



# Changing the Course of Autism

## The Science and Intervention



## Speaker Biographies and synopsis



### **Martha Herbert, MD PhD, Harvard Medical School, USA**

Dr. Martha Herbert is an Assistant Professor of Neurology at Harvard Medical School, a Pediatric Neurologist at the Massachusetts General Hospital in Boston, and an affiliate of the Harvard-MIT-MGH Martinos Center for Biomedical

Imaging, where she is Director of the TRANSCEND Research Program (Treatment Research and Neuroscience Evaluation of Neurodevelopmental Disorders).

Dr. Herbert trained in Pediatrics at Cornell University Medical Center and in Neurology and Child Neurology at the Massachusetts General Hospital, where she has remained. Her background in pediatric neurology, evolutionary biology and history of science has oriented her toward systems biology, brain connectivity and dynamism, and brain-body interrelationships.

Prior to her medical training Dr Herbert obtained a doctoral degree at the University of California, Santa Cruz, followed by some postdoctoral in the areas of evolutionary biology and history of science.

Her main research interests are in addressing autism as a "dynamic encephalopathy" rather than a "static encephalopathy" and in how environmental vulnerability affects brain and body health and function. Dr Herbert takes three approaches:

- 1) Taking a whole body systems approach to how autism emerges;
- 2) developing a multi-modal brain imaging and biomarker approach to studying the interface between metabolic/immune disturbances and altered brain

signalling; and

- 3) applying these approaches to the systems biology of improvement and recovery in autism.

### ***Taking a Fresh Look at Autism: Chronic Dynamic State, not Fixed Trait***

Autism has been considered a genetically caused and fixed, lifelong brain deficit. However emerging science is making that framing of autism outdated. There is more than genes and brain, there is lots of variability even for any one individual, and it is not in itself a "deficit." An emerging model includes environment and physiology as well as genes, and looks at strengths as well as difficulties. It may well be that what we call "autism" is not the fixed output of a static wiring diagram but the moment-to-moment recreation of atypical patterns of brain wave oscillations that arise from a brain with differences in cell and tissue physiology. Emerging multi-scale systems biology points us toward a whole-body dynamic model of autism where many aspects of life can be made easier so that each person has the best chance to reach their optimal potential.

### ***The Biology of Brain Change in Autism: A Whole-Body Approach to the Brain***

The study of the brain has been called "neuroscience" and has focused on neurons. But we are learning that other cells and tissues in the brain play a much more important role in how the brain functions than we had previously suspected. "The Other Brain" (to use the title of the book by Douglas Fields) also includes glial cells (like astrocytes and microglial cells), the health or dysfunction of mitochondria, inflammation, blood and blood vessels, cerebrospinal fluid and the "stuff between the cells" -- the extracellular matrix. The quality of function of this more inclusive picture of the brain is greatly affected by the health, metabolism and immune status of the whole body. All of this can greatly



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affect how neurons perform. It's important to advance to a more inclusive model of the brain if we are to aim most effectively for the best possible outcomes.



**Prof Mady Hornig, MD, MA,**

**Prof Mady Hornig is Associate Professor of Epidemiology and Director of Translational Research in the Jerome L. and Dawn Greene Infectious Disease Laboratory at the Mailman School of Public Health, Columbia University.**

Dr Hornig is widely recognized for her animal model and clinical research on the role of microbial, immune, and toxicologic factors in neuropsychiatric disorders, including autism, schizophrenia, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, and mood disorders. Her work integrates data from animal models and epidemiologic studies to understand the mechanisms by which environmental factors, including viruses, bacteria, and toxins, or common host responses to these agents during brain maturation, may act as triggers or amplifying factors in the pathogenesis of some neuropsychiatric conditions. Findings from animal models of immune-mediated neurodevelopmental damage are employed to sharpen the focus of investigations in human cohorts, creating the basis for translation into novel biomarkers and intervention strategies; and hypotheses generated from epidemiologic studies are rigorously tested in animal models. In 2004, Dr. Hornig presented to the Institute of Medicine Immunization Safety Review Committee and testified twice before congressional subcommittees regarding the role of infections and toxins in autism pathogenesis. She leads a project on immune and neuroendocrine factors in West Nile virus encephalitis within the Northeast Biodefense Center, an NIAID regional center of excellence in biodefense and emerging infectious diseases, where she is a member of the Core Oversight Committee and the Governing Council. She was recently elected to the President's Council of Cornell

Women.

