

Potential Treatment of Autism with Traditional Chinese Medicine

NAJMS
August 18, 2013

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Autism Prevalence Is Now At 1 In 50 Children

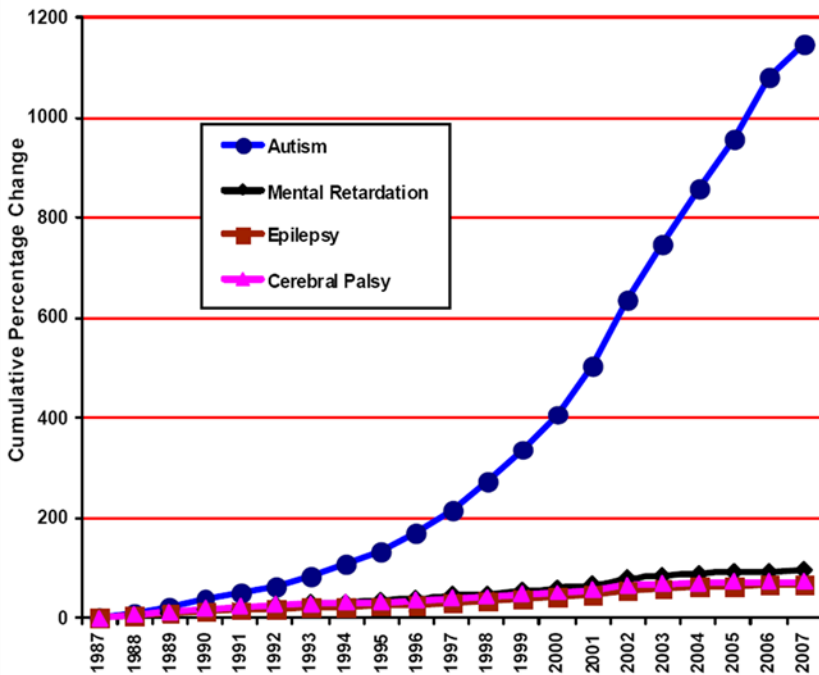


In 2002 the Center for Disease Control estimated that autism affected about 1 in 150 children. By 2012 the CDC estimate had increased to 1 in 88. Now, according to the latest revision of the estimate recently released, autism affects 1 in 50 children.

Autism: The Facts

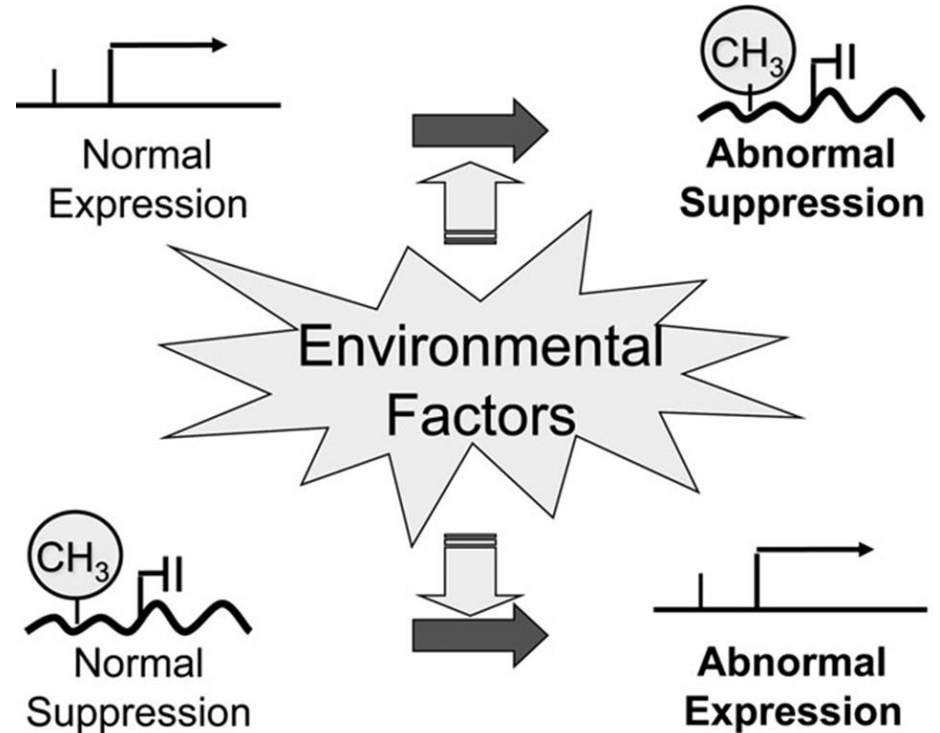
- Fastest growing developmental disability
- Annual growth 10-17%
- 1/10000 in 1960's, now **1/50** in USA
- More children was diagnosed with Autism this year than with Cancer, diabetes and AIDS combined
- Boy: girl 4:1
- Autism cost nation over **\$35 billion per year**
- **CDC has called autism a national public health crisis**

Intrusion of an experience for you and for many others



2009 California report: http://www.dds.ca.gov/Autism/docs/AutismReport_2007.pdf

**1200% increase in
reported cases**



**Gene expression
impacted by environment**

Autism is a Whole-Body, Whole-System Condition

- Seizures (~30%+)
- Cognitive deficits
- Sensorimotor abnormalities
- Disordered sleep
- Immune impairments
- GI distress
- Food allergies
- Systemic metabolic disturbances

Autism: The Facts

How much do we know about the etiology of Autism?

Identified etiology is only **10%!**

Do we have clues for the rest of 90%?

