Unlocking Neuropsychiatric Disease In Children: PANDAS and PANS

Madeleine W Cunningham,Ph.D.
University of Oklahoma Health Sciences Ctr

SPEAKER DISCLOSURES

Grant Support :

National Heart Lung and Blood Institute

American Heart Association

National Institute of Mental Health

American Diabetes Association

Oklahoma Center for the Advancement of Science and Technology

International OCD Foundation

PepsiCo/Global Giving

David Judah Fund - Harvard University

Autism Speaks

Autism Research Institute

FINANCIAL AFFILIATION: Moleculera Labs, Oklahoma City, OK
Weislab, Sweden

Group A Streptococcal Diseases

- Pharyngitis
- Impetigo
- Cellulitis
- Necrotizing Fasciitis
- Scarlet Fever
- Septicemia
- Acute Glomerulonephritis
- <u>**Acute Rheumatic Fever**</u>

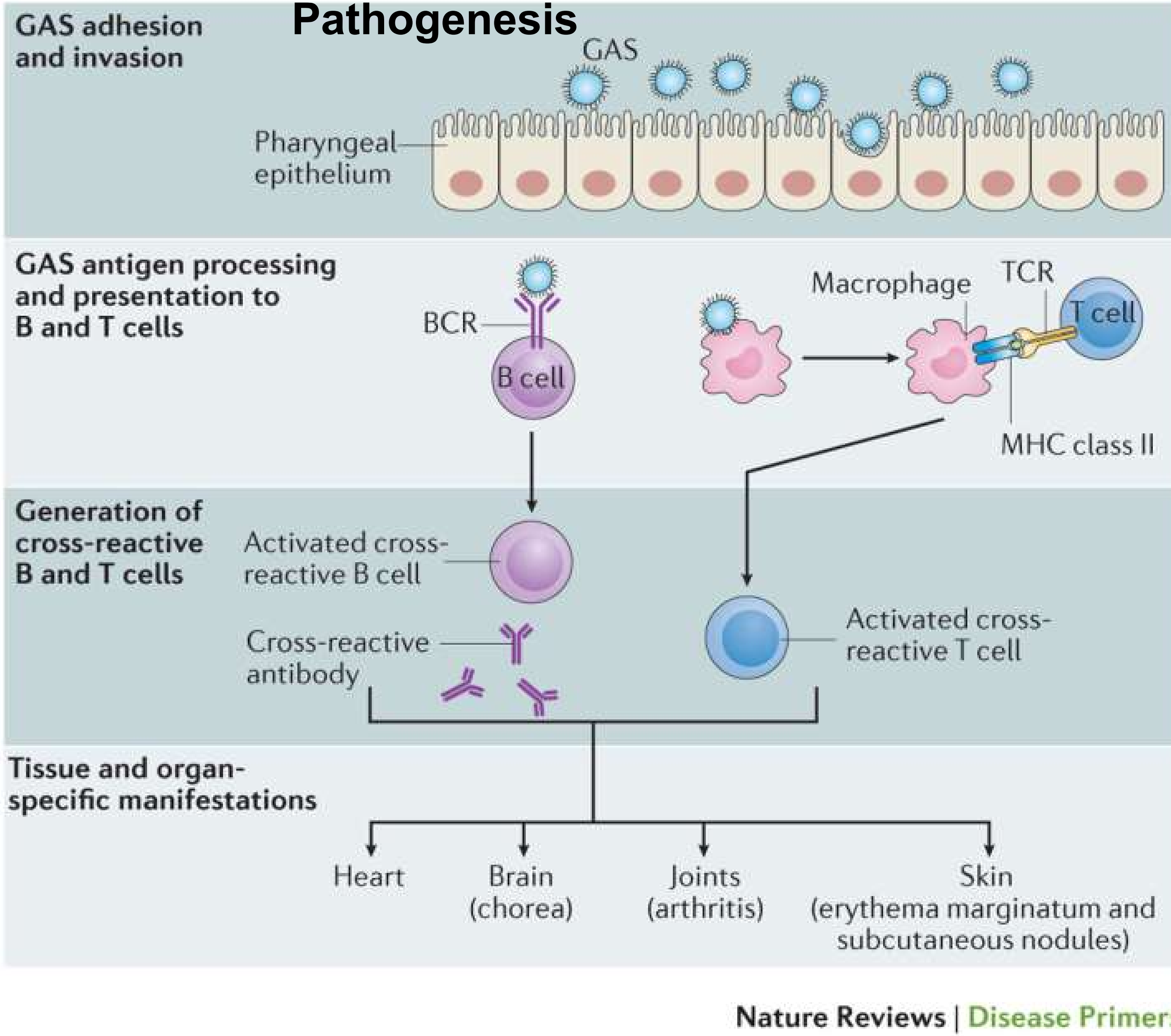
EM from VA Fischetti

Major Manifestations of Acute Rheumatic Fever

- Polymigrating Arthritis
- Carditis
- Sydenham Chorea
- Erythema marginatum
- Subcutaneous Nodules

Gewitz, M. H. *et al.* Revision of the Jones Criteria for the Diagnosis of Acute Rheumatic Fever in the Era of Doppler Echocardiography: A Scientific Statement From the American Heart Association. *Circulation*. 131; 2015.

