“How Microbes Can Change Your Mind-
Microbial Metabolites in Neurodevelopmental Disorders”

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Translational Nutrition ACN (San Diego, CAL), 2016
Website: kpearg.com
Why the increase?
Why is this happening?
Nature of Things "Autism Enigma" (CBC)
<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Nature of Relevant Financial Relationship (Include all those that apply)</th>
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<td>What was received</td>
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<td>• None</td>
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Presentation Learning Objectives

After participating in this presentation, learners should be better able to:

• To examine evidence for possible dietary, gastrointestinal, metabolic and infective links to autism spectrum disorders (ASD)
• To examine, from a biological perspective that the microbiome, may have evolved to modulate host metabolism and behavior to ensure their survival and spread.
• To explore the possibility that alteration of the enteric microbiome via the Western diet and antibiotics select for ASD associated enteric bacteria (Clostridia, Desulfovibrio), whose metabolic short chain fatty acid fermentation products (i.e. propionic acid) may be environmental triggers of (ASD) in a subset of patients
After participating in this presentation, learners should be better able to:

- Through the use of a novel animal model and clinical studies show that enteric short chain fatty acids can induce many behavioral and brain changes, including reversible hyperactive, perseverative, antisocial behavior, seizure and movement disorder, and brain neuroinflammatory, mitochondrial, lipid/acylcarnitine and epigenetic changes consistent with ASDs.

- To consider possible heritable and iatrogenic risk factors (maternal/infant long term antibiotics, C-section, hospitalization, colitis, Westernized diet) leading to early alteration in the host microbiome and resultant impairment of carnitine/mitochondrial function being central to ASD pathogenesis and ASD like behaviors in related neurodevelopmental conditions.
After participating in this presentation, clinicians should be better able to:

- Potential long term benefits of normal birth practices (vaginal birth, breast feeding) and reduction of inappropriate use of antibiotics when medically appropriate
- Potential physiological mechanisms where diet, gastrointestinal dysfunction, opportunistic infections and metabolic augmentors (i.e. omega 3s, carnitine) may play a role in brain development and behavior
- Cautious optimism regarding ongoing research where preservation or manipulation of the host microbiome may play a role in brain health and disease
Enlarged Brain Size
Increased Neuronal Density
Altered Cell Migration
Seizure Disorder

Systemic Changes
Immune System
Gastrointestinal System
Metabolic Disorder
Detoxification Systems (glutathione)

Hormonal
Sex Hormones
Oxytocin
Vasopressin

Genetic Factors
Neurotransmitter
Growth Factors
Cell-cell Interaction
Sex Linked (Fragile X)
Metabolism (carnitine synthesis)

White Matter Disorder
Glial/microglial Changes
Neuroinflammation
(Impaired Neurodevelopment and Cortico-cortical processing)

Environment
Metals
Hydrocarbons
Infectious
Drug (valproate)
Diet- Wheat
Casein Allergy
Carbohydrate?

AUTISM (1 in 68)
Genetics is why you look like your father…

And if you don’t why you should!

Identical twins often disparate for autism/severity
Many environmental/infectious factors mimic/impact on
Genetic transmissibility
(i.e. Tuberculosis, twins with same/different placenta)
Genetic sensitivity to infection (similar pattern in ASDs!)
Neurodevelopment- “Lets Build a Brain”

- Complex development
timing important
- Many neurons die

Genetic (instruction)- Cell Adhesion
Environment
Insults:
Infection (virus)/inflammatory (IL-6)
toxins (alcohol)/metals/drugs (valproate)
Oxidative stress-Redox change- cell fate
(germ cell-fetus-neonate)
Cell to Cell Communication is
Important in the organization of the
developing nervous system
(programmed cell death and ordered cell migration)
Reelin, neurexins, gap junctions, see later……..
environmental factors may alter neurodevelopment
Autism- A Disorder of Energy Utilization and Toxin Elimination

Oxidative Stress (Chauhan, James):
Inflammation, impaired metabolism
Process similar to memory!!!
Antioxidants- glutathione, NAC
Facilitators of mitochondrial function-
carnitine, methylation-Methyl B12
(accessibility to CNS?)
A mitochondrial disorder?- Frye
(Mitochondrial DNA mutations- risk)
Mitochondrial dysfunction in ASD: Rossignol and Frye 2011
Mitochondrial disease /dysfunction (Frye)
Heterogeneous tissues affected/families/ complex inheritance
Inherited/Acquired mutations/Environmental Worsening
Autism- The Blind Men and the Elephant

Some common underlying cause involving behaviour, brain changes, GI/dietary symptoms, immunology, genetics, oxidative stress, mitochondrial disorder, environment, increase??????