Autism and Genes

Brain Pathology-Selective area/Neurotransmitters

GI dysfunction

Immune dysfunction

Impaired detoxification system

Toxic exposure/increased burden

Inflammation and oxidative stress

:

The immune response in autism: a new frontier for autism research.

J Leukoc Biol. 2006 Jul;80(1):1-15. Epub 2006
May 12.

Ashwood P, Wills S, Van de Water J.

UC Davis, Wet Lab Building, 50th Street, Sacramento, CA 95817.

(partial abstract)

There is potential that such aberrant immune activity during vulnerable and critical periods of neurodevelopment could participate in the generation of neurological dysfunction characteristic of ASD. **This review will examine the status of the research linking the immune response with ASD.**

Immune dysfunction in Autism

1. Allergy problem/Autoimmune dysfunction

Eczema as marker of Th2 shift

Allergic rhinitis, seasonal exacerbation

Asthma

Food allergy

Cerebral autoimmunity, antibodies detected, Myelin basic Ab, etc

2. Chronic low grade infections

Bacteria, strep. elevated urinary bacterial metabolites in 50% patients

PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcus) OCD

Fungal, dermatitis, candidiasis

Virus, MMR, HSV, EBV, HPV warts,

Mycoplasma, Gulf War phenomenon

Lyme

3. Chronic inflammation

Cytokines elevation

4. Immunogenomic profile

IL-1beta almost 100% with mutation in autism

TH-1 cytokine—TNF-alpha, viral infection and cancer

TH-2 cytokines--- IL-4,6,10,13, allergy/atopy

Autism: New Research Frontier

- **Autism represents an immunological and inflammatory disorder with definable biomarkers, mainly targeting GI and Brain**

The Every Day of Some Autisms

What we need:
**Clinical labs that will
detect and report
pertinent gut
pathogens**



Gut dysfunction in Autism

Chronic diarrhea

Food allergy/sensitivity

Endoscopy: inflammation

Infection: bacteria, yeast, virus

Stool analysis: Maldigestion and Malabsorption

Leak bowel syndrome

GI enzyme deficiency, Secretin, DDP-IV

Urinary peptides

Nutritional deficiency

Low B6 50%

Low Magnesium almost 100%

Low zinc almost 100%

Low selenium, vitamin A, biotin, B1, B3, B5, B12, Vitamin C,

Immune dysfunction in Autism

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J. Leukas et al., Biol. 2006, 80 (1): 1-15.

Immune dysfunction in Autism: A New Frontier for Autism Research

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Immunological profile

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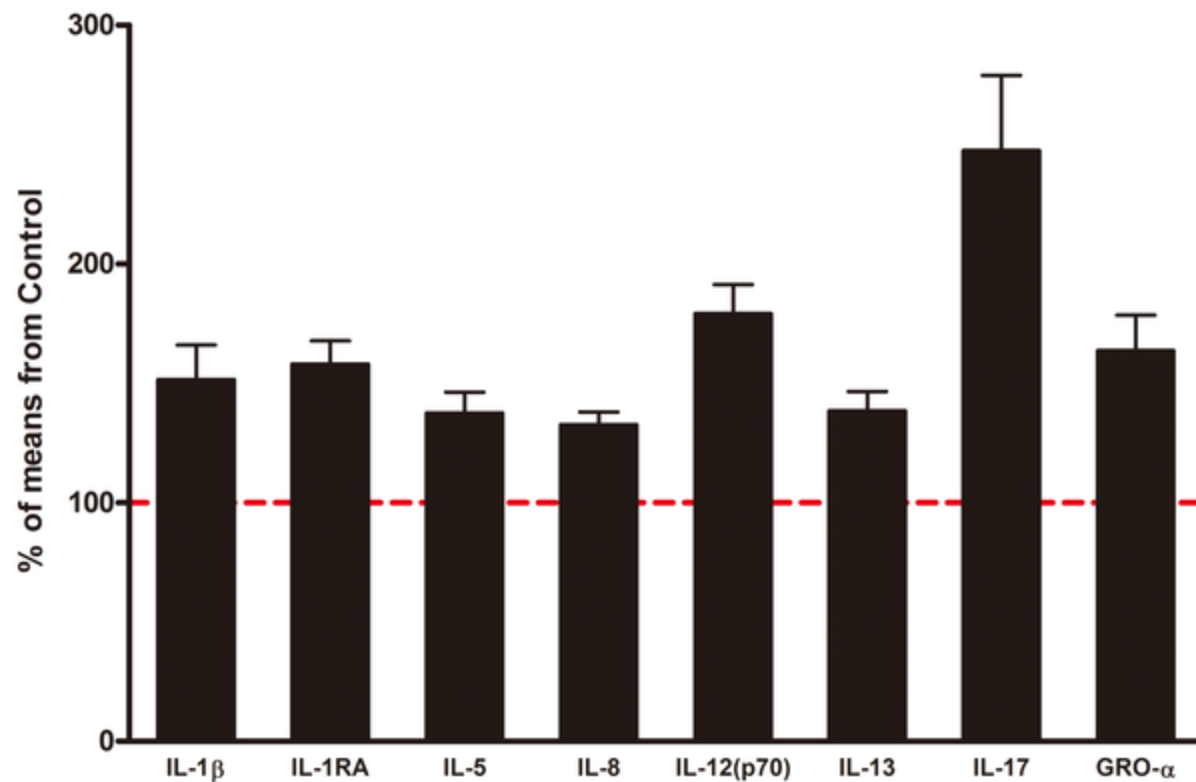
Mycoplasma

