

support for families and alternative jobs for prostitutes, along with conventional treatment programs. This comprehensive approach has lessons for contemporary HIV/AIDS prevention and control strategies nationally and globally.

#### PAST HIV/AIDS CONTROL AND PREVENTION STRATEGIES AND FUTURE CHALLENGES

*Myron Cohen, University of North Carolina, Chapel Hill*

This presentation will provide a global overview of trends and key strategies employed in HIV/AIDS prevention and control efforts. It will evaluate new strategies, including the testing and immediate treatment modeling by WHO scientists, analyze the challenges facing global efforts and suggest practical options for improving prevention and control strategies, with particular reference to developing countries.

#### THE USE OF ANTIRETROVIRALS (ARVS) FOR PREVENTION OF HIV AND TB: TIME FOR ACTION

*Ying-Ru Lo, World Health Organization, Geneva, Switzerland*

There is considerable scientific evidence supporting the use of antiretroviral drugs (ARV) for prevention of human immunodeficiency virus (HIV) and tuberculosis (TB). Recent results from the HPTN052 trial have clearly demonstrated the effectiveness of combination antiretroviral therapy (cART) given to the HIV-infected partner as prevention of HIV in serodiscordant couples. This confirms prior evidence from observational studies that earlier ART has a prevention benefit for HIV at both the individual and population level and as secondary benefit for TB prevention. Four trials (CAPRISA 004, iPrEx, Partners PrEP and TDF2) have shown the effectiveness of ARV pre-exposure prophylaxis (topical and oral) to prevent HIV acquisition. We now know that oral TDF and TDF/FTC work for both, women and men in serodiscordant couples and in men who have sex with men. Topical PrEP will go through regulatory approval, manufacturing and should also undergo WHO prequalification. The complex nature of the HIV and TB prevention response, potential individual and population level benefits, resource constraints, remaining questions about cost-benefits and feasibility require major investments. We need to address enormous challenges when translating research into implementation. It will require a well-organized and coordinated process for development of policy guidance on the strategic use of antiretrovirals for prevention and a sustained commitment of communities, policy makers, donors and drug manufacturers. Available evidence, ongoing and planned research projects and programmatic use of ARVs to prevent HIV and TB will inform WHO policies regarding the delivery of ARVs as part of combination prevention strategies.

#### HISTORICAL FOUNDATIONS AND FUTURE DIRECTIONS OF CHINA'S HIV/AIDS STRATEGY

*Yiming Shao, National Center for AIDS/STD Control and Prevention, Beijing, China; Jianhong Wu, York University, Toronto, ON, Canada*

Though much progress made in past 30 years, with over 2.5 million infections and close to 2 million deaths each year, AIDS remains a big challenge. There is a striking overlap between the global map of human development index and HIV prevalence, which indicates that just tackling the epidemic's surface with medical approaches without vigorously addressing its social and economical roots will not stop AIDS. In 1950s, China successfully conducted STDs eradication campaign with a dual strategy of combining medical approaches, such as diagnosing and treating all patients free of charge, with strong social interventions, such as closing brothels, providing alternative jobs and community support for all prostitutes. In about 10 years, China had virtually eliminated STDs in the country with syphilis dropping from over 10% to 0.004% in dermatology patients. This comprehensive approach has lessons for contemporary HIV/AIDS prevention and control strategies nationally and globally. Liangshan is a remote mountain ethnic residents region with the highest HIV prevalence in China. To better control the epidemic, we propose a new model of rural economical enterprise (REE), where jobs in agriculture and manufacture will be provided through government subsidization and combine with centralizing healthcare at working place. We then build a mathematical model with basic reproduction number  $R_0$  matched to the local epidemiologic parameters and simulated it to representing the past epidemic. The mode is then used to test various control strategies and predict their results. In REE model, economic reasons driving migration and contributing to poor compliance to antiviral treatment and drug abuse interventions are removed. The efficacy of existing care and interventions is greatly improved, while program running costs are significantly reduced. The  $R_0$  under current

control strategy in Liangshan is likely between 2 and 3, indicating a sustained and growing epidemic. Under the REE model however, the number of new infections declined dramatically within 5 years and falling to baseline after 10 years. In REE model, no major difference is seen between immediate therapy or treatment at CD4 count 350. In a survey conducted in 3 counties of Liangshan, 73.9% to 84.7% of the 1000 HIV positive and negative drug users are willing to work in REE and participate the prevention care program. With support from local and central government, the REE model is moving into pilot trial.