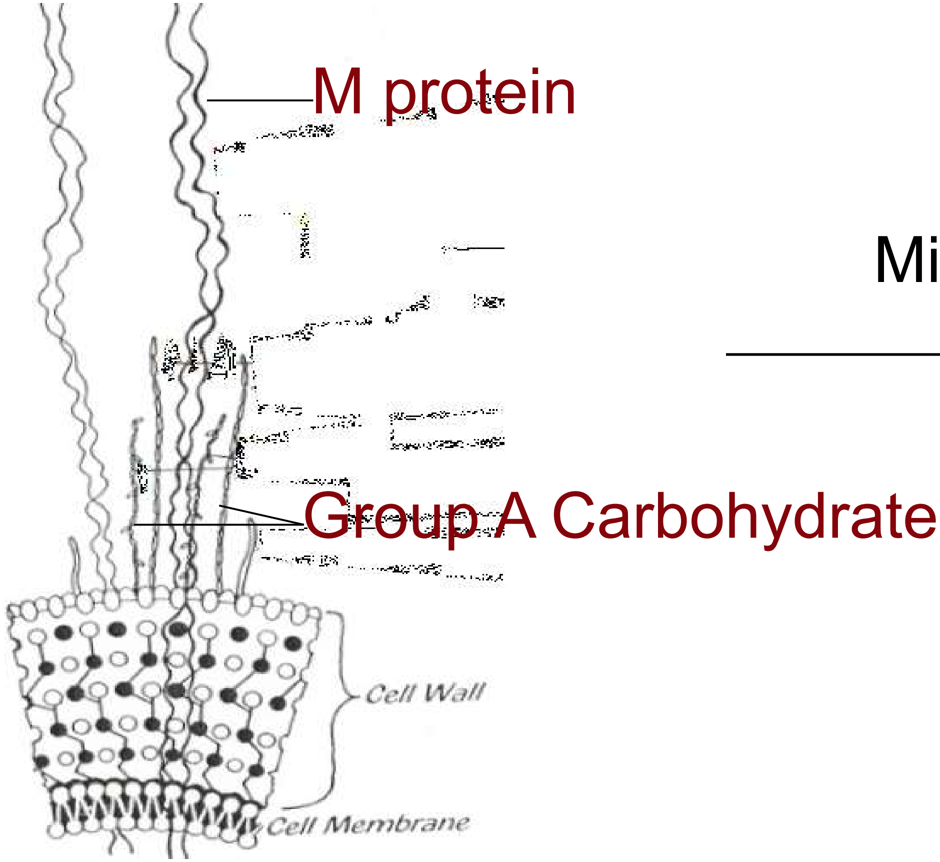
Pathogenesis



Carapetis, JR, A Beaton, MW Cunningham *et al.* (2015) Acute rheumatic fever and rheumatic heart disease Nature Reviews: Disease Primers doi:10.1038/nrdp.2015.84

Molecular Mimicry

Sharing of antigenic determinants between host and invading microorganism



Streptococcal Cell Wall

Mimicry

Heart (carditis)
[cardiac myosin/laminin]
Joint (arthritis)
Brain (chorea)
[lysoganglioside/tubulin]

Sydenham Chorea and Neuropsychiatric Disease

Streptococcal Associated Behavior and Movement Disorders

<u>SYDENHAM CHOREA</u>

Mild incoordination to severe disruption of movements + Emotional lability

<u>PANDAS or PANS</u>

<u>Pediatric autoimmune neurologic disorders associated with streptococci or Pediatric acute neurologic syndrome</u>

Obsessive-compulsive behaviors

Hyperactivity and emotional lability

Tic-like Symptoms

Historical Evidence of Group A Streptococcal Association with Neuropsychiatric Conditions

- 1- Dr Sydenham in the 17th and 18th century publications: Association of Sydenham chorea and rheumatic fever with psychosis.
- 2- Among 100 patients with schizophrenia, 9% had rheumatic valvular heart disease while the normal population had an incidence of 1.7% in 171 subjects.

  Bruetsch et al (1938, 1940, 1942). Am J Psychiatry.
- 3-Retrospective study of 2, 658 schizophrenia patients from state hospital, 9X more prevalent rheumatic fever than in the normal population.Wertheimer, 1961. Rheumatic Schizophrenia. Arch Gen Psychiatry.
- 4-2X more mental illness in children with rheumatic fever~~6.1% incidence
- mental illness in 943 RF and SC patients compared to 3.1% in non-RF/SC children.
- 5- Siblings of rheumatic fever patients had increased rates of functional psychiatric disorders. Wertheimer. 1961. Arch Gen Psychiatry.
- 6- High rate of histories of rheumatic chorea in psychiatric patients with psychosis compared to other types of patients in the same psychiatric hospital. Wilcox. 1986 Neuropsychobiology.

Story about PANDAS_______Washington Post 9/2011

QUOTE from the Washington Post 9/2011……

A mother "barely had time to react as her son lunged for the door of her car full of children, trying to wrench it open while yelling frantically, "I've got to get out!" The mother "managed to pull to the side of the winding country road near their Charlottesville home as her son, nearly 8, leapt out of the car.

"He kept saying, 'The car smells funny,' and refused to get back in," she recalled, astonished that her normally self-possessed second-grader would fall apart in front of his little sister and her friends, who stared, goggle-eyed, from the back seat. When the mother's efforts at reassurance failed, she called her husband, who left work. After an hour, the child's father managed to coax their son into his car, and they drove home.

Criteria for PANDAS

*Presence of OCD and/or Tic Disorder

*Prepubertal onset

*Episodic course of symptom severity (Acute/abrupt onset & exacerbations)

*Association with neurological abnormalities (choreiform movements)

*Temporal relationship between symptom exacerbations and streptococcal infections