Lyme

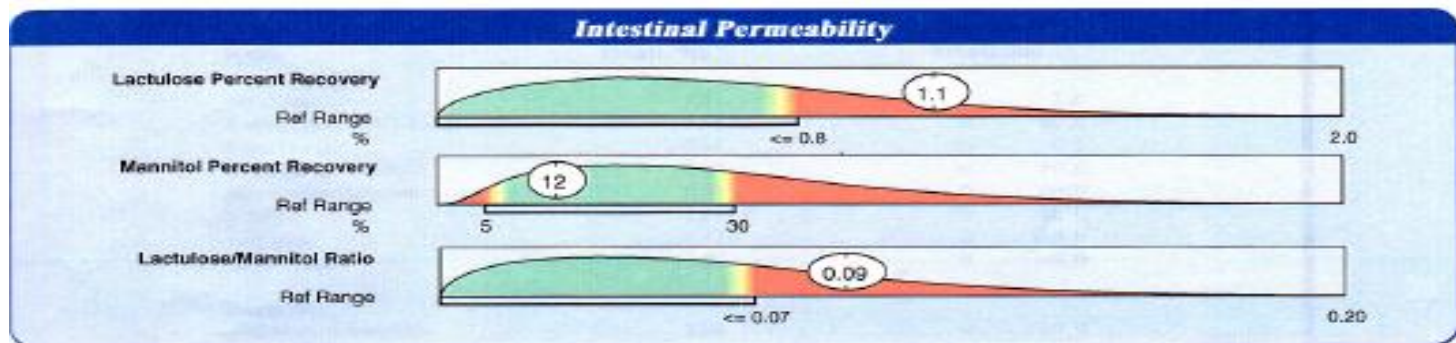
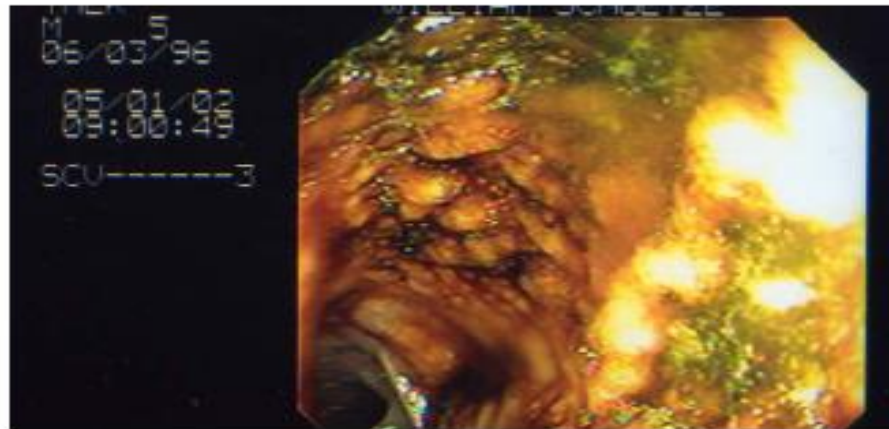
3. Chronic inflammation

Cytokines elevation

Changes of Plasma Cytokine Profiles in Subjects with High-Functioning Autism Spectrum Disorders



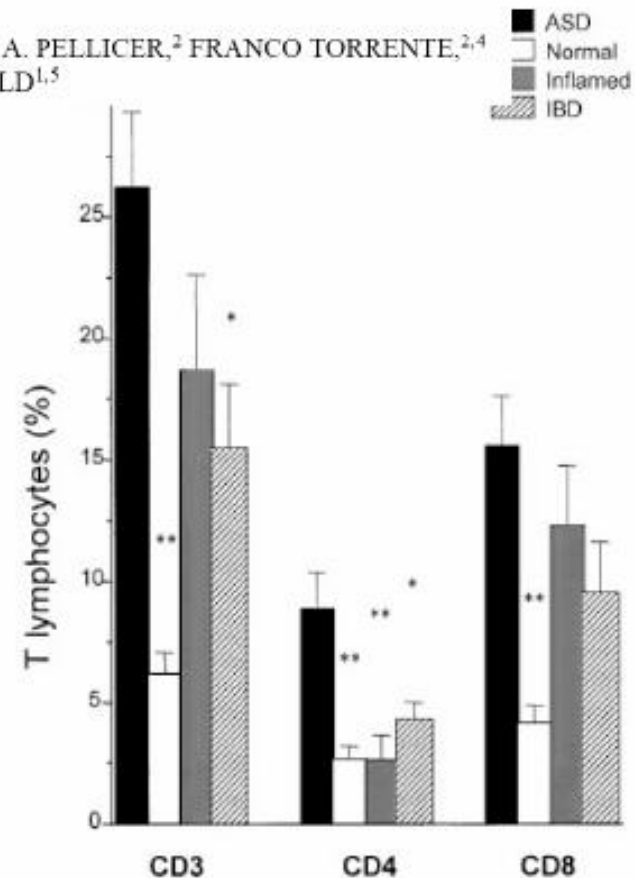
Intestinal immune changes lead to *increased intestinal permeability*



Intestinal Lymphocyte Populations in Children with Regressive Autism: Evidence for Extensive Mucosal Immunopathology

Journal of Clinical Immunology, Vol. 23, No. 6, November 2003 (© 2003)