#### HIV/AIDS SITUATION AND PREVENTION IN THAILAND

*Punnee Pitisuttithum, Mahidol University, Bangkok, Thailand*

The presentation will focus on the evolution of Thailand's HIV/AIDS control strategy, especially the 100% condom campaign. Dr. Punnee will analyze the political, social and cultural factors that have made the campaign such a success and discuss whether the Thai experience can be applied to other nations.

#### THE EVOLUTION AND RESULTS OF UGANDA'S HIV/AIDS POLICIES

*Nelson Sewankambo, Makerere University, Kampala, Uganda*

East African countries have implemented different HIV/AIDS control and prevention programs, ranging from limited to comprehensive interventions. The rationale, debates and results from different approaches will be examined with primary reference to Uganda.

#### INFORMING PUBLIC HEALTH POLICIES

*John Lavis, McMaster University, Hamilton, ON, Canada*

There is a vast literature on HIV/AIDS prevention and control strategies but greater efforts are required to translate this research into policy. In particular, there is a need to understand how public health agencies learn and how researchers interact with policymakers. This presentation will share insights from a cross-national study on health policy formation in Africa to illuminate what steps need to be considered for shaping the future public health agenda.

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#### Autism: Genetic, Epigenetic, and Environmental Factors Influencing Neural Networks

*Organized by: Isaac Pessah, University of California, Davis; Cindy Lawler, National Institute of Environmental Health Sciences, Research Triangle Park, NC*

Autism is a heterogeneous set of developmental disorders with complex etiologies. The goal of the symposium is to present a multidisciplinary perspective of how genetic, epigenetic, and environmental factors can interact to promote autism risk. The speakers will critically evaluate the evidence from human and animal studies that gene x environment interactions influence autism susceptibility, severity, and treatment outcomes. Genetic risk factors for autism will be reviewed. New evidence that autism may be associated with an increased copy number burden especially in regions of genomic instability, will be presented and discussed in relationship to environmental causes. How epigenetic mechanisms alter expression of genes relevant to autism will be reviewed in light of environmental chemicals that alter global and gene-specific DNA methylation patterns. Recent progress in understanding how impairments in neural connectivity contribute to autism will be reviewed. The role of methionine (MET) polymorphisms in autism risk and how polyaromatic hydrocarbons found in air pollution differentially influence individuals with the cMET autism risk allele will be presented. Evidence that low-level chemical exposures influence molecular and cellular processes that alter the balance of excitation and inhibition and neuronal connectivity relevant to the development of autism will be evaluated.

#### BEYOND LINKAGE ANALYSIS AND GENOME-WIDE ASSOCIATION STUDY

*Scott Selleck, Pennsylvania State University, University Park*

Recent work has demonstrated that copy number variation constitutes a substantial proportion of genetic differences among human beings, and provides an important contributor to disease susceptibility. Copy number variants (CNVs) are not randomly distributed throughout the genome but cluster in regions where sequence architecture contributes to genomic instability. One class of sequences affecting genomic instability is segmental duplications (SDs), or low copy repeats (LCRs). These sequence elements are large (10 kb),