### ***Inflammation, Infection and Autoimmunity in Autism***

Growing evidence suggests that the environment plays a role in the pathogenesis of autism. A diverse set of factors is implicated, ranging from toxicants and dysnutrition to microbes. For some environmental agents, exposure is a relatively rare phenomenon, but many environmental challenges proposed in the development of autism occur quite commonly. Explaining who gets sick, and when and why, is especially challenging when exposures are ubiquitous in a given population. To account for these variations in neurodevelopmental outcomes after exposure, we have proposed the "three strikes" hypothesis, wherein disease risk depends on the specific developmental age at which an environmental exposure occurs and on the intersection of this timed environmental exposure with genetic vulnerability factors. Inflammatory and autoimmune parameters may be persistently altered in a subset of individuals with autism as a result of exposure to infectious or immunotoxic agents from the environment, before or after birth, and the susceptibility of the individual to these environmental challenges due to unfortunate genetics, bad timing, or prior harmful exposures. A persistent elevation in the levels of certain immune molecules can, in turn, compromise the integrity of the normally protective blood-brain barrier, allowing both exogenous (infectious, xenobiotic) and endogenous (autoantibodies, cytokines) substances to invade the central nervous system from the blood. Immune molecules can also alter the microflora and healthy functioning of the gastrointestinal tract and other peripheral organs; immune-triggered dysfunction of the intestines and of certain endocrine organs can also have a negative impact on the maturation and function of the brain. We hypothesize that this susceptibility to abnormal immune responses is a consequence of the unfortunate convergence of genes, environment and timing - the "three strikes" - and that the subsequent dysregulation of brain-immune signaling is a critical component of the complex mechanisms



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leading to the development of autism and to the exacerbation of its clinical features. The evidence for immune dysregulation in autism and its potential role in the development and maintenance of the disorder will be presented.



### **Dr Nicola Antonucci,** **Biomedical Centre for Autism** **Research and Treatment,** **Bari, Italy**

Dr. Antonucci became involved in biomedical treatment of autism in 2006, when his daughter was diagnosed with ASD, drawing on the knowledge and resources of the

Autism Research Institute, in San Diego, California. Dr. Antonucci followed further medical training for several months at the "The Rimland Centre" in Lynchburg, Virginia, under the mentoring of Dr E. Mumper and he is attending regular annual scientific meetings and training courses organised by the Autism Research Institute.

Dr. Antonucci is now Director of the "Biomedical Centre for Autism Research and Treatment" in Bari, Italy, and works exclusively with children affected by ASDs in several locations in Italy and abroad. In 2010, in collaboration with Dr. Dario Siniscalco, Second University of Naples, he founded a research group to study molecular and cellular changes in ASDs. This group is conducting several research trials and has already published in international peer-reviewed journals in the field of autism.

### ***A Clinical Approach to Treating Autism***

Recent scientific and medical developments in autism points to autism resulting from an encephalopathy disease with metabolic and inflammatory disturbances characterized by the presence of brain microglial activation. The presentation will review the use of clinical biomarkers, in areas of inflammatory and metabolic diseases to guide the medical treatment of autism in a targeted and individualized way.

Specifically, the talk will emphasize the use of sensitive diagnostic tests to identify the presence of deficits in metabolic detoxification and in the control of oxidative stress and cellular energy production. Currently available therapeutic strategies as indicated in the international literature will be also described.