ASDs
The Kilee Patchell-Evans Autism Research Group
THE UNIVERSITY OF WESTERN ONTARIO

- The paradigm of understanding Autism is changing
- Autism is a whole body disorder with many potentially treatable features
- We are an international multi-disciplinary team of neuroscientists working towards a cure

Scientists Listening to Parents

Multidisciplinary International Collaboration - Open Sharing
Examining Animal Behaviour to Study Autism

- Decreased/altered socialization
- Fixation on objects
- Sensitivity to sensory input
- Repetitive behaviour/ seizure/dystonia
- Aggression, variable course
- Other factors normal/improved?

Animal autism models
Pre/post natal factors

Examine brain
Development
Electrical Activity
Neuropathology
Gut, Immune
Metabolic markers
for subtle abnormalities
“GRAIFs” Gut Related Autism Inducing Factors
Microbiome NIH (10x host cells, 100x genes!)

Bacterial metabolites- symbiosis/dysbiosis

Opportunistic Infections- key risk factor
i.e clostridia, yeast (chronic antibiotics)

Cell wall- LPS, beta glucan- innate immunity

Fermentation products of dietary carbohydrate
- Short chain fatty acids*

Barriers, variable metabolism

Acquired/genetic (met receptor tyrosine kinase)

Dose, Location & Timing of exposure
Digestive system issues in autism – initially poorly studied
But renewed interest/technology (Horvath, Williams, Fasano, Frye et al., 2015 rev)

Intestinal pathology on a subset of autistic patients
Associated with regressive onset and GI symptoms
Impaired carbohydrate digestion, inflammation
Unique bacteria- carbohydrate craving
Co morbidity? Consequence? Cause?
The Human Microbiome
Gut Microbiome - Complex Ecosystem - Alteration with Antibiotics
Obstetrical/Neonatal Microflora

- C section / Prophylaxis of B Haem Strep
- Hospitalization, Antibiotic resistance
- Early antibiotic exposure for infection
- Early alteration of microbiome - risk factor for ASD
Can Enteric Bacteria Affect Brain Development/Behaviour?

Clinical- Food Craving/Symptom Worsening/ GI symptoms
Gut changes (gluten/casein) poorly studied (antigenic mimicry)
Early gut colonizers- alteration with antibiotics (increased incidence)
Unique bacterial species (clostridials, desulfovibrio, bacteriodetes)
“Leaky” or malabsorbtive digestive tract (impairment of barriers)
Production of bacterial metabolites (fuel for brain)
Effect on Brain development, physiology, behaviour, immune function
Pathogen “Control” of Host Nervous System for Propagation

Cordyceps Fungus       Rabies
Climbing (insects)       biting (mammals)
**Leucochloridium paradoxum** - parasitic flatworm of snails, birds

Parasite passed in feces of bird- eaten by snail
Pulsating eyestocks (mimic caterpillar), attraction to light,
eye eaten by bird, but snail has **increased** longevity!
Parasite infects predatory birds, eggs eaten by snails, then infects tadpoles, increased limb development of frog, easier To be eaten by bird etc.!
Borna Disease

Brain specific
Mammals, birds
Nasal transmission
Movement disorder
Oral movements
“food in mouth”
Human infection?
(mood disorder
Schizophrenia)
Toxoplasma Gondii

Cat reservoir (gut, stool)
Infected rodent, less “fear” of feline predator, increased dopamine
Link to human depression, risky behaviour, schizophrenia
Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection (PANDAS)- (Swedo)

Associated with Group A Beta Strep infections”
Clingy- OCD/Tick symptoms, relapsing remitting
Licking, clingy, Autoantibody to basal ganglia
Similar behaviour in family (sensitive population)
Carbohydrate Craving, Unique Opportunistic Bacteria Diarrhea Licking and Fecal Smearing in Autism

*Behaviour facilitates growth and spread of autism implicated gut pathogens (clostridials)?*