highly related to one another (>90% identity), and found in modest numbers of copies compared to smaller repeats such as LINES and SINES. LCRs can promote instability in part via errors in homologous recombination, creating duplications, deletions, inversions and translocations. We have been interested in understanding the contribution of CNVs to autism spectrum disorder (ASD), particularly in LCR-rich intervals. We report on two studies, one focused on small variants detected by a finely-tiled array that examined 5 LCR-rich genomic intervals at high resolution, and a second that examined larger CNVs (>50 Kb) found among approximately 130 SD-rich intervals. The first study employed an array designed to detect CNVs as small as 1000 bp both within and surrounding the LCR-rich segments. We detected significant increases in the total length of duplicated sequences in children with autism compared to typically developing controls matched for age and sex. Validation of the copy number burden using Illumina sequence read-representation will also be presented. The second study included 274 autism cases and 245 typically developing individuals assembled through the CHARGE study, a population-based case control study. We have determined the prevalence of a number of CNVs previously implicated in autism or other behavioral disorders in this ethnically diverse cohort, as well as identified a number of novel variants not previously described nor found in large sets of control subjects. These findings suggest that discovery of the many genetic contributors to autism spectrum disorder remains incomplete. At both a fine scale (CNVs as small as 1 Kb) and a large scale (CNVs >50 Kb) our data indicate ASD is associated with elevated copy number burden in LCR-rich regions. The CHARGE cohort includes detailed clinical and environmental data allowing us to examine the range of phenotypes associated with a given disease-contributing CNV, as well as explore gene x environment interactions.

## EPIGENETICS OF AUTISM: THE INTERFACE BETWEEN GENETIC AND ENVIRONMENTAL RISKS

Janine LaSalle, University of California, Davis

### Epigenetics of Autism: The Interface Between Genetic and Environmental Risks

Rima Woods<sup>a, b, c</sup>, Roxanne O. Vallero<sup>a, b, c</sup>, Mari Golub<sup>d</sup>, Joanne K Suarez<sup>a, b, c</sup>, Tram Anh Ta<sup>e, f</sup>, Dag H. Yasui<sup>a, b, c</sup>, Lai-Har Chih, Paul J. Kostyniak, Isaac N. Peshah, e, g, Robert F. Berman<sup>c, e, f</sup>, Janine M. LaSalle<sup>a, b, c, e</sup> <sup>a</sup>Medical Microbiology & Immunology, <sup>b</sup>Genome Center, <sup>c</sup>M.I.N.D. Institute, <sup>d</sup>Environmental Toxicology, <sup>e</sup>Center for Children's Environmental Health, <sup>f</sup>Neurological Surgery, <sup>g</sup>Molecular Biosciences, UC Davis, CA; <sup>h</sup>Toxicology Research Center, University at Buffalo, NY

Epigenetic mechanisms, such as DNA methylation, are responsive to environmental influences and can have long-lasting consequences. Autism spectrum disorders (ASD) have complex neurodevelopmental origins whereby both genetic and environmental factors are implicated. Rett syndrome is an X-linked ASD caused by mutations in the epigenetic factor methyl-CpG binding protein 2 (*MECP2*). The widespread use of persistent organic polybrominated diphenyl ethers (PBDEs) as commercial flame-retardants has raised concern about potential long-lived effects on human health. This study was designed to reduce the complexity in a controlled experimental system by examining the effects of perinatal exposure to PBDE in a genetically and epigenetically susceptible mouse model. A *Mecp2* truncation mutant mouse (*Mecp2*<sup>308</sup>) with social behavioral defects was used to explore the long-lasting effects of PBDE exposure in a genetically and epigenetically susceptible model. *Mecp2*<sup>308/+</sup> dams were perinatally exposed daily to PBDE and bred to wild-type C57BL/6J males, and the offspring of each sex and genotype were examined for developmental, behavioral, and epigenetic outcomes. Perinatal PBDE exposure negatively impacted fertility of *Mecp2*<sup>308/+</sup> dams and preweaning weights of females. Global hypomethylation of adult brain DNA was observed specifically in female offspring perinatally exposed to PBDE and coincided with reduced sociability in a genotype-independent manner. A reversing interaction of *Mecp2* genotype on PBDE exposure was observed in a short-term memory test of social novelty that corresponded to increased *Dnmt3a* levels specifically in BDE-47 exposed *Mecp2*<sup>308/+</sup> offspring. In contrast, spatial learning and long-term memory in the Morris water maze was impaired by PBDE exposure in female *Mecp2*<sup>308/+</sup> offspring. These results demonstrate that a genetic and environmental interaction relevant to social and cognitive behaviors shows sexual dimorphism, epigenetic dysregulation, compensatory molecular mechanisms, and specific behavioral deficits.