### **Prof Mike Snape, MD PhD,** **Autism Therapeutics Ltd**

Mike Snape is the Chief Executive Officer at Autism Therapeutics Ltd. Dr Snape specializes in development of medications which will help all disorders on the autism spectrum. Prior to becoming a founding partner in Autism Therapeutics, Professor

Snape was the founder and Chief Scientific Officer of Neuropharm Group PLC, a UK based autism focused drug development company, and was part of the team that took Neuropharm through an Initial Public Offering less than twelve months after the first private financing. Dr Snape was an Associate Director and Head of Pharmacology for Vernalis PLC, a UK based CNS focused drug development company. Prior to this Dr Snape was also a principal scientist at Cerebrus Ltd, the first UK based CNS focused biotech company, where he was responsible for the neurodegeneration drug discovery group and the project initiator of CEB 1050 for autism. Dr Snape began his career as a senior scientist at Astra Neuroscience Research Unit. Dr Snape is also on the faculty at CASE Western University in Cleveland, Ohio.

Dr Snape has been involved in clinical studies in autism since 1997, and has been responsible for conceiving and executing multiple clinical studies in autism and related neurodevelopmental disorders. Dr Snape is presently a consultant to Neuren Pharmaceuticals Ltd. Neuren have a clinical stage program primarily focused on progressing a compound called NNZ-2566 for the rare and severe genetically-linked disorder Rett Syndrome





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Medical treatments for symptoms of ASDs comprise a variety of pharmacologic agents that are generally intended to treat common comorbidities of ASDs. There remains an unmet medical need for an effective pharmacotherapy to treat the core symptoms of this serious disorder given that there are no approved marketed drugs for this indication. Only two medications have received FDA approval to treat irritability (an associated, not “core”, symptom of autism) in children with autism. Dr Snape will speak more on the medical treatments in August.

### ***NNZ-2566 in Rett Syndrome and Autism Spectrum Disorders – Role and Update***

Biologically, autism is a disorder of synaptic connectivity, involving neuroinflammation. Syndromic disorders that cause signs of autism include Rett Syndrome and Fragile X Syndrome. These disorders also involve problems with synaptic connectivity and involve microglia and inflammatory cytokines.

IGF-1 (Insuline-Like Growth Factor 1) is a naturally occurring growth factor having functions throughout the body including the CNS (Central nervous system), via the IGF-1 receptor. IGF-1 is cleaved to the terminal tripeptide IGF-1[1-3] by endogenous peptidases. NNZ-2566 is a novel, modified analog of IGF-1[1-3] that crosses the blood-brain barrier, is orally available and which reduces neuroinflammation. This effect may be mediated by modulation of the PI3K-Akt-mTOR pathway and normalisation of microglial function. NNZ-2566 has a profile suitable for investigation in Rett Syndrome and Fragile X Syndrome. Fmr1 knockout and mepc2 knockout mice represent preclinical models for assessment of putative drug treatments. Fmr1 KO mice manifest phenotypic changes compared with wild-type mice, including hyperactivity and short and long term memory deficits in the open-field and successive alley tests, decreased contextual-fear condition learning, activities of daily living and sociability, reduced dendritic spine density and decreased phosphorylation of

ERK and Akt. Treatment with NNZ-2566 significantly ameliorates these aberrant features. Published data report mepc2 KO mice show significant reductions in life expectancy, behavioural abnormalities and cardiorespiratory irregularities. The terminal tripeptide of IGF-1[1-3] significantly reverses these aberrant features.

Neuren is progressing a clinical study of NNZ-2566 in Rett Syndrome (ClinicalTrials.gov Identifier: NCT01703533) commencing at Baylor College of Medicine. This is a Phase IIa safety study in 60 adolescents and adults with Rett Syndrome. The study assesses the safety and tolerability of NNZ-2566 in Rett Syndrome effects on potential signals of efficacy including EEG, cardio-respiratory function and functional measures. The study has an estimated primary completion date of March 2014.



**Dario Siniscalco,**  
**Chem D PhD**  
Department of Experimental  
Medicine, Second University of  
Naples, Italy. Centre for Autism – La  
Forza del Silenzio, Caserta, Italy.  
Cancellautismo – non profit  
association for autism care, Florence,  
Italy.

Research Associate for the Department of Experimental Medicine of the Second University of Naples (SUN) in Italy. He graduated in Chemistry from the University of Naples “Federico II” in 2000 and received his PhD in Pharmacological Sciences from SUN in 2004. He completed his Neuropathology fellowship at University of Alabama at Birmingham in USA before joining the Second University of Naples staff in 2006.