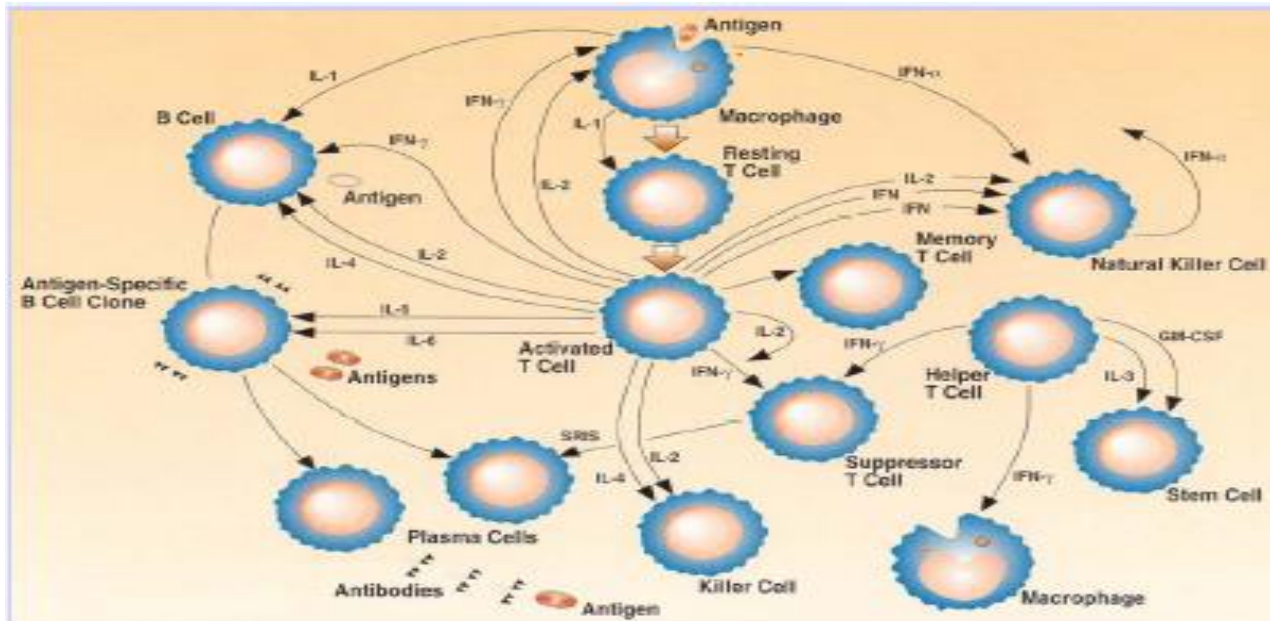
PAUL ASHWOOD,^{1,2,6} ANDREW ANTHONY,^{1,3} ALICIA A. PELLICER,² FRANCO TORRENTE,^{2,4}
JOHN A. WALKER-SMITH,² and ANDREW J. WAKEFIELD^{1,5}



PRBC testing often reveals deficiencies in zinc and selenium

NUTRIENT ELEMENTS							
ELEMENTS	RESULT µg/g	REFERENCE RANGE	PERCENTILE				
			2.5 th	16 th	50 th	84 th	97.5 th
Calcium	13	8- 31					
Magnesium	53	36- 64					
Potassium mEq/g	85	65- 95					
Phosphorus	662	480- 745					
Copper	0.87	0.52- 0.89					
Zinc	6.2	8- 14.5					
Iron	909	745- 1050					
Manganese	0.018	0.007- 0.030					
Chromium	0.0024	0.0003-0.0060					
Selenium	0.10	0.19- 0.38					
Boron	0.012	0.01- 0.110					
Vanadium	0.0003	0.0001-0.0020					
Molybdenum	0.0023	0.0005-0.0020					