## NEURAL NETWORKS IN AUTISM: LINKING MET POLYMORPHISMS AND POLYAROMATIC HYDROCARBONS

Pat Levitt, University of Southern California, Los Angeles

A significant challenge in improving the clinical manifestations of autism spectrum disorder (ASD) is placing descriptive findings of genetic and environmental risk in a functional context. This can be accomplished by determining the underlying cellular and molecular disruptions that lead to ASD cognitive and behavioral phenotypes, and the non-genetic environmental factors that contribute to spectrum cause and clinical heterogeneity. This presentation will illustrate the power of a translational research strategy to generate an emerging picture that includes improved definition of biological mechanisms and emergent concepts of clinical heterogeneity. Our human genetic studies have led to the discovery of a novel ASD risk gene, the *MET* receptor tyrosine kinase. The only known growth factor ligand for *MET* is hepatocyte growth factor (HGF). *MET* promoter variants, ASD-relevant transcriptional regulators, including *FOXP2*, and specific pollutants, such as benzo-a-pyrene, all reduce the levels of *MET* gene expression. Developmental regulation of expression is functionally essential, as *MET* expression is reduced in postmortem brain samples from subjects with ASD compared to control samples. How does *MET* participate in increasing ASD risk? Our studies on the biological significance of *MET* in the brain have revealed a number of important functions that relate to ASD risk, including 1) a gene for which expression is among the most highly restricted in the primate cerebral cortex, particularly in ASD-relevant circuits; 2) regulation of axonal and dendritic growth, and spine and synapse maturation; 3) a dominant effect of a graded decrease in *Met* expression that causes dramatic changes in local excitatory connectivity in the neocortex; 4) a dominant effect of the *MET* ASD risk variant that correlates with disrupted circuitry that functions to process emotional faces in the human; 5) enrichment of the *MET* risk variant in children with ASD and co-occurring gastrointestinal disorders, reflecting important pleiotropic functions of *MET* outside of the brain. These data provide a significant foundation for future studies that will lead to a better understanding of pathogenic mechanisms and clinical heterogeneity of ASD.

## TIPPING THE BALANCE OF NEURAL NETWORKS: ENVIRONMENTAL CHEMICALS AND AUTISM RISK

Isaac Pessah, University of California, Davis

Research into the pathophysiology and genetics of autism may inform the identification of environmental susceptibility factors that promote adverse outcomes in brain development. Conversely, understanding how low-level chemical exposure influences molecular, cellular, and behavioral outcomes relevant to the development of autism will enlighten geneticists, neuroscientists, and immunologists about autism's complex etiologies and possibly yield novel intervention strategies. The inherent imbalances in neuronal connectivity in children at risk for autism are likely to provide the biological substrate for enhanced susceptibility to environmental triggers that are known to target signaling systems. These systems establish the basic patterns of connectivity, from early neuronal migration and axonal pathfinding to postnatal refining of neuronal connections. Three examples of gene x environment interactions that likely contribute to autism risk are illustrated: pesticides that interfere with (1) acetylcholine (ACh) and (2) g-aminobutyric acid (GABA) neurotransmission; and (3) the persistent organic pollutants that directly alter Ca<sup>2+</sup> signaling pathways and Ca<sup>2+</sup>-dependent effectors. One fundamental way in which heritable genetic vulnerabilities can amplify the adverse effects triggered by environmental exposures is if both factors (genes and environment) converge to dysregulate the same neurotransmitter and/or signaling systems at critical times during development. Recent results from studies conducted by investigators at the UC Davis Center for Children's Environmental Health and Disease Prevention will highlight examples of gene x environment interactions relevant to autism risk. Supported by NIEHS and US EPA.