Dr Siniscalco is a registered member of the following scientific societies: Order of the Chemists of Campania, National Council for Chemistry, Stem Cell Research Italy, European Association for Chemical and Molecular Sciences,



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Italian Pharmacological Society, Cell Death Research Group - University of Alabama at Birmingham in USA.

In 2010, in collaboration with Dr Nicola Antonucci, he founded a research group to study cellular and molecular changes in autism spectrum disorders. He is author and co-author of 39 scientific peer-reviewed papers and nine book chapters. He has presented his work to 92 national and international conferences. He is serving as an editorial board member of reputed journals and is a reviewer of more than 25 journals.

His main research interests are gene expression and molecular regulation in autism spectrum disorders, the use of stem cells as therapeutic tool in autism and the role of macrophage activation in autism. Other research interests are stem cells therapy for the neuronal recovery and the study of neuronal apoptosis, as well as the role of bcl-2 family, caspases, and cell cycle regulator genes.

### ***Stem Cell Therapy in Autism***

Autism spectrum disorders (ASDs) are heterogeneous neurodevelopmental pathologies characterized by impairments in social interaction and communication and by restricted, repetitive, and stereotyped patterns of behaviour. ASDs have been recognized as a major public health issue. The prevalence rate of ASDs is fast increasing. There are currently no approved treatments for ASD core symptoms. Pharmacological intervention does not affect all core symptoms, providing partial relief for some dysfunctional behaviour. Current available strategies for ASDs can be divided into behavioural, nutritional, and drug therapy.

Stem cell therapy represents the great promise for the future of molecular and regenerative medicine. Several types of stem cells offer a valid approach to curing several untreatable human neurodegenerative diseases. Based on the recent advances in ASD molecular mechanisms, stem cells could be a potent treatment for autistic syndromes.

Indeed, three properties defining stem cells make them potential therapeutic agents for ASDs:

- 1) self-renewal ability with their capacity to generate more identical stem cells;
- 2) their capacity to give rise to more differentiated cells;
- 3) their paracrine regulatory functions.

Due to the particular immune and neural dysregulation observed in autistic children, cell-mediated applications could offer extraordinary potential as a treatment modality. Once transplanted, stem cells are able to modulate the immune system through synthesis and release of several bioactive molecules, i.e. cytokines, which in turn are able to affect the host immune system. Due to their immunoregulatory properties, stem cells could restore the imbalanced immune system seen in ASDs.

This talk will focus on recent advances in stem cell biology useful for ASD treatment, as well as on newest results on stem cell therapy in autistic subjects.



### **Dr Alex Richardson**

Senior Research Fellow, Centre for Evidence-Based Intervention, University of Oxford; Visiting Research Fellow, Dept of Physiology, Anatomy and Genetics, University of Oxford; Founder Director of FAB Research

Alex Richardson is best known for her research into how nutrition (and particularly fatty acids) can affect behaviour, learning and mood, although her work also involves several large-scale collaborative programmes that include studies of epidemiology, genetics, brain imaging, biochemistry and nutrition as well as physiological and psychological functioning. Her primary research interests include:

- the role of nutrition in brain development and function, and its implications for behaviour, learning and mood.
- the biology of individual differences in personality,



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perception and cognition, particularly in relation to developmental and psychiatric disorders.

Her current research centres on the role of fatty acids in relation to both normal individual differences and developmental and psychiatric disorders such as dyslexia, dyspraxia, ADHD, autism, depression and schizophrenia. Recent and ongoing work includes controlled treatment trials to investigate the effects of dietary supplementation with fatty acids in relation to features of these conditions, experimental studies of possible underlying mechanisms, and collaborative investigations of the epidemiology and genetics of neurodevelopmental disorders.

Alex's research has always been aimed at developing new methods of identification and management that will have real practical benefit. She therefore works closely with a range of education and health practitioners as well as local and national support groups and charities. In addition to her role as a founder director of FAB Research, she also helped to found the Dyslexia Research Trust, was a co-opted Trustee and Scientific Advisor to the Dyspraxia Foundation, serves on the Biomedical Research Committee of Autism Unravelled and the Autism Treatment Trust, and liaises closely with the Hyperactive Children's Support Group among others.