Approach to the Study of Sydenham Chorea and Related Disorders

Human Monoclonal Antibodies Produced from Disease

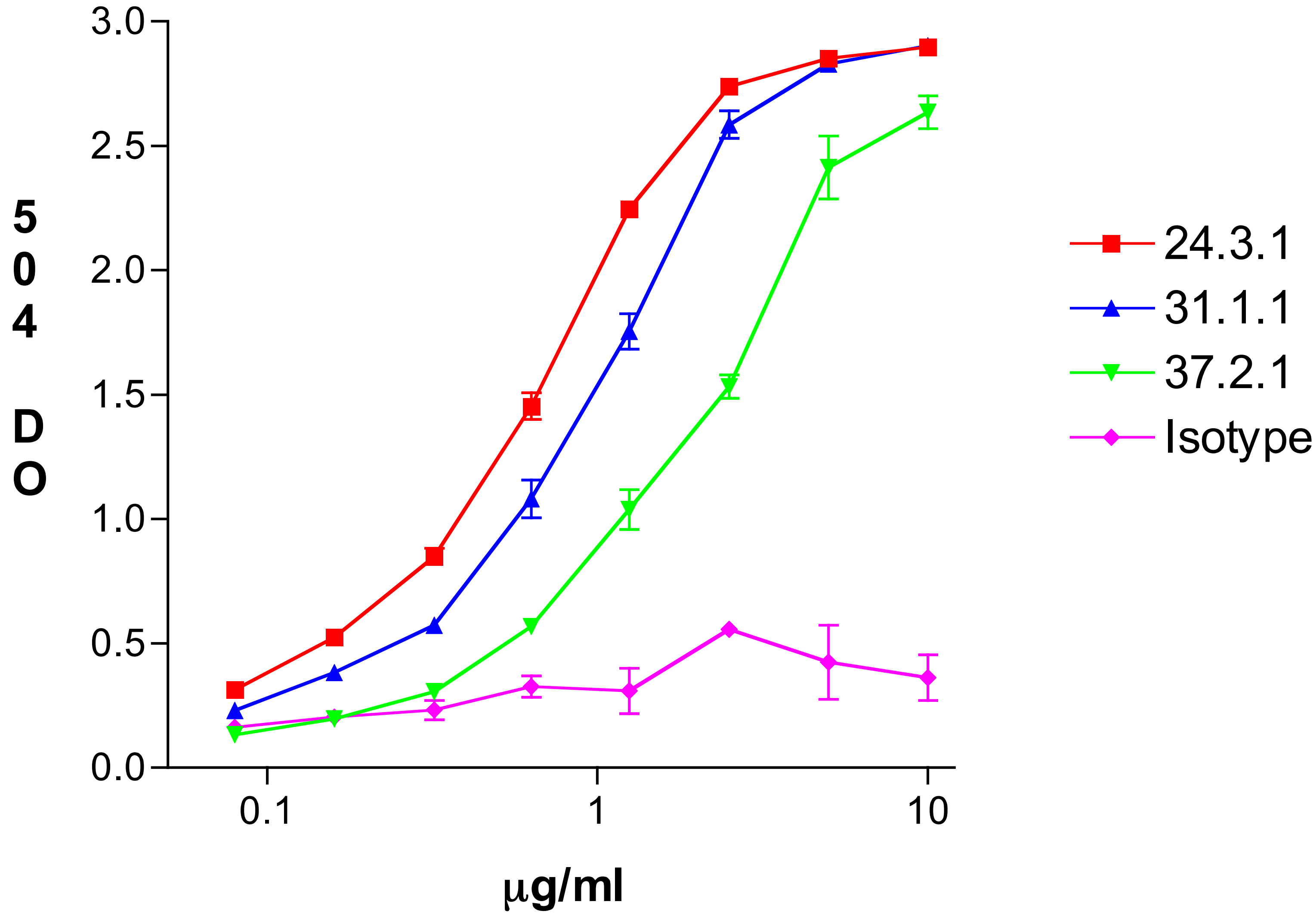
↓

Identification of Brain Autoantigens and Streptococcal Antigens

↓

Study of Pathogenesis of Disease

Reactivity of Sydenham Chorea-Derived mAbs with Lysoganglioside G_{M1}



Kirvan et al. 2003. Nature Medicine 9:914-920

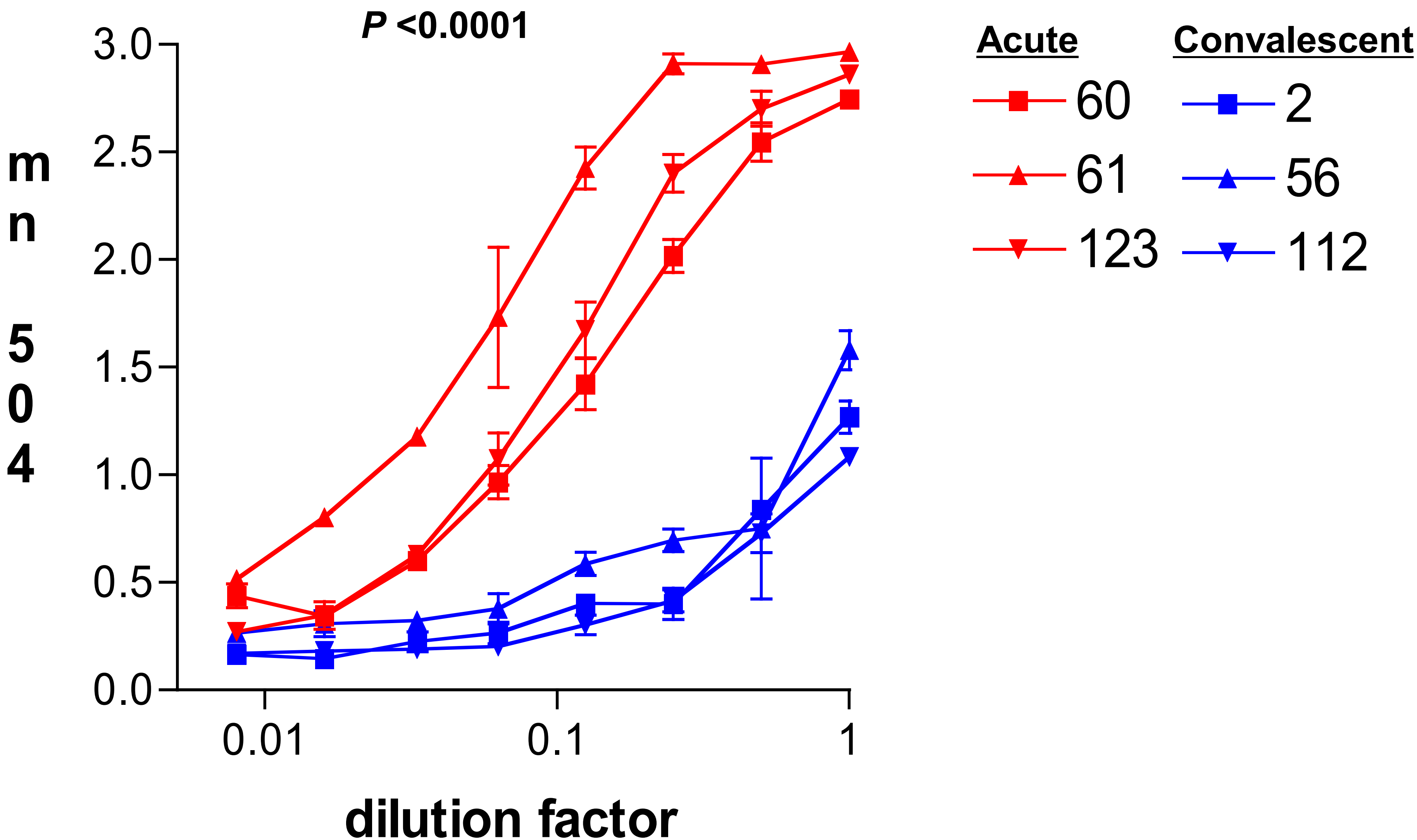
Table 1. Lysoganglioside G_{M1} Inhibition of Chorea mAbs Binding to Streptococcal Group Carbohydrate GlcNAc

