Arch Neurol*. 2009;66(2):216-225.
7. Bierhaus A, Nawroth PP. The Alzheimer's disease/diabetes angle: inevitable fate of aging or metabolic imbalance limiting successful aging. *J Alzheimers Dis*. 2009;16(4):673-675.
8. Minich DM, Bland JS. Dietary management of the metabolic syndrome beyond macronutrients. *Nutr Rev*. 66(8):429-444.
9. Kong WJ, Zhang H, Song DQ, Xue R, Zhao W, et al. Berberine reduces insulin resistance through protein kinase C-dependent up-regulation if insulin receptor expression. *Metabolism*. 2009;58(1):109-119.
10. Planel E, Tatebayashi Y, Miyasaka T, Liu L, Wang L, et al. Insulin dysfunction induces in vivo tau hyperphosphorylation through distinct mechanisms. *J Neurosci*. 2007;27(50):13635-13648.

11. Hirsch IB, Boyle PJ, Craft S, Cryer PE. Higher glycemic thresholds for symptoms during beta-adrenergic blockade in IDDM. *Diabetes*. 1991;40(9):1177-1186.
12. Craft S, Newcomer J, Kanne S, Dagogo-Jack S, Cryer P, et al. Memory improvement following induced hyperinsulinemia in Alzheimer's disease. *Neurobiol Aging*. 1996;17(1):123-130.
13. Watson GS, Peskind ER, Asthana S, Purganan K, Wait C, et al. Insulin increases CSF Aβ42 levels in normal older adults. *Neurology*. 2003; 60(12):1899-1903.
14. Craft S, Asthana S, Cook DG, Baker LD, Cherrier M, et al. Insulin dose-response effects on memory and plasma amyloid precursor protein in Alzheimer's disease: interactions with apolipoprotein E genotype. *Psychoneuroendocrinology*. 2003;28(6):809-822.
15. Watson GS, Craft S. The Role of Insulin Resistance in the Pathogenesis in the Pathogenesis of Alzheimer's Disease: Implications for Treatment." *CNS Drugs*. 2003;17(1):27-45. Review.
16. Fishel MA, Stennis Watson G, Montine TJ, Wang Q, Green PA, et al. Hyperinsulinemia provokes synchronous increases in central inflammation and beta-amyloid in normal adults. *Arch Neurol*. 2005;62(10):1539-1544.
17. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. *Curr Alzheimer Res*. 2007;4(2):147-152. Review.
18. Stennis Watson G, Craft S. Insulin resistance, inflammation, and cognition in Alzheimer's disease: lessons for multiple sclerosis. *J Neurol Sci*. 2006;245(1-2):21-33.
19. Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. *Arch Neurol*. 2009;66(3):300-305.

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