*Pathogen affecting host behaviour*

Photo- M. Herbert
Autism in Somali Diaspora in North America

3% of general population, 35% of autism in some regions
All conceived in Receiving Country- NOT Somalia
Large exposure to antibiotic/++ gastrointestinal infections
Norwegian cohort/MAL-ED Study (Gates Foundation) – Lange et al.
Effect of early medical intervention by Western medicine in 3rd world
Bangladesh, Brazil, India, Nepal, Pakistan, Peru, S. Africa, Tanzania
Nutrition, antibiotic exposure - impaired immunity, vaccine efficacy
Neurodevelopmental disorders
Altered development of infant microbiome
Gut Microbial Metabolites- Short Chain Fatty Acids
Propionic Acid- Neuroactive Properties

Weak organic acid: lipid/water soluble- “small” molecule
Uptake passive active (monocarboxylate transporters) ketones
Specific G protein coupled receptors (brain, gut, immune, fat)
Intracellular concentration (intracellular acidification)
Unique CNS/GI immunological properties
Short Chain Fatty Acids – Propionic Acid (PPA)

Propionic Acid/Propionate:
Byproduct of bacterial metabolism
Clostridium, propionibacteria (gut/acne)
Desulfovibrio, Bacteriodes (Finegold)
(butyrate, acetate)- short chain fatty acids
Increased in ASD stool, wheat substrate
Common preservative of wheat and dairy products, weight loss agent
Increased by ethanol, B12/biotin deficiency
carnitine deficiency, aspartame

Variable metabolism of propionate in population – Multiple mechanisms and multiple clinical presentation (organic acidemias) shares similarities with autism- underreported???

Role of diet, gut bacteria/barriers and “sickness” in propionate levels (other short chain fatty acids and metabolites)
Rodent Model of Autism- Behavioural and Brain Effects of Propionic Acid Administration
MacFabe et al, *Behavioural Brain Research* 2007), and MacFabe *Microbial Ecology in Health and Disease* 2012/13/15 for Reviews
Autism Model – Propionic Acid (PPA) - behaviour/EEG

Effect immediate, transient (45min) but some permanent

PBS

- Dose approx. that in propionic acidemia (now down to 1/20th)
- Pulse injected into cerebral ventricles
- NB buffered to pH 7.5
- Reversible repetitive behaviour
- Fixation on objects
- Seizure +/behaviour cortex
- Subcortical spiking

Propionate Autism Model
Enteric short chain fatty acids (gut bacterial metabolite- PPA, butyrate) induce reversible repetitive, antisocial behaviour, perseveration, object fixation, tics, seizure- Reversible
Early exposure (pre or post natal)- major developmental effects

Control

gut bacterial metabolite (propionic acid- PPA)
Intraventricular PPA- “ritual”

Hippocampal EEG- Repetitive motor loop
Normal EEG
Propionic acid causes movement disorder with caudate spiking
Social Behaviour (Ignoring/Mean Distance Apart) (Shultz et al. Neuropharmacology, 2008)

- **vehicle**
- **PPA**
  - Effect apparent after one dose, reversible post metabolism
  - Reduced play behaviour (Ethovision)
Social “Ignoring” of Normal Rat

PBS

PPA

MacFabe et al; Behavioural Brain Research (2010)
PPA Rats Prefer “Favourite Objects” to other Rodents (MacFabe et al, 2010 BBR)
Long term effects- Ethovision- stereotypies/ object fixation
Neuropathology of PPA in Rodent Model:

- Similarities to metabolic/autism spectrum disorders
- Innate neuroinflammation, oxidative stress, BBB
- Altered lipid metabolism/mitochondrial function
- Altered gene expression (epigenetics)
- Reversibility?
Hippocampal formation: GFAP (neuroplastic marker) reactive astrogliosis

PBS

High PPA

Microinjections of propionate - very brief exposure
Astrogliosis - prominent, hippocampus, cingulum, white matter
Neuroinflammation (TNF alpha)
Toxic or compensatory (neuroplastic response)
Results – CD68 Microglia – 14 day

Control (PBS)  
PPA

PPA increases activated microglia (neuroinflammation)
Nitric oxide, cytokines, fatty acid receptors on microglia
Endovascular involvement (microcirculation/ BBB)
(c/f human autism!)
Central PPA Infusions: Immunohistochemistry

Innate Neuroinflammation (astrocytes, microglia)
No apoptosis
Activation of CREB (memory)
increased Monocarboxylate Transporters (PPA/Ketones)
(consistent with ASD)

Neuropathology of dorsal hippocampus (CA2) and external capsule of adult rats with ICV infusions of PPA or SAL. PPA induced significant astroglisis (anti-GFAP), microglial activation (anti-CD68), without apoptotic neuronal cell loss (cleaved caspase 3) in rat hippocampus. Nuclear translocation of anti-CREB and an increase of anti-phosphoCREB immunoreactivity is observed in neural, glial, and endovascular epithelium by PPA treatment. PPA increases Monocarboxylate Transporter 1 immunoreactivity, primarily in white matter external capsule. Black bars indicate PPA treated animals; white bars indicate PBS (vehicle) treated animals.