- Tells us where to begin with supplements
- Easy to follow over time



Immune dysregulation Especially in the GI tract and Brain

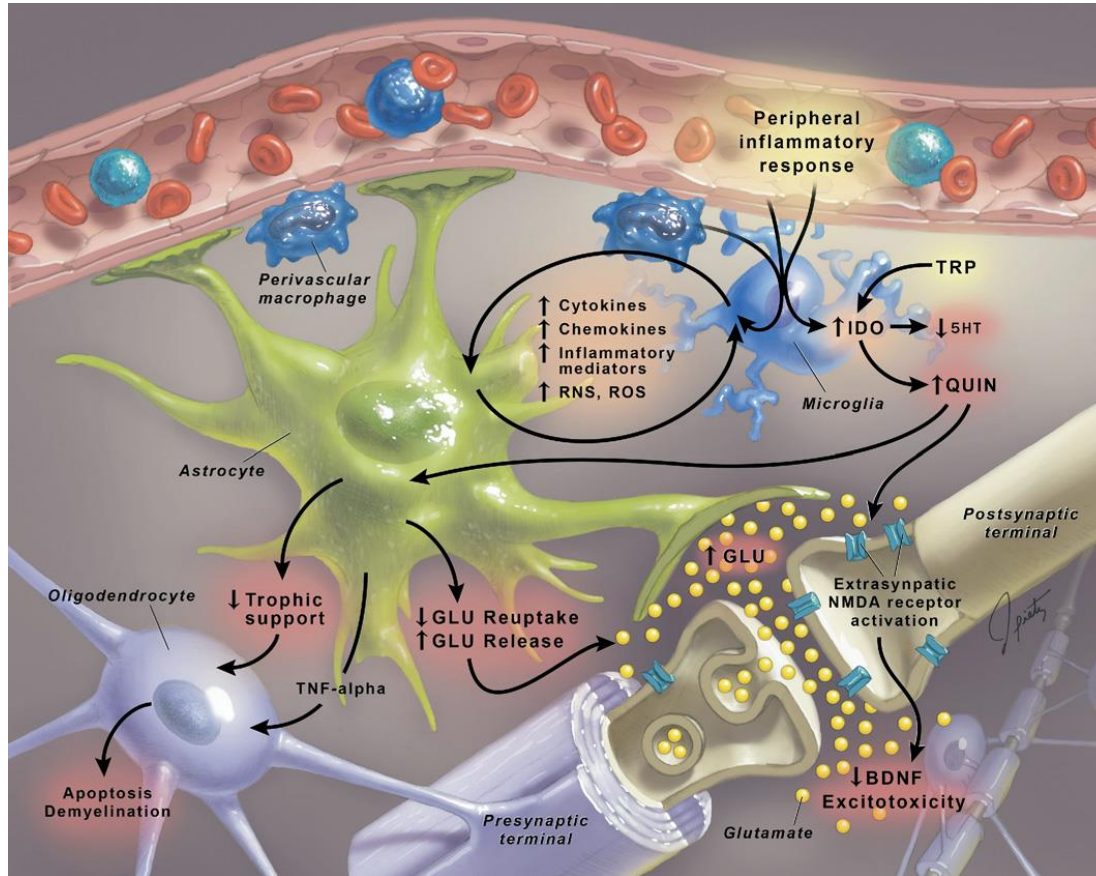
Brain Inflammation in Autism

- Neuroglial Activation particularly in cerebellum**
- Responses are primarily from Innate Immunity**
- Adaptive immunity markers like T cells or antibody reactions not found**
- Cytokines significantly elevated in brain and CSF of autistic patients**

Pro-inflammatory: MCP-1, IL6 and IFN γ

Anti-inflammatory: TGF β 1

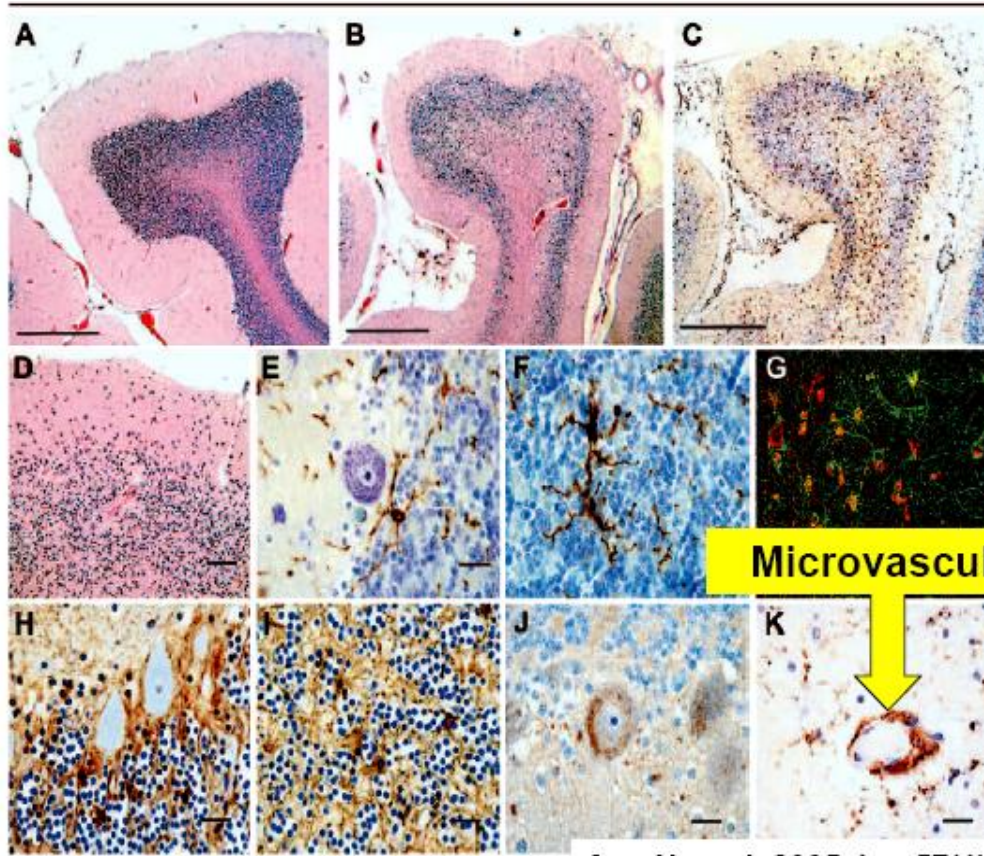
Brain cells in inflammation



- Excitatory chemicals created by activated glial cells
- Normal housekeeping functions of glial cells get neglected
- Chronic inflammation is irritating and promotes excitotoxicity
- Chronic inflammation can cause damage

Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression.

Miller et al., BIOL PSYCHIATRY 2009;65:732–741



Ann Neurol. 2005 Jan;57(1):67-81

Neuropathology of Brain

1. Enlarged brain size in autistic children

Autopsy data: 5-13 years old, fresh brain weight increase by 100-200g when compared with expected age and sex, 20% head circumferences over 97th percentile, mostly above average.

2. Overgrowth and enlargement of white matter

Axon and myelination process (Herbert, MGH)

3. Evidence of inflammation and oxidative stress in autistic brain tissue from childhood and middle age (Ann Neurol 57:67-81,2005)

4. impairment in synaptic function [N A J Med Sci. 2011;4(3):112-115.].....