Inhibitor (µg/ml)*	24.3.1	31.1.1	37.2.1
Lysoganglioside G_{M1}	6	9.9	11.5
Asialoganglioside G_{M1}	>500	>500	>500
Monosialoganglioside G_{M1}	24	75	125
Monosialoganglioside G_{M2}	>500	201	>500
Monosialoganglioside G_{M3}	>500	389	>500
Disialoganglioside G_{D1a}	>500	>500	>500
Disialoganglioside G_{D1b}	254	210	500
Trisialoganglioside G_{T1b}	>500	>500	>500
Gangliosides Type III	>500	>500	>500
Galactocerebroside	>500	>500	>500
Lactocerebroside	>500	>500	>500
M protein	>500	>500	>500
BSA	>500	>500	>500

Competitive-inhibition of mAb reactivity by inhibitors to bound GlcNAc-BSA in ELISA. The amount of LysoGM1 needed to inhibit 50% of mAb 24.3.1 binding to immobilized streptococcal carbohydrate was significantly less than required for mAbs 31.1.1 and 37.2.1 [$P < 0.05$ for comparison of curves, two-way analysis of variance (ANOVA)]

* µg/ml required to produce 50% inhibition of mAb reactivity with GlcNAc-BSA.

Chorea Sera Reacted with Lysoganglioside



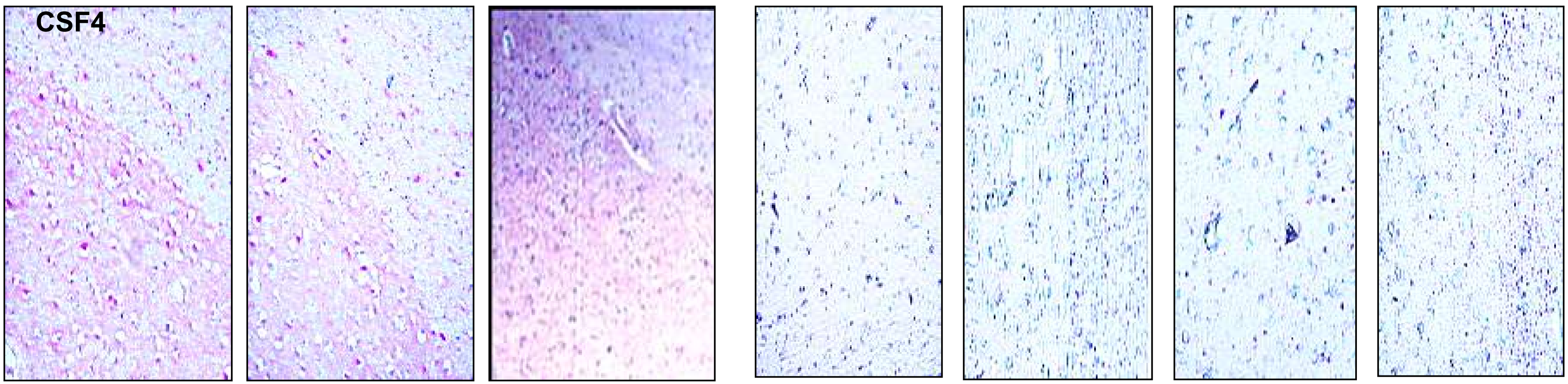
Kirvan et al. 2003. Nature Medicine 9:914-920

ANTI-LYSOGANGLIOSIDE ANTIBODY

ANTI-TUBULIN ANTIBODY

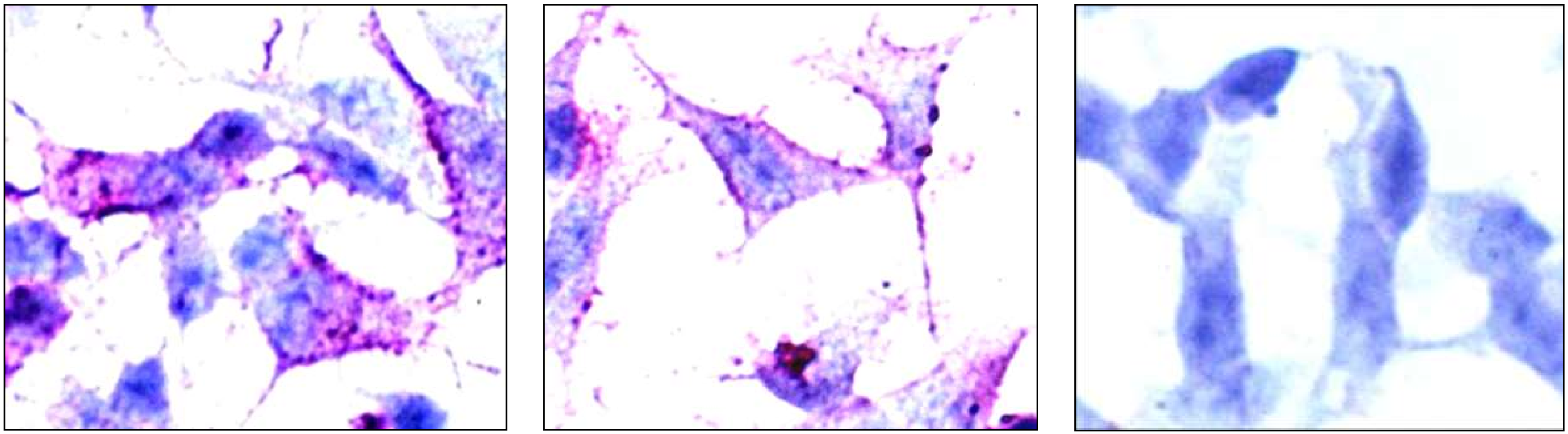
Sydenham Chorea and PANDAS Cerebrospinal Fluid Reactivity with Human Caudate Putamen Tissue

a. Sydenham b. PANDAS c.PANDAS d.control e. control f.control
g. control
chorea CSF CSF1 CSF 2 CSF1 CSF2 CSF3
CSF4