(MacFabe 07/11/13)
PPA causes increase anti Nitro-tyrosine immunoreactivity in hippocampal formation increases “oxidative stress”
Increased Oxidative Stress in PPA Autism Model

PPA increases oxidative stress markers and impairs Glutathione metabolism (sequestration?)
- brain “sensitive” to broad spectrum of environmental agents (ie metals, xenobiotics, Tylenol!!)
- similarity to evidence of metabolic dysfunction in ASD patients
- broad effects - metabolic encephalopathy
Functions of Fatty Acids

• Main functions:
  – Energy storage
  – Structural components of cell membranes, membrane fluidity
  – Act as signal molecules in many metabolic processes
  – Abnormal fatty acid composition in Autism (lower omega 3/6 ratio)
  – Relative carnitine deficiency
  – Mitochondrial disorder?
  – (acquired?)
Thomas et al, J.Neurochem, 2010

I.E Phosphatidylethanolamine
Increase saturates
Decrease:
monosaturates
omega 6/3
Plasmalogens (antioxidant)

Same trend in
Phosphatidylcholine
Phosphatidylserine/inositol
Sphingomyelin (White matter)
Cardiolipin (mitochondria)

SCFA alter membrane fluidity,
Signalling, Antioxidant,
mitochondrial function
PPA Rodent Model  
217 patients-17% Similar short and long chain acylcarnitines  
Also decreased glutathione, Redox changes  
Gut Bacteria Products Impairing Cellular Energy Metabolism (Mitochondria/Fat metabolism) biomarkers/therapeutics (carnitine)
Common Infections, Chronic Antibiotics, Clostridia and Carnitine Collapse Leads to Constipation, Carbohydrate Malabsorption, Convulsions and Compulsions!

Carnitine- Shuttle for mitochondrial fatty acid beta oxidation

Routine pre- peri or post natal infections-
Long term antibiotics (beta lactams)- deplete carnitine transport
“Barren Gut”->Growth of clostridials- increased SCFA production

Further sequestration of carnitine
Impaired fatty acid metabolism- mitochondrial encephalopathy
### Causes
- Long term antibiotics for routine infection (maternal/infant) Treatment of maternal β hemolytic strep
- Hospitalisation (colonization of nosocomial bacteria) i.e. C-section, neonatal distress
- Prenatal drugs (valproate, ethanol)
- Opportunistic infection (*Clostridium*, *Desulfovibrio* spp.)
- Maternal/Infant gut dysbiosis
- Organic acidemias (propionic/methylmalonic, biotinidase/holo coenzyme deficiency)
- (B12/biotin deficiency)
- Genetic/acquired impaired carnitine synthesis/absorption (TMLHE/OCTN: genes, β-lactam antibiotics)
- Mitochondrial disorder/dysfunction (inherited, acquired)
- Colitis (Impaired barrier/SCFA metabolism), i.e. celiac disease, Met-receptor tyrosine kinase mutation
- Increased refined carbohydrate consumption — substrate for bacterial fermentation

### Consequences of SCFAs
- Gut dysmotility/inflammation/carbohydrate malabsorption/altered gut permeability (tight junction impairment)
- Active uptake of SCFA to CNS (monocarboxylate transporters)
- pH dependent intracellular concentration of SCFA
- Neurotransmitter synthesis and release (catecholamines, enkephalins) CNS/sympathetic nervous system
- Receptor activity (+NMDA, -GABA) SCFA G protein coupled receptors/Ca++ influx
- Gap junction closure, altered neurodevelopment, neuroinflammation
- Impaired mitochondrial function/ increased oxidative stress
- Reduced glutathione/increased sensitivity to xenobiotics (i.e. acetaminophen)
- Decreased carnitine/altered lipid metabolism/membrane fluidity
- Altered gene expression (CREB activation, histone deacetylase inhibition)
- Antisocial/perseverative/anxiety-like behavior, seizure/movement disorder, Restrictive food interests/carbohydrate craving

Many Roads Lead to Rome!
PPA increases mitochondrial function in concentration manner.