Brain Inflammation in Autism

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Responses are primarily from Innate Immunity

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Pro-inflammatory: MCP-1, I-L6 and IFN γ

Anti-inflammatory: TGFbeta1

Autism Treatments:

Traditional:

Behavioral and educational training
Medications

Biochemical and Alternative

Diet and nutritional supplement
Treatment for infection
Chelation
Immunomodulation: LDN, Actos
RNA therapy
TMS
Stem cell

Current Medications for Autism

There is no known cure for autism and not everyone with Autism has the same symptoms, and not all symptoms can be treated with the same drugs.

Most often, the prescription is intended to address specific symptoms such as anxiety, depression, mood swings (bipolar disorder), obsessions, compulsions, inattention, and hyperactivity.

SSRIs

Antipsychotics

Anticonvulsants

Stimulants.

Because these medications give only symptomatic relief, and there is a large individual differences, therefore clinical improvement is quite limited.

Osteoarthritis

- It is estimated that Osteoarthritis (OA) alone will reach 7 billion and the total market size for arthritis drug will reach 20 billion in 2010.
- Modern COX2 type anti-inflammatory drug, such as (Vioxx) was recalled by FDA in 2004 and currently there is no effective prescription drug for OA.

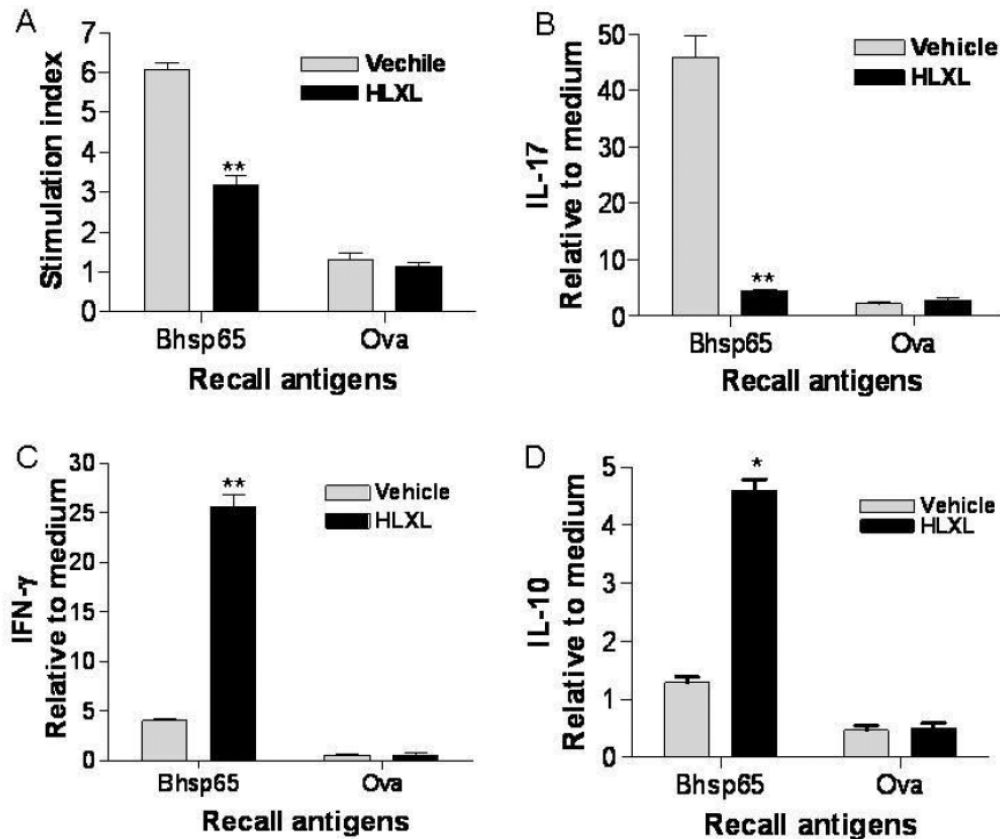
Traditional Chinese Medicine (HLXL) for Osteoarthritis

**HLXL (Huo-Luo-Xiao-Lin Dan): A Traditional Chinese Remedy
which consists of 11 herbs for treatment of arthritis**

**HLXL has been studied in the US for over 10 years and funded
continuously by NIH (NCCAM-AT-P01-002605)**

HLXL is under Phase II Trial (IND#70324) in the US

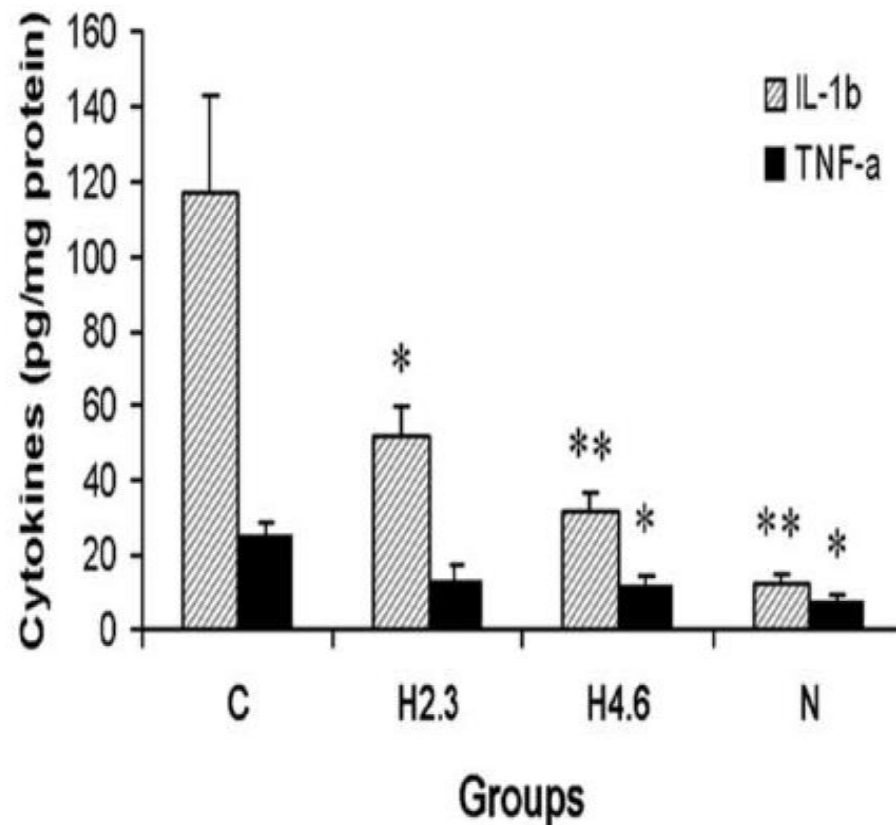
HLXL modulates the T cell proliferative and cytokine responses to Bfsp65 of arthritic LEW rats.