Kirvan et al. 2003. Nature Medicine 9:914-920

Chorea mAb 24.3.1 Reactivity with the SK-N-SH Neuronal Cell Surface



SC mAb 24.3.1 | Anti- ganglioside mAb (commercial) | Isotype

Kirvan et al. 2003. Nature Medicine 9:914-920

Mimicry in Sydenham Chorea

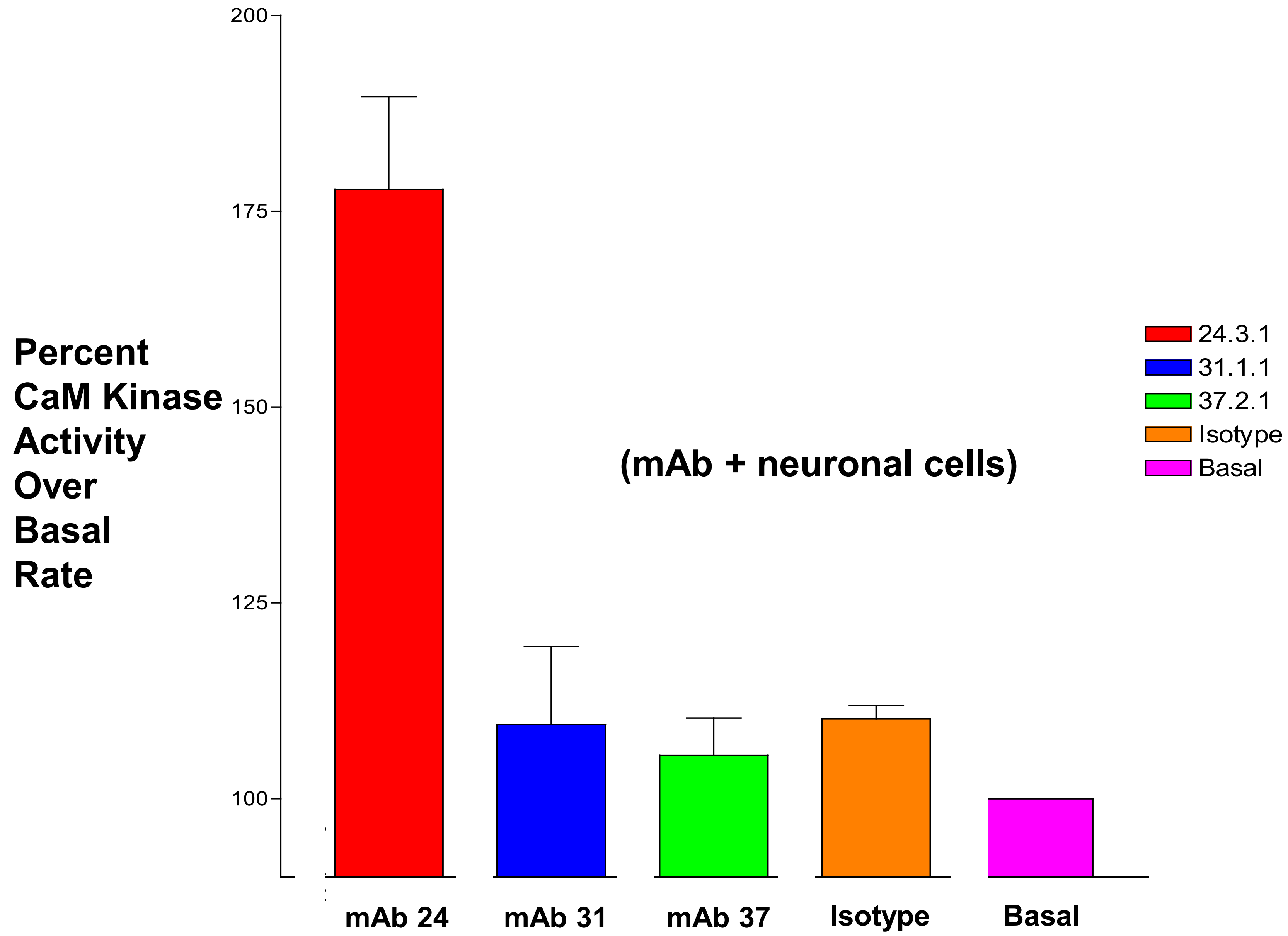
Human mAbs Derived from Sydenham Chorea
Identified:

Streptococcal Group A Carbohydrate Epitope N-acetyl-beta-D-glucosamine

Lysoganglioside and Tubulin brain antigens

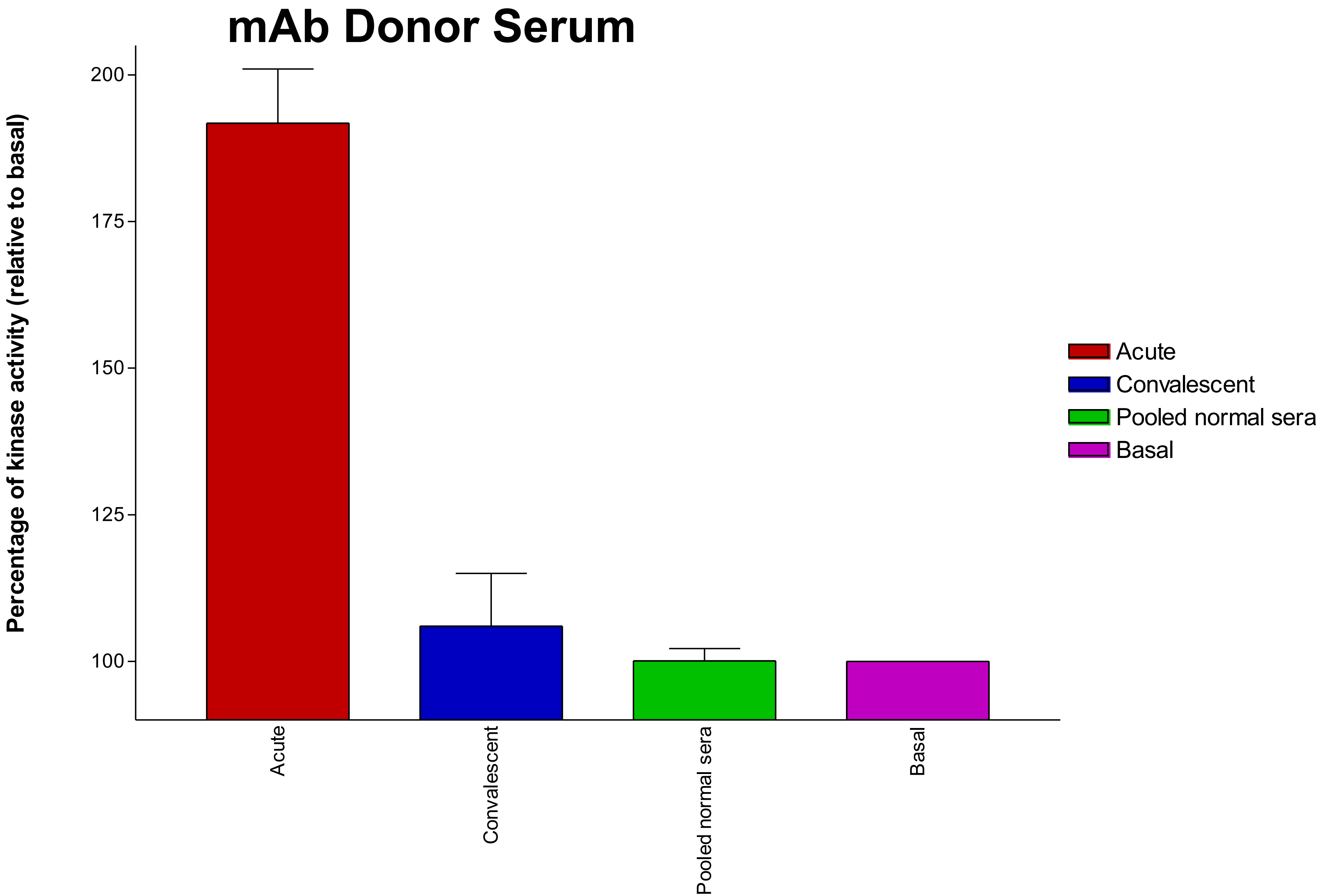
Chorea mAbs and chorea sera demonstrate cell signaling through calcium/calmodulin dependent protein kinase II in neuronal cells

Antibody-induced CaM kinase activity in SK-N-SH cells



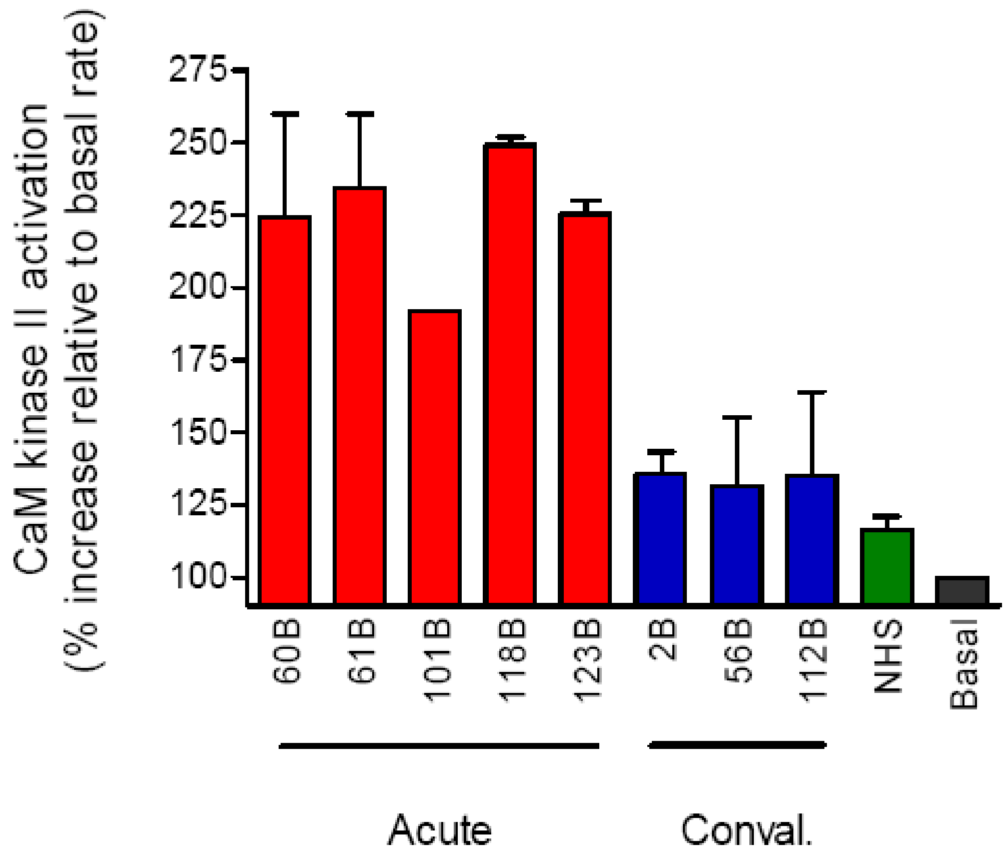
Kirvan et al. 2003. Nature Medicine 9:914-920