ASD lymphoblasts have altered PPA metabolism, pretreatment with oxidative stress challenge (DMNQ) reverses this (worse in ASD Cell lines) Frye et al- Translational Psychiatry in press.
**Critical Developmental Windows:**
Adolescent Behavioural Changes in Response to Early Exposure to PPA: Locomotor, Social, Sensory, Sex diff. - (Foley et al 2014abc, Ossenkopp et al 2014)

During first few days of life, rat pups are injected with sub cut PPA or PBS and Behaviourally tested as adolescents.

The amount that an animal is startled (“jumps”) in response to an acoustic stimulus is measured. PPA animals are more sensitive to stimuli – jump more – than PBS animals. -Reduced inhibition (i.e GABAergic dysfunction), also hyperactive, social impairment

SENSITIVE TIME WINDOWS
SCFA activate the transcription of TH gene- PC12
Nankova et al, 2014 PLoS

PPA, BUT and valproate induce tyrosine hydroxylase RNA-PC12 cells
(valproate modified SCFA- autism risk factor)
Via a CREB dependant mechanism (same in brain homogenate)
Epigenetic control of catecholamine synthesis, neuroligins, FMR
(Neuroplasticity, oxidative stress, mitochondria/lipid metabolism)
<table>
<thead>
<tr>
<th>Category/ gene product/ Description</th>
<th>PPA</th>
<th>BA (Fold change)</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>Immune system related genes (cell-cell communication, differentiation, cell cycle regulation, chaperone system)</td>
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<tr>
<td>GADD45 (growth arrest and DNA damage inducible 45)</td>
<td>2.4</td>
<td>2.1</td>
<td>Garbett K. et al., 2008</td>
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<td>IFITM3 (interferon induced transmembrane protein 3)</td>
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<td>3.9</td>
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<td>SPPI (osteopontin precursor)</td>
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<tr>
<td>MAP2K3 (MAP kinase kinase 3)</td>
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<td>CYR61 (Cysteine rich 61/CCN)</td>
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<td>HLA-A (human leukocyte antigen)</td>
<td>6.7</td>
<td>6.5</td>
<td>Torres AR et al., 2006</td>
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<tr>
<td>Innate immune inflammation</td>
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<td>PAF (PCNA associated factor)</td>
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<tr>
<td>IL2RG (interleukin 2 receptor)</td>
<td>5.4</td>
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<td>Gregg JP et al., 2008</td>
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<tr>
<td>Synaptic cell adhesion molecules</td>
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<tr>
<td>NLGN3 (neuroligin 3, postsynaptic)</td>
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<td>Tabuchi K. et al., 2007, Jamain S. et al., 2008</td>
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<td>NRXN3 (neurexin N3, presynaptic)</td>
<td>-2.1</td>
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<td>Kim, HG et al., 2008; Bourgeron T. 2007</td>
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<td>Hyperserotonemia (Altered levels of serotonin)</td>
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<td>TPH (tryptophan hydroxylase)</td>
<td>15.1</td>
<td>8.8</td>
<td>Hranilovic D. et al., 2008, Wendland JR et al., 2008</td>
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<td>GCH1 (GTP cyclohydrolase)</td>
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<td>Mitochondrial disfunction (DNA damage/caspase activation)</td>
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<td>PARP9 (ADP-ribose polymerase)</td>
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<td>PARP10</td>
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<td>PARP12</td>
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<td>PARP14</td>
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<td>Neurodevelopmental genes (reelin signaling/infectious etiology)</td>
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<td>GABRD (GABA receptor delta)</td>
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<td>McCauley, JL et al., 2004</td>
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<td>GABRG1 (GABAreceptor gamma 1)</td>
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<tr>
<td>SLC6A11 (GABA transporter 3)</td>
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<td>ADA (Adenosine deaminase)</td>
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<td>CP (ceruloplasmin)</td>
<td>17.2</td>
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<td>Fatemi et al., SH 2005</td>
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<td>IL-6*, IL-6R</td>
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<td>Smith S.E.P. et al.</td>
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<td>James SJ et al., 2006</td>
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<tr>
<td>Oxidative Stress</td>
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<tr>
<td>Mitochondrial damage!!</td>
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<td>Modulates ASD related genes! (histone deacetylase inhibition)</td>
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<tr>
<td>Activation of Learning Pathways Epigenetics</td>
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**SCFA dependant gene expression:**

- neurodevelopment,
- decreased GABA, Neurexins, Neuroligins, Reelin

Many GI expressed

**Increased Serotonin,**

- Innate Neuroinflammation,
- Oxidative Stress,
- Mitochondrial damage!!