LNC of arthritic rats harvested on d 7 after initiation of the daily feeding of HLXL or water were tested for their T cell proliferative (A) and cytokine response (B-D) to antigenic re-stimulation with Bfsp65 in vitro. Ova served as the control antigen.

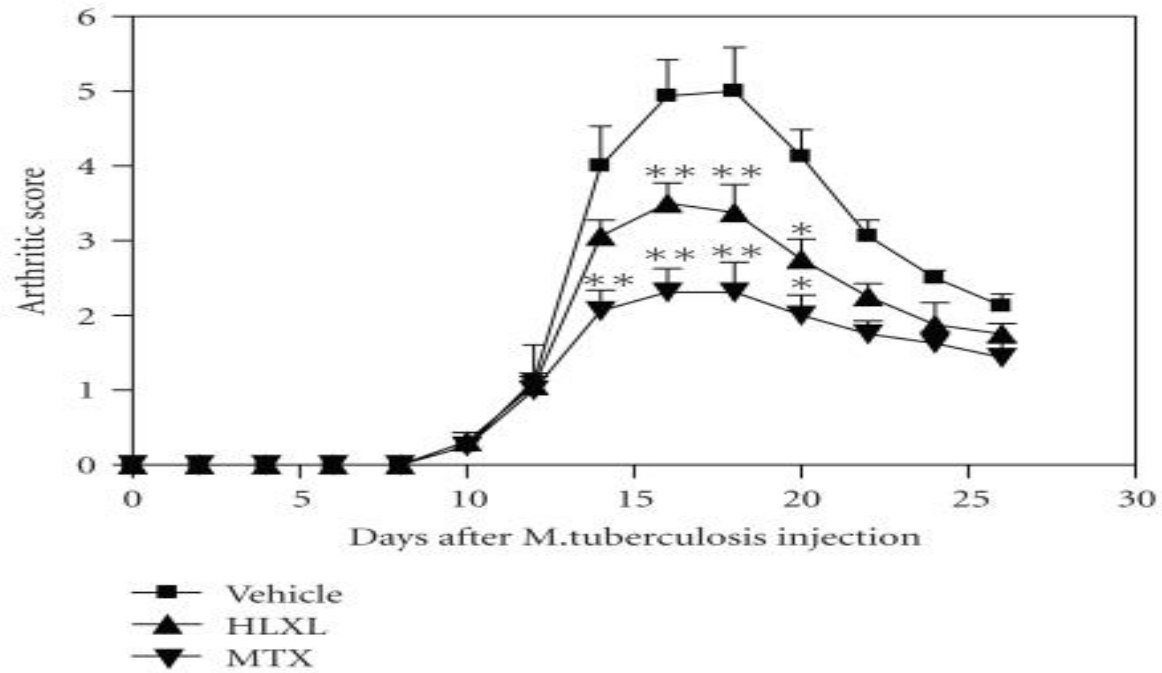
Effect of HLXL on IL-1 β and TNF- α levels (pg/mg protein, Mean \pm S.E.) 25 days post-CFA injection.

Tissue was obtained from four groups of rats: group N (no arthritis + vehicle treatment, n=4), group H4.6 (arthritis + HLXL treatment at 4.60g/kg/day, n=7), group H2.3 (arthritis + HLXL treatment at 2.30g/kg/day n=6), and group C (arthritis + vehicle treatment n= 6). Data showed that both IL-1 β and TNF- α increased significantly in local tissue following development of arthritis. However, after HLXL treatment, local tissue IL-1 β and TNF- α decreased significantly, *p<0.05 and **p<0.01, compared to the

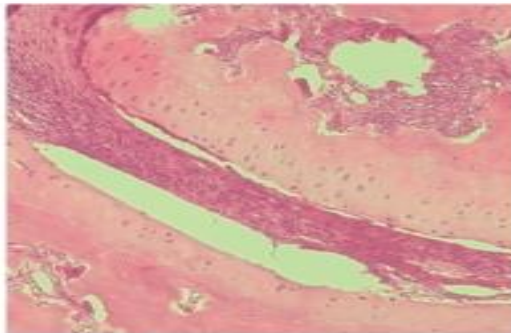


Effect of HLXL on Arthritis in Rats

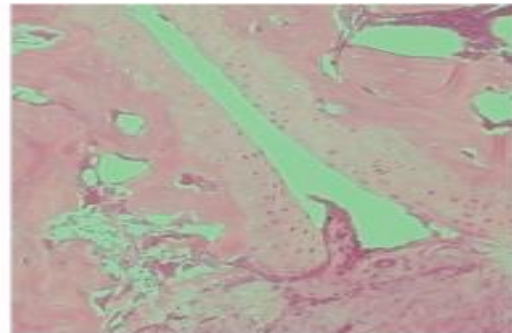
(Arthritic Scores: Mean \pm S.E., n = 4/group)