## AUTISM AND THE ENVIRONMENT: CHALLENGES AND OPPORTUNITIES FOR ADVANCING THE SCIENCE

Cindy Lawler, National Institute of Environmental Health Sciences, Research Triangle Park, NC

In response to the urgent public health significance of autism spectrum disorder (ASD), research efforts in this field have increased markedly over the past five years. Important advances have been made in some areas, including autism surveillance and genetics, yet the role of the environment remains

poorly understood. There is an urgent need for more environmental health scientists to bring their expertise to bear on this problem. Clues emerging from clinical and genetic studies in autism point to perturbation of specific pathways (e.g., immune, synaptic homeostasis), but more work is needed to translate these findings to animal models and model systems. Few exposures have been studied with sufficient rigor and a systematic effort to assess autism risk from the universe of potential exposures is past due. Traditional epidemiologic clues that derive from variation in time and space are elusive in the case of ASD because secular changes in awareness, diagnosis and service provision can obscure real increases in prevalence. Improved infrastructure is needed to support reliable prevalence estimation in many other countries and enable comparison of prevalence in populations with varying exposures. Most of the available evidence supports prenatal origins of ASD, yet measuring exposures during pregnancy requires costly prospective pregnancy cohorts or careful retrospective assessments in other study designs. The collection of environmental data, when it occurs, is not standardized in ways that allow pooling across studies. This is in contrast to the autism genetics field, where combining of data sets is accomplished routinely. Rare structural variants (copy number variation) have been identified as playing key roles in autism causation, yet how and whether environmental exposures contribute to CNVs are unknown. Results from ASD genome wide association studies (GWAS) of normal genetic variation have been inconclusive. This may reflect a failure to consider gene environment interplay. An appreciation of epigenetics as an interface between environment and genes is emerging, yet is only slowly being applied to address questions of autism etiology. In summary, there are many exciting translational challenges in autism research that could benefit from greater involvement of environmental health scientists.

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### Has the Women's Health Initiative Hormone Therapy Trial Helped Improve Women's Health?

Organized by: Gilbert S. Omenn, University of Michigan, Ann Arbor; Andrea LaCroix, Fred Hutchinson Cancer Research Center, Seattle, WA

In 1991, the U.S. National Institutes of Health (NIH) launched the biggest clinical trial of all time to evaluate important risk factors for multiple disease endpoints in women, the Women's Health Initiative (WHI). The randomized clinical trial of hormone-replacement therapy, vitamin D, calcium, and other risk factors and exposures in about 50,000 women was accompanied by an observational study of 160,000 women. Breast cancer, endometrial cancer, cardiovascular disease, and osteoporosis were among the multiple endpoints. Findings for hormone replacement therapy were particularly surprising and led to major changes in practice by physicians and patients worldwide. Important new findings continue to be released. The latest information suggests that the trial's results may have influenced the prevention of heart disease, but not stroke. The importance of long-term follow-up of randomized prevention trials is well demonstrated by the emergence of new findings showing very different long-term effects and different effects by age from estrogen alone versus estrogen plus progesterone. These findings are a model for comparative effectiveness research. Long-term results from dietary modification and calcium and vitamin D supplements are being analyzed. Finally, there is debate about the costs and benefits of such large projects. The symposium is dedicated to Dr. Bernadine Healy, the first female director of NIH, who fundamentally changed the medical community's approach to women's health.