Modulates ASD related genes!

(Histone deacetylase inhibition)

**Activation of Learning Pathways Epigenetics**
Diabetes                        Autism
Type 1 Type II
Can’t metabolize glucose                             Can’t metabolize SCFAs?
Multi- system involvement
Multiple Causes (Genes/diet/environment)
Present with Metabolic Crisis (i.e. infection)
Treatment-Carbohydrate restriction (direct/indirect) GCFD?  Inulins/carnitine/NAC
Treatment-Insulin/glyburide                          probiotics/microbiome alteration?
Multi- system approach
Fad Diets vs. Rational Evidence Based Approach to Nutrition
Feed Yer Bugs:
Less refined (hidden) carbohydrates (high fructose corn syrup)
Less white bread, pastas (propionic)- and if so more whole grains
more whole vegetables (inulins, beta glucans) prebiotic (BUT/PPA)
“Bright” foods- antioxidants
Fermented foods (yogurt, kefir, sauerkraut)
Lean meats, fish (omega 3s), eggs
Evolutionary Psychiatry - population vs individual

Are the Microbes in Charge?
Metabolism/Immune/Neurodevelopment
Mitochondrial Function/Epigenetics

Some direct/indirect advantage to behavioural trait
The future is already here…

Anxiety, Obesity, Eating Disorders, OCD, Nodding Disease, Autism
Microbial message to our “spaceship”
The world is changing- Please listen to us!!!
Meta-genomics, metabolomics, microbiome-longitudinal studies
Pre-symptomatic biomarkers – metabolic, immune, microbial
Risk reduction (pre/post natal infection/GI/gyn/obstetrics/nutrition/ID
Therapeutics (metabolic augmentors-carnitine, microbiome reconstitution)
Kilee Patchell-Evans Autism Research Group
Director - Dr. Derrick MacFabe

HUMAN TISSUES/CLINICAL
- Dr. Mohammad Alanazi (Chair)
- Dr. Afaf Al Ansary Dept. of Biochemistry, King Saud University, Yamam Al Jadaani (Jeddah)
- PPA metabolomics, oxidative stress markers in Saudi children
- Dr. Laila Al-Ayadhi, Director KSU Autism Research Treatment Centre (EEG, neurometabolic screening)
- Dr. Richard Frye-Neurology (Paed Neuro) U.of Arkansas
- Dr. B. Devryer (Ob/Gyn) Lawson, UWO
- Dr. Clive Friedman (dentistry) UWO
- Dr. Erica Claud (Neonatology) U. of Chicago - NEC

Needs to further productivity:
- Development of Twin Saudi/Canadian Center/ PAFC (UBC)
- Infrastructure/Personnel: fellowships, studentships

EPIGENETICS
- Dr. Bistra Nankova, New York Medical College
  molecular, gene arrays, tissue culture, PC12
- Dr. Edmond LaGamma, New York Medical College
  Neonatologist-Infection in Devel. Disabilities
- Dr. Marco Aztori (U. Texas) electrophysiology
- Dr. Rochellys-Diaz-Heijtz (Karolinska) SCFA CNS develop.
- Dr. Koen Venema (University Med Centre,Amsterdam) SCFA in gut

Needs to further productivity:
- Seed funding – molecular biology/lipid screening/  neonatology
- Personnel: Postdoctoral fellowships, studentship
  Simmons Foundation, US Dept of Defense, CHIR

METABOLISM
- Dr. Fred Pospisay (Emeritus) Biochem, (Ob/Gyn), UWO
- Dr. Charles McKenzie, Biophysics-Lawson, UWO
- Dr. Jim Staples, Biology, UWO
- Dr. B. Devryer (Ob/Gyn) oxidative stress, mitochondrial function, lipid profiles, cytokines
  (autism, at risk mothers)

