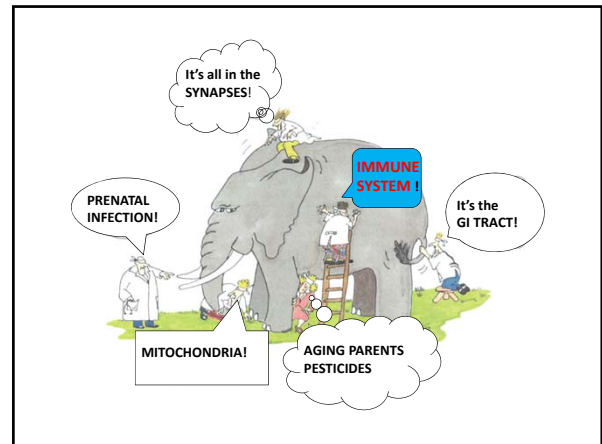


## ASD: NEUROINFLAMMATION -- OR IMMUNE DYSREGULATION?

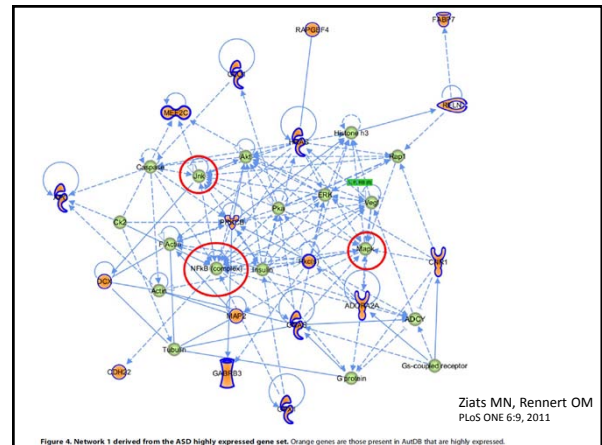
Andrew W. Zimmerman, MD  
UMass Memorial Medical Center  
UMass Medical School  
Worcester, MA, USA  
A.R.I. Webinar  
June 11, 2014

*Financial Disclosures: None*



## OUTLINE

- Review immune findings in Autism Spectrum Disorder
  - Immunogenetics: gene expression profiles, HLA
  - Maternal and child autoantibodies: causes or effects?
  - Microglial activation: neurotoxic or neuroprotective?
- Neuroglial functions: a broader perspective
- Prenatal insults: reprogramming -- arrested development?
- Immunomodulatory therapies – Rx at which level?
- Cellular metabolic and synaptic dysfunction: the “fever effect”



Pediatric Neurology 2006;35:303-307

## HLA-DR4 in Families With Autism

Li-Ching Lee, PhD, Andrea A. Zachary, PhD, Mary S. Leffell, PhD,  
Craig J. Newschaffer, PhD, Karla J. Matteson, PhD, John D. Tyler, PhD, and  
Andrew W. Zimmerman, MD

Odds Ratio (C.I.)

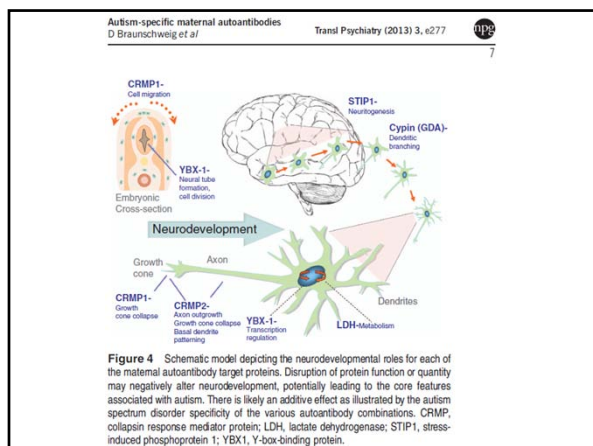
**DR4 - Tennessee Mothers:** **5.54** (1.74, 18.67)  
Fathers: 1.57 (0.44, 5.42)  
Children: **4.20** (1.37, 13.27)

AGRE (USA) Mothers: 1.10 (0.47, 2.49)  
Fathers: 0.94 (0.40, 2.20)  
Children: 0.94 (0.40, 2.20)