### HEALTH EFFECTS OF ESTROGEN PLUS PROGESTIN AND SOLELY ESTROGEN FOR POSTMENOPAUSAL WOMEN

Garnet Anderson, Fred Hutchinson Cancer Center, Seattle, WA

Dr. Anderson will describe the design and key results of the Hormone Therapy Trials of Estrogen plus Progestin and Estrogen Alone, highlighting the similarities and differences between these two hormone therapies. She will present the latest findings from extended follow-up of women enrolled in these two trials, including post-intervention health effects.

### THE INITIATIVE'S INFLUENCE ON THE HEALTH CARE AND ALTERED RATES OF DISEASE AMONG WOMEN

Andrea LaCroix, Fred Hutchinson Cancer Research Center, Seattle, WA

Dr. LaCroix will review the evidence about whether or not the Women's Health Initiative changed physicians' views about the risks and benefits of hormone therapy, prescriptions for hormone therapy, and rates of breast cancer, heart

disease, and fracture among postmenopausal women in the U.S.

### CHANGING CONCEPTS: MENOPAUSAL HORMONE THERAPY AND CANCER

Rowan Chlebowski, University of California, Los Angeles

Dr. Chlebowski will describe how recent results from the WHI randomized trials of hormone therapy and large cohort analyses have substantially changed concepts regarding the influence of hormone therapy on common cancers in postmenopausal women. The findings include preclinical results and potential mechanisms of action.

### IMPACT OF RESULTS ON GYNECOLOGICAL PRACTICE AND WOMEN'S CHOICES

Susan Reed, University of Washington, Seattle

Dr. Reed will discuss how emerging evidence from the Women's Health Initiative Hormone Therapy Trials has changed gynecologic health care for peri- and postmenopausal women. The National Institutes of Health advised women to discuss the WHI findings with their physicians and together to pursue a personal risk-based decision about whether to initiate, continue or stop postmenopausal hormone therapy. Dr. Reed will provide a clinical perspective.

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### Genomics and Cancer: A Global Challenge Needing Global Solutions

Organized by: Joseph Connors, BC Cancer Agency, Vancouver

Deciphering cancer biology has emerged as the most demanding biomedical challenge of the 21st century. Cancer is now the single most common cause of death worldwide, accounting for more than 12 million new cases and 7 million deaths annually. Incidence and mortality will more than double by 2020. Investigators are realizing the power of genomics, anchored in the sequencing of the entire human genome and amplified by extraordinary reductions in cost and increases in efficiency, to identify a growing catalog of mutations and genomic alterations that are present across multiple types and stages of cancer. The broad effort to address this challenge has elicited unprecedented international collaboration. Specimen assembly, analysis, correlation with treatment outcomes, and cross-comparison require extensive exchange of ideas, materials, and information. A global effort is addressing, and is needed to address, this global problem. This symposium will explore three aspects of cancer genomics: insights into cancer biology emerging from genomic analysis of breast cancer; challenges and solutions for global exchange of genomic information; and the promise of next-generation sequencing techniques for analysis of cancer biology. The emphasis will be on the ways in which international collaboration facilitates these efforts. The global toll of cancer is obvious and growing. The global genomics research community must respond to this challenge.

### GENOMICS AND BREAST CANCER

Samuel Aparicio, BC Cancer Agency, Vancouver

Focus on breast cancer genomics and molecular biology as an example of an internationally common cancer with biologically distinct subtypes and therapeutic options.

### EVOLUTION OF THE CANCER GENOME

Michael Stratton, Wellcome Trust Sanger Institute, Cambridge, United Kingdom

All cancers carry somatically acquired changes in their genomes. Some, termed "driver" mutations, are causally implicated in cancer development. The remainder are "passengers", and bear the imprints of mutational processes operative during cancer development. Following the advent of second generation sequencing technologies the provision of whole cancer genome sequences has become a reality. These sequences generate comprehensive catalogues of somatic mutations, including point mutations, rearrangements and copy number changes and provide insights into the evolutionary processes underlying the development of individual human cancers including the factors generating variation and the forces of selection. These insights will