Alex is a regular speaker at national and international research meetings and has more than 80 research publications in peer-reviewed journals and academic books. She originally trained as a teacher, and her excellent communication skills and clear presentation style are such that she is frequently invited to give lectures and talks to health and education professionals, support groups, charities and other organisations. Her work has received substantial media coverage in recent years, and she has given numerous interviews for the press, radio and TV both in the UK and abroad. Alex is also the author of *They Are What You Feed Them* - a widely-acclaimed book written for parents and professionals that explains how and why children's diets can affect their behaviour, learning and mood, and offers easy-

to-follow practical advice based on the latest scientific evidence. All author proceeds from this book are dedicated to the FAB Research charity.

### ***The Role of Nutrition in Mental Health and Performance: Changing Diets, Changing Minds***

Human diets have changed dramatically over the last century, and abundant evidence now links modern, western-type diets – rich in highly processed, refined foods - not only to increased rates of 'degenerative' physical health problems such as cardiovascular disease, cancers, obesity and Type II diabetes but also to a wide range of conditions affecting mental health, development and wellbeing. Nutrition affects the development and functioning of the brain as well as the body, and is now recognised as making a significant contribution to the most common and disabling mental health conditions, including depression, psychosis and dementia as well as childhood developmental conditions such as ADHD and the autistic spectrum of disorders. Brain development and function are inextricably linked with the health of the gut and the immune system, and industrialisation has changed the nutritional composition of human diets in many ways that are known to be pathological for both brain and body. These include (1) dramatic increases in sugar and other refined carbohydrates (and a corresponding lack of fibre and essential micronutrients); and (2) substantial changes in the type and balance of dietary fats – with a particular increase in the ratio of omega-6/omega-3 polyunsaturated fatty acids (PUFA). Conditions affecting mental health and wellbeing show high comorbidity with many physical health conditions, and increasing evidence shows that dietary interventions can be helpful in the management of both.

The scale of the mental health 'epidemic' the world is now facing is immense. In any one year, 38% of the European population has a fully diagnosable psychiatric or neurological disorder. The cost burden is equally enormous. UK government figures showed that in 2007, the annual cost of mental health disorders was £77 billion, and by 2010, this





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had already risen to £105 billion. This presentation will explore how diets can and do affect mental health, performance and wellbeing, with particular reference to the autistic spectrum of disorders. A multi-disciplinary perspective will be taken, drawing on evidence from epigenetics and neuroscience as well as epidemiological studies and clinical trials, and discussing the implications for research, policy and practice.



**Dr Lorene Amet DEA, DipBiotechnol, D Phil, MEd (Autism)**

Research Director, Autism Treatment Trust, Edinburgh

Dr Lorene Amet is trained as a neuroscientist (brain development, brain ischemia and epilepsy) and

has worked at Edinburgh, Oxford and Princeton Universities before working as the Principal Scientist at the Autism Treatment Trust in Edinburgh. Dr Amet has been involved in several research and clinical projects and has also completed a Masters in Special Education – Autism, at the University of Birmingham where her work has been published. Dr. Amet is also trained in administering the Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview-Revised (ADI-R), used for the diagnosis of autism. Dr. Amet works in collaboration with scientists, educators, physiotherapists and medical doctors to assist the life of people affected by autism. More recently she has worked with the group Chronimed in France which focuses on infectious diseases underlying autism and related neurological impairments, including Lyme disease.

### **Autism: Where Are We At?**

Autism is a mosaic disease, it presents in different shapes and colours. Previously thought to be a rare genetic disorder, it has over the last two decades become increasingly prevalent, affecting between 1 in 38 and 1 in 100 children, depending on the geographical location. There is mounting

evidence that autism is not just a behavioural disorder, but in fact, is associated with a range of treatable health abnormalities called co-morbidities. Furthermore, there is also growing evidence that the disorder is in many cases at least, triggered by the environment and not solely genetic in origin. The current scientific and medical knowledge we have of the condition calls for a proper diagnosis and treatment. The talk will review the current state of understanding and outline the immediate implications with regard to intervention.