## Cytokines-plasma of children

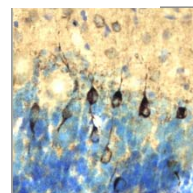
Study Description	Reference
Elevated levels of IL-1b, IL-6, IL-8 and IL-12p40. Associated with regression	(Ashwood, et al., 2011b)
Increase in chemokine MCP-1, Rantes and Eotaxin levels in ASD subjects compared to age-matched typically developing controls. An association between increases chemokines levels with aberrant behaviors.	(Ashwood et al., 2011c)
In male ASD subjects, an increase in cytokines IL-1beta, IL-1RA, IL-5, IL-8, IL-12(p70), IL-13, IL-17 and GRO-alpha.	(Suzuki et al., 2011)
Increase in leptin levels in ASD subjects compared to age-matched controls.	(Ashwood et al., 2008b)
Increase in macrophage migration inhibitory factor (MIF) in ASD subjects compared to age-matched controls.	(Grigorenko et al., 2008)
Decrease in TGF-beta in subjects with ASD compared to controls.	(Ashwood et al., 2008a; Okada et al., 2007)
Increase in IL-12 and IFN-gamma in ASD subjects compared to age-matched controls.	(Singh, 1996)





## Autoantibodies in Children

- Intense Golgi cell staining in ~21% of patients with ASD compared with 0% of normal controls (BBI, 2008). This staining pattern correlates with a ~52 kDa protein by blot (Wills et al, 2008).

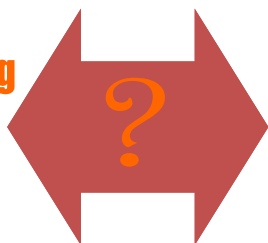


- In addition to antibodies against the cerebellum, there is intense reactivity to proteins in the thalamus and hypothalamus (Cabanlit et al, ANYAS, 2007).