Needs to further productivity:
- Seed funding – interface with U. of Alberta metabolomics
- Personnel: Postdoctoral fellowships, studentship
- Equipment: GC Mass Spec, clinical FA assays

METABOLIC IMAGING
- Dr. David Shoesmith-Surface Science Western, UWO
- Dr. Heng-Yong Nie, Surface Science Western, UWO
- Mary Jane Watack, Surface Science Western, UWO
  Tof-SIMS metabolic Brain/tissue imaging
- Drs. Charlie McKenzie/Tim Scholl –Lawson Research-
  fatty acid metabolic imaging

Needs to further productivity:
- Personnel: Postdoctoral fellowships, studentship
- Equipment: cryostat, tissue preparation area
- Imaging time, seed funding
- NSERC funding applied for

AUTISM RODENT MODEL-NEUROSCIENCE

Kilee Patchell-Evans Autism Research Group, University of Western Ontario

Core Faculty:
- Core Staff: Lisa Tichenoff
  - Francis Boon
  - Roy Taylor
- Students: Kelly Foley
  - Stacey Holbrook

Main studies conducted principally on site in facility:
- Neurobiology of GRAIFS (Gut Related Autism Inducing Factors)
- Behavioural rodent model (hyperactivity, OCD, perseveration, social impairment, anxiety)
- Central/peripheral/diet/colitis
- Developmental studies
- Genetic ASD model (i.e. GABARB ko mice- Dr. Tim Delorey)
- Pathology, Immunology, in Situ
- Tissues (brain, liver, gut, blood, placenta, liver, muscle, stool)

Needs to further productivity:
- Personnel: stable salaries, chairs, postdoctoral fellowships, studentships
- Equipment: cryostat, tissue preparation area
- Imaging time, seed funding

MICROBIOLOGY
- Dr. Emma Allen-Vercue, University of Guelph-microbiology (clostridia from ASD patients), metabolic profiling of microbiome isolates, synthetic stool
- Dr. Terry Van Raay, University of Guelph-teratogenicity of clostridial isolates (zebrafish model)
- Dr. Sydney Finegold, UCLA infectious disease, bacterial isolates from ASD patients
- Dr. Gregor Reid, Jeremy Burton (Lawson- Probiotics)
- Dr. Ingrid Surono (Bogor, Indonesia)-probiotics, GI
- Dr. Lee Yuan Kun (U. of Singapore)-Asia-microbiome
- Dr. Tore Midvedt (Karolinska) microbiome/development

Needs to further productivity:
- Seed funding
- Personnel: Postdoctoral fellowships, studentship
- Partnership- Food/Agriculture (Fed, Govt.-Guelph)

EDUCATION/PHILANTHROPY
- Dr. Suzanne Lewis (Genetics/ Paeds- ASD-CARC) Director PAFC (clinical patient base)
- Dr. Xudong Liu, Genetics (Queen’s University)
- Dr. Helen Ouellette-Kuntz, Epidemiology
- Dr. Clive Friedman, Paed. Dentistry (Western)
- Dr. Garth Smith, Developmental Paeds
  - Genetic/environmental interactions, Somali population
  - ASD/ARDC consortium- 8000 subjects

Needs to further productivity:
- Seed funding /collaboration with Life Science Inst.
  UBC)
- Personnel: Postdoctoral fellowships, studentship
- linkage to Beijing Genomics Institute (genetics) and PAFC

POPLATIONS/GENETICS
- Dr. Stephen Chan - GoodLife Fitness/Special Projects
- Dr. Megan Cameron - GoodLife Fitness/Special Projects
- Stephen Chan - (Dasapof) and Niall Wallace (Infonaut)
  - Surveillance of clostridial infections in obstetrical/paediatric populations- interface with UBC
- Research/Clinical Education, video conferencing, liaison with ministry of Public Health
- Fatima Kedyie- Somali expatriates
- Sergio and Wendy Cocchia- PAFC

Needs to further productivity:
- Personnel: translation, English/French/Somali/Arabic
- Government awareness/lobbying
Active uptake to CNS

SCFA G protein receptors
Neurotransmitter Synthesis and release
Increased intracellular Calcium

Neuroinflammation/neurodevelopment

Gap Junction Closure

Short Chain Fatty Acid Bacterial Fermentation Products

Gut motility and inflammation
Malabsorption

Repetitive/antisocial behaviour/Seizure

Altered lipid/membrane metabolism

Mitochondrial function/oxidative stress
Altered gene expression