**Professor Vera Stejskal, PhD**  
MELISA Diagnostics Ltd & Associate Professor of Immunology at Stockholm University, Sweden

Prof Stejskal obtained the title RNDr (Rerum Naturalium Doctoris) at the Charles University in Prague. She left Czechoslovakia after the Russian

invasion in 1968 and continued her research in immunology at Stockholm University in Sweden. Later she became Associated Professor of Immunology and left academia to build the first pharmaceutical immunotoxicology laboratory in Scandinavia, at Astra pharmaceutical (Astra Zeneca). She played a key role developing Losec, Astra's multi-billion-dollar stomach ulcer drug. She is the inventor of the MELISA test, which diagnoses type IV allergies to metals and other environmental antigens including gluten and casein. Prof Stejskal left Astra in 1996 and continued her research in clinical immunotoxicology. She has published over 100 scientific articles and is an international speaker on the subject of environmentally-induced inflammation.

### **Inflammation, Metals and Other Allergens in Autistic Disorders: What Do We Know?**

There is growing evidence supporting the view that autism can be triggered by environmental factors. However it remains unclear why some children are more vulnerable



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than others. An overactive immune system and increased systemic inflammation are often seen in these children. This can be caused by food allergies, especially to gluten and casein, as well as exposure to environmental pollutants, such as nickel, mercury or other chemicals like tobacco smoke and car exhaust.

We have studied the cellular hypersensitivity to a range of environmental toxins in children with ASD and healthy controls. The results of our findings will be reported.



**Angelette Muller, MSc (Nutrition Therapy), MSc (Clinical Neuroscience & Immunology)**

Angelette Müller, MSc., MSc is a Nutrition Therapist and Culinary Health Specialist. She received her MSc in Clinical Neuroscience & Immunology from the University of Surrey, Roehampton; and her MSc in Nutrition Therapy from University of Worcester where she

focused her research on nutrition applied to autistic children. She has worked for several years in the field of autism using an integrated approach. She currently runs a private clinic in nutritional therapy helping children and young adults with autism, as well as other health issues. Angelette Müller's experience includes teaching and lecturing in the area of nutrition. She is also a natural health chef, writer and food photographer. She is currently working on a full-colour nutrition/cookbook for individuals with autism.

***Simple Dietary Interventions in Autism***

Food is the building blocks of our bodies. Food can repair or inflame, regulate or impair, and powerfully programme our genes; and the genes of our gut bugs. In this presentation we will cover the five food groups as presented in the eat well plate (but with a difference). We will look the food groups within the context of autism, showing parents and practitioners simply how to optimise the diet to promote healthier function.



**Dr Daniel Goyal, MBChB, DTM&H**

Dr. Goyal qualified from Aberdeen Medical School in 2001 and after three years in Occupational and Environmental Medicine, he chose to focus specifically on Environmental Medicine. He is a Clinical Researcher in the Neurosciences Department at the University of Manchester

specialising in the neuro-immunological approach to ASD. Dr Goyal is also the Medical Director at Sincere Health.



**Sue Simmons, DNMed, CNHC, mBANT, BSc Hons**

Sue has been in practice as a Nutritional Therapist for 10 years and has specialised in helping children and young adults with Autistic Spectrum Disorders (ASD) for the last seven years. She did her Nutritional Therapy training with Plaskett Nutritional Medicine

College (part of Thames Valley University). Sue then attended three annual Defeat Autism Now! Clinician's training courses and conferences in the USA. She is registered with the Complementary and Natural Healthcare Council and is a member of the British Association for Applied Nutrition and Nutritional Therapy (BANT). Sue works as part of the Sincere Health team and practices an integrated functional medicine approach.

***Nutritional Supplementation - Where to Start***

Clinical Research has shown ASD children have lower levels of many nutrients, an increased incidence of gastrointestinal and mitochondrial disorders and increased levels of inflammatory cytokines. Nutritional supplements can play an important role in addressing these and other issues.