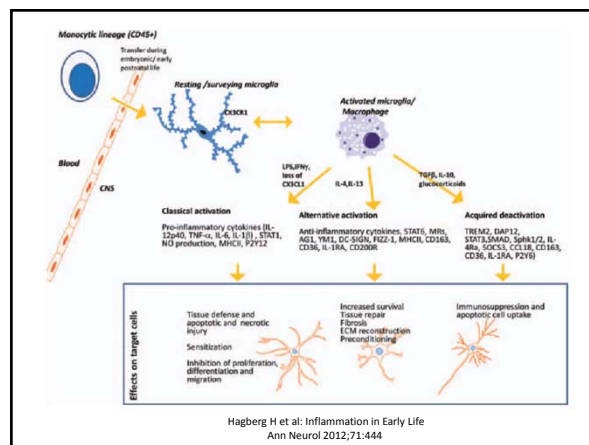


Van de Water, J. 2008

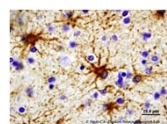
**Circulating  
Immune  
System**



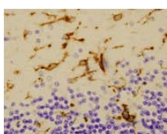
**CNS**



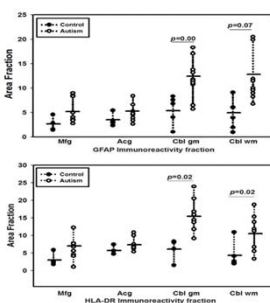
## Neuroglial Activation in Autism



Astroglia activation



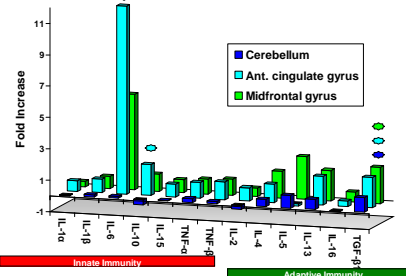
Microglia activation



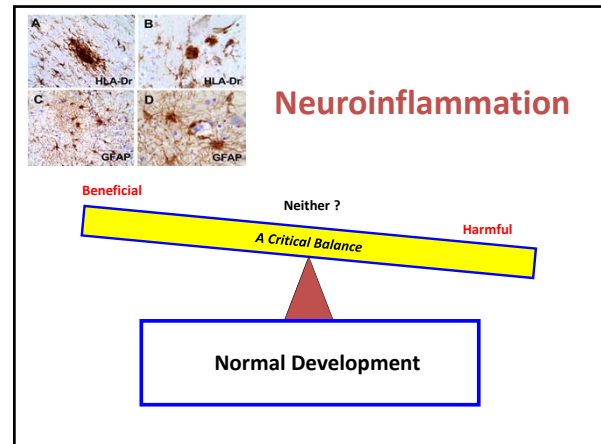
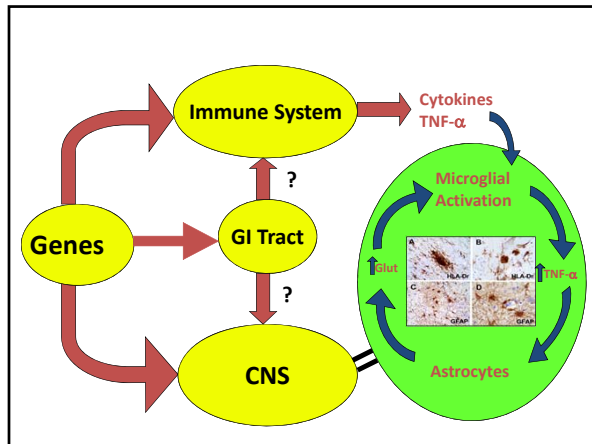
JHU/Neuroimmunopath/CA Pardo

Vargas DL et al. Ann Neurol 2005

## Pattern of increased cytokines in brain regions of patients with autism



Vargas DL et al. Ann Neurol 2005



Neuroscience and Biobehavioral Reviews 38 (2014) 160–172

Contents lists available at ScienceDirect

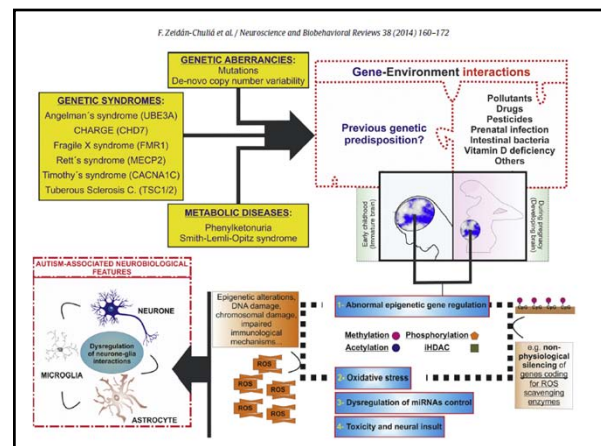
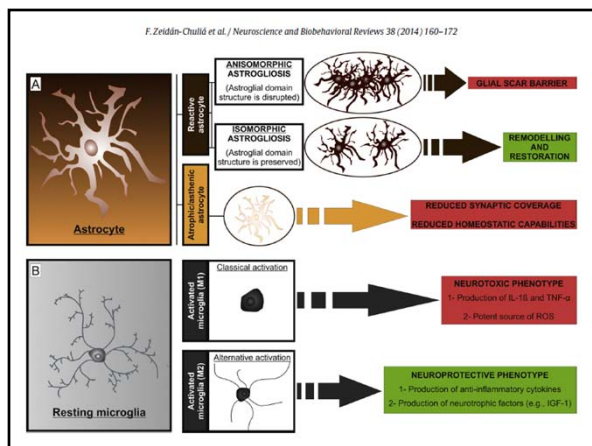
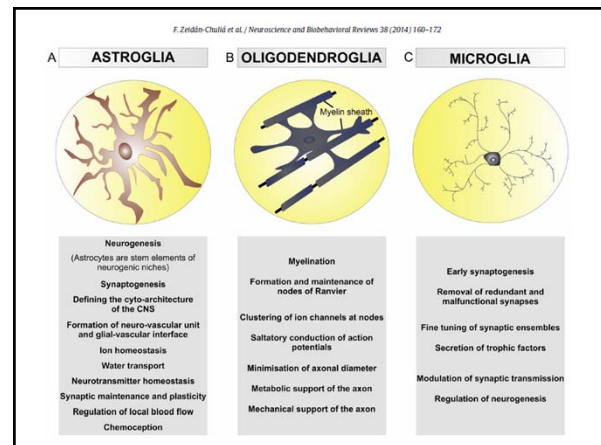
Neuroscience and Biobehavioral Reviews