(a)

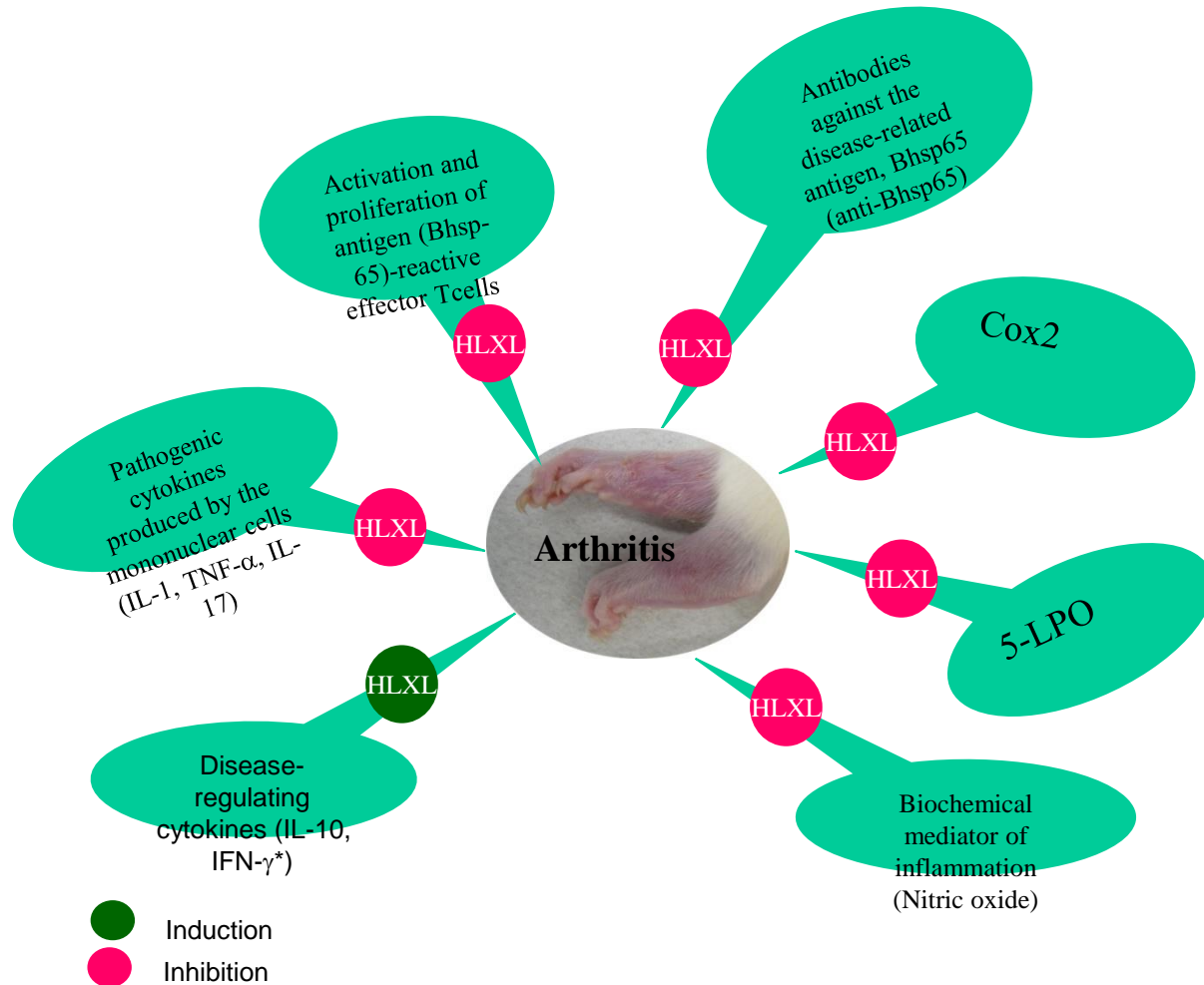


(b)



(c)

HLXL: Mechanism of Actions



TCM for Treatment of Human Diseases

1. A large number of bioactive natural products with medium potencies vs highly potent single chemical entity
2. A multi-components and multi-targeted vs single targeted approach
3. Re-discovery the wisdom of traditional Chinese medicine

Summary

- **Autism represents an immunological and inflammatory disorder with definable biomarkers, mainly targeting GI and Brain**
- **Application of clinical measures to address the abnormalities identified by the biomarkers would be a viable approach for treatment of Autism**
- **Evidence based TCM with immune-modulatory and anti-inflammatory activities such as HLXL may have the potential as an alternative treatment for Autism**

Acknowledgements

Harvard Medical School/Beth Israel Deaconess
Medical Center
Dr. Xuejun Kong, MD

University of Maryland
Dr. Brian Berman
Dr. Kamal Moudgil
Dr. Lao Licing

Harvard Medical School/McLean Hospital
Dr. David Y-W. Lee
Dr. Ma Zhongze
Dr. Liu Yanze

NIH/NCCAM: P01-AT-002065