Serum-induced CaM kinase activity in SK-N-SH cells



Kirvan et al. 2003. Nature Medicine 9:914-920

SC sera-induced CaM Kinase II activity in SK-N-SH cells



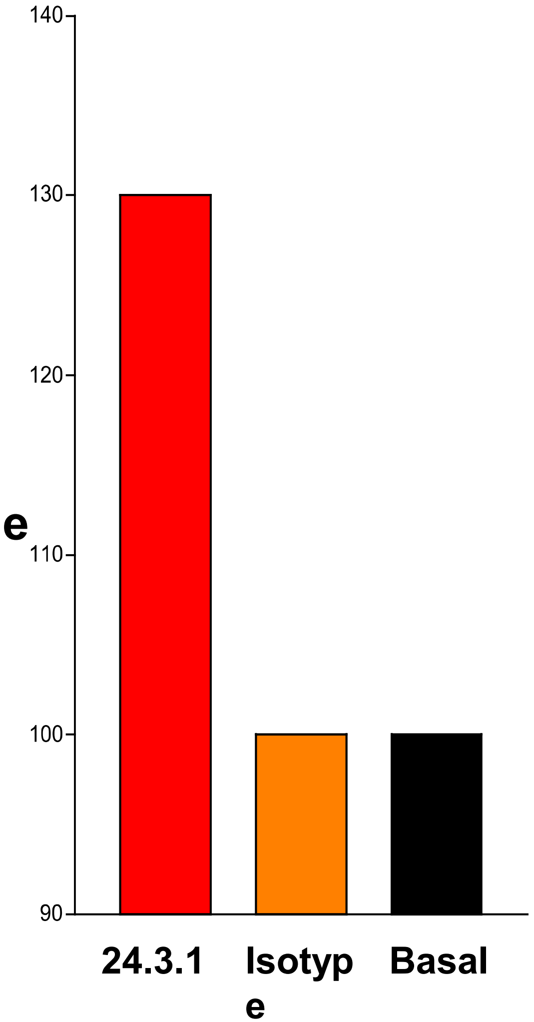
Kirvan et al. 2003 Nature Medicine 9:914-920

Mechanism of Anti-Neuronal Ab:

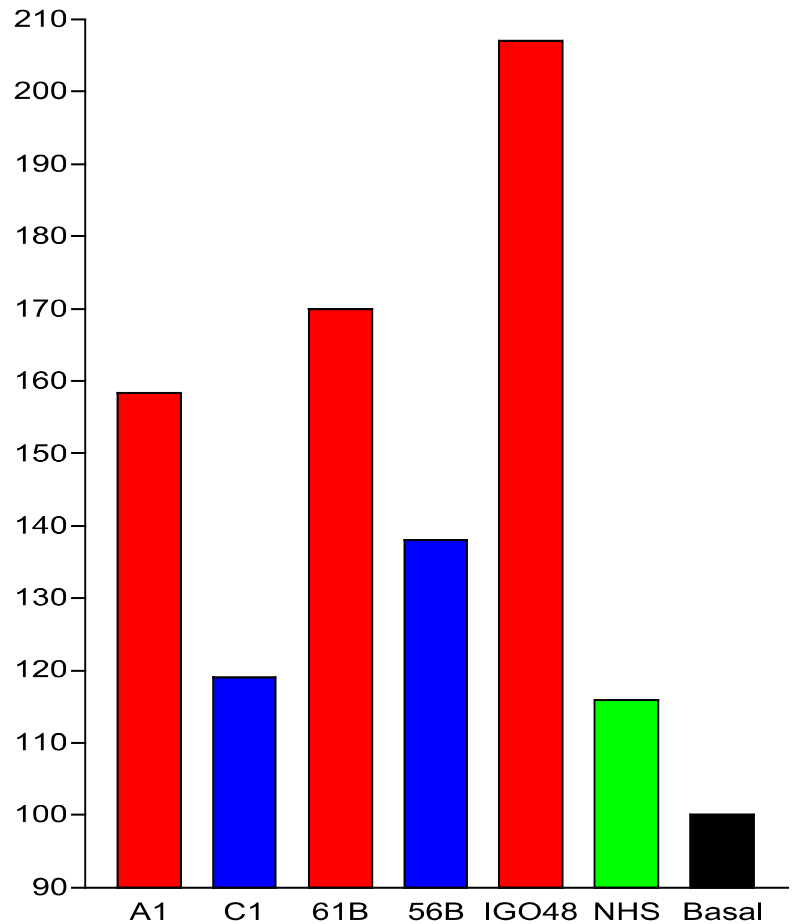
Chorea mAb and Acute Chorea Sera Induces Dopamine Release