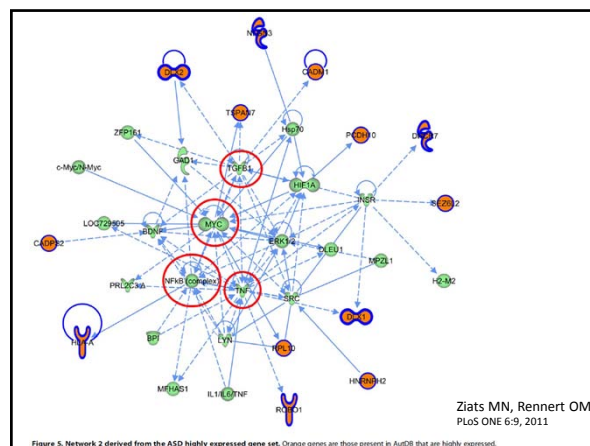
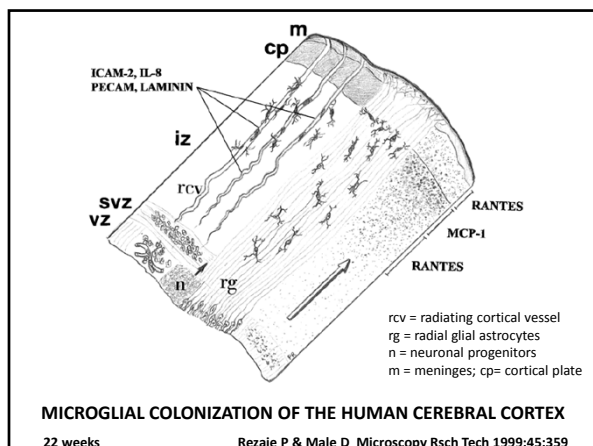
Journal homepage: [www.elsevier.com/locate/neubiorev](http://www.elsevier.com/locate/neubiorev)

Review

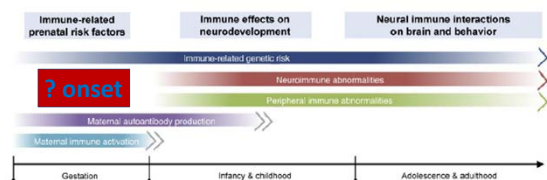
The glial perspective of autism spectrum disorders

Fares Zeidán-Chuliá<sup>a,\*</sup>, Alla B. Salmina<sup>b</sup>, Natalia A. Malinovskyaya<sup>b</sup>, Mami Noda<sup>c</sup>, Alexei Verkhatsky<sup>d,e,f</sup>, José Cláudio Fonseca Moreira<sup>g</sup>





## IMMUNE DYSREGULATION IN ASD



Hsiao, EY Int Rev Neurobiol 2013;113:269

## IMMUNOMODULATION ?

- IVIG
- Prednisone
- Minocycline
- Pioglitazone
- Infliximab
- Experimental models?
  - VPA
  - fraX mice
  - Bone marrow transplant
  - Stem cells

## Fever in Children with Autism

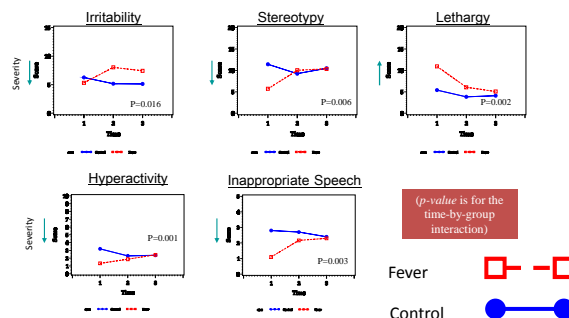


30 children with autism, *with fever*;  
30 age-matched with autism, *afebrile*.

Overall, 83% of children improved on at least one domain of the A.B.C. during fever: irritability, stereotypy, hyperactivity, and inappropriate speech.

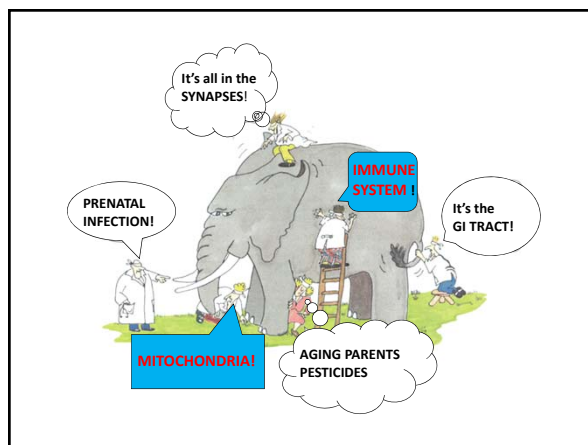
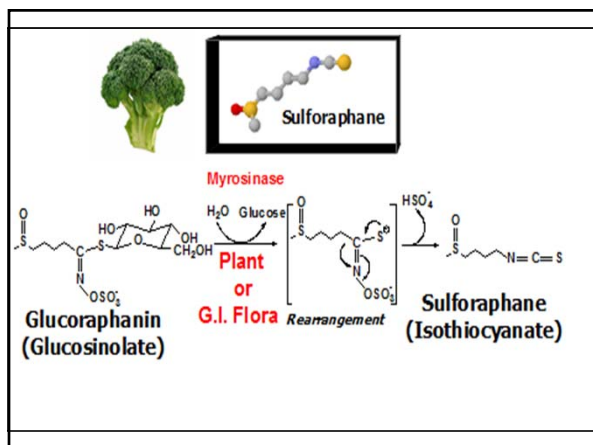
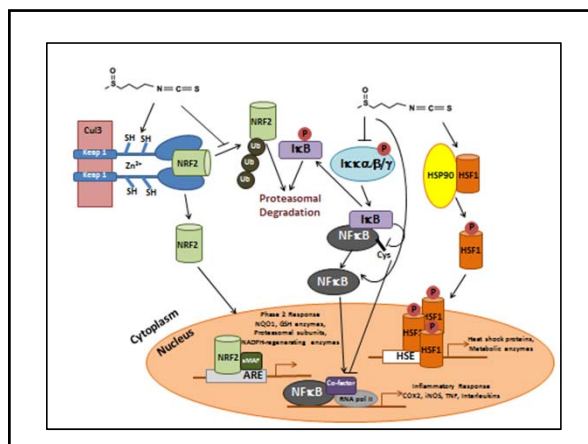
Curran LK et al, Pediatrics 2007

## Results: Mean ABC Subscale Scores and RM-ANOVA Findings (n=30 pairs)



### Biochemical and Metabolic Abnormalities in ASD Compared to Neurotypical Children

- Oxidative Stress Increased and Antioxidant Enzymes Lower
- Total Glutathione Levels are Lower
- Ratio of Oxidized to Reduced Glutathione Levels is Higher
- Capacity for Reducing Glutathione is Impaired
- Enhanced Lipid Peroxidation
- Increased Neuroinflammation in Selected Brain Regions
- Elevated NO Synthesis
- Impaired Mitochondrial Function and Energy Generation
- Nrf2 Levels are Depressed and Genes under its Control are Lower

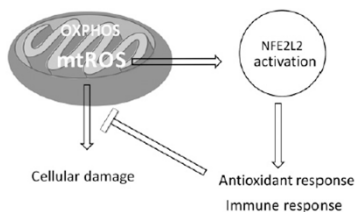


## PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

### Deficits in Bioenergetics and Impaired Immune Response in Granulocytes From Children With Autism

Eleonora Napoli, Sarah Wong, Irva Hertz-Picciotto and Cecilia Giulivi  
*Pediatrics*; originally published online April 21, 2014;  
 DOI: 10.1542/peds.2013-1545



### Metabolism of Granulocytes in Children with ASD

	ASD	Neurotypical development	p
Resting O <sub>2</sub> Uptake	0.38±0.09	1.1±0.3	.05
NADH Oxidase	4.6±3.1	10.9±4.9	.01
Succinate Oxidase	1.6±1.2	5.2±2.0	.001
ATPase	46±28	123±54	.005
Nrf2 Gene Express Level	0.45±0.01	1.00±0.03	.01
[nmol x (min x mg protein) <sup>-1</sup> ]			

(Napoli et al, *Pediatrics* 2014)

**POSSIBLE CAUSES OF  
NEUROINFLAMMATION AND  
IMMUNE DYSREGULATION IN AUTISM**

- A. EXOGENOUS: e.g., infections, valproate, "environmental factors"
- B. AUTOIMMUNE ACTIVATION
- C. ALTERED (IMMUNE) GENE EXPRESSION AND BRAIN DEVELOPMENT
- D. CELLULAR METABOLIC DYSFUNCTION
- E. All of the above.

**REINING IN AUTISM**

WHAT'S YOUR  
OBSESSION?  
-COM



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Diana Vargas	Paul Talalay
Harvey Singer	Kanwaljit Singh