Chorea mAb

Percent Tritiated Dopamine Release

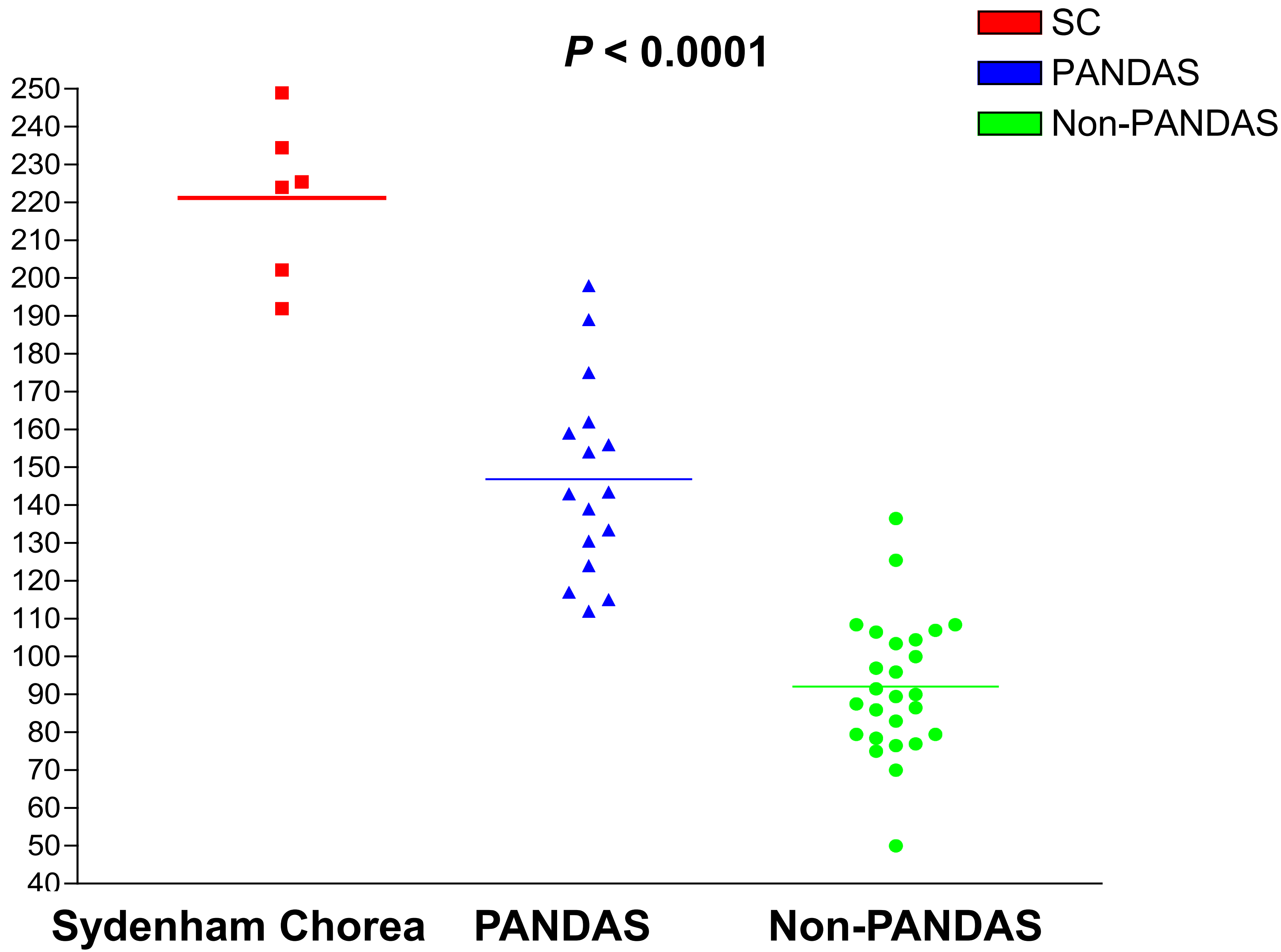


Chorea Sera

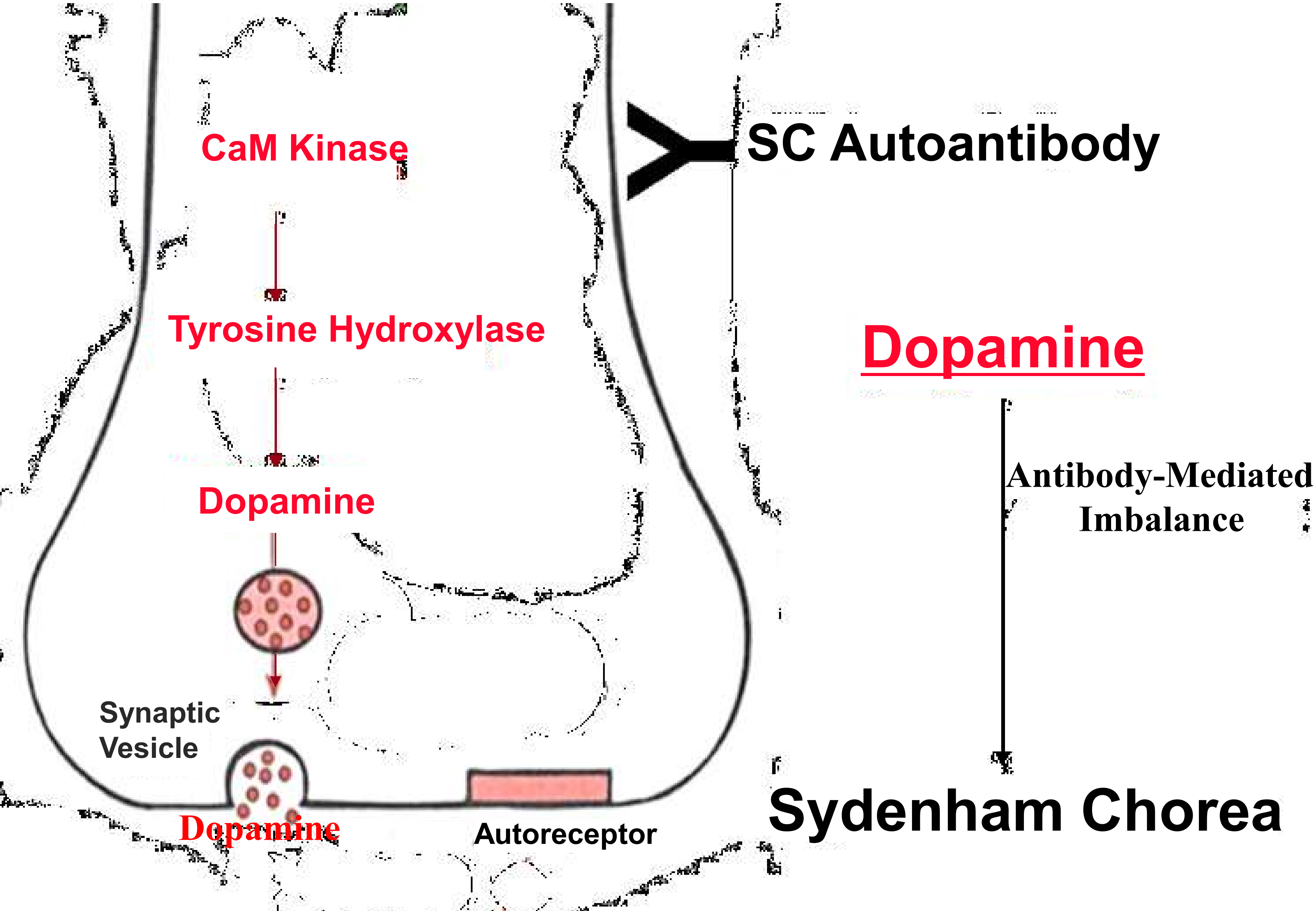


Kirvan et al. 2006. Autoimmunity 39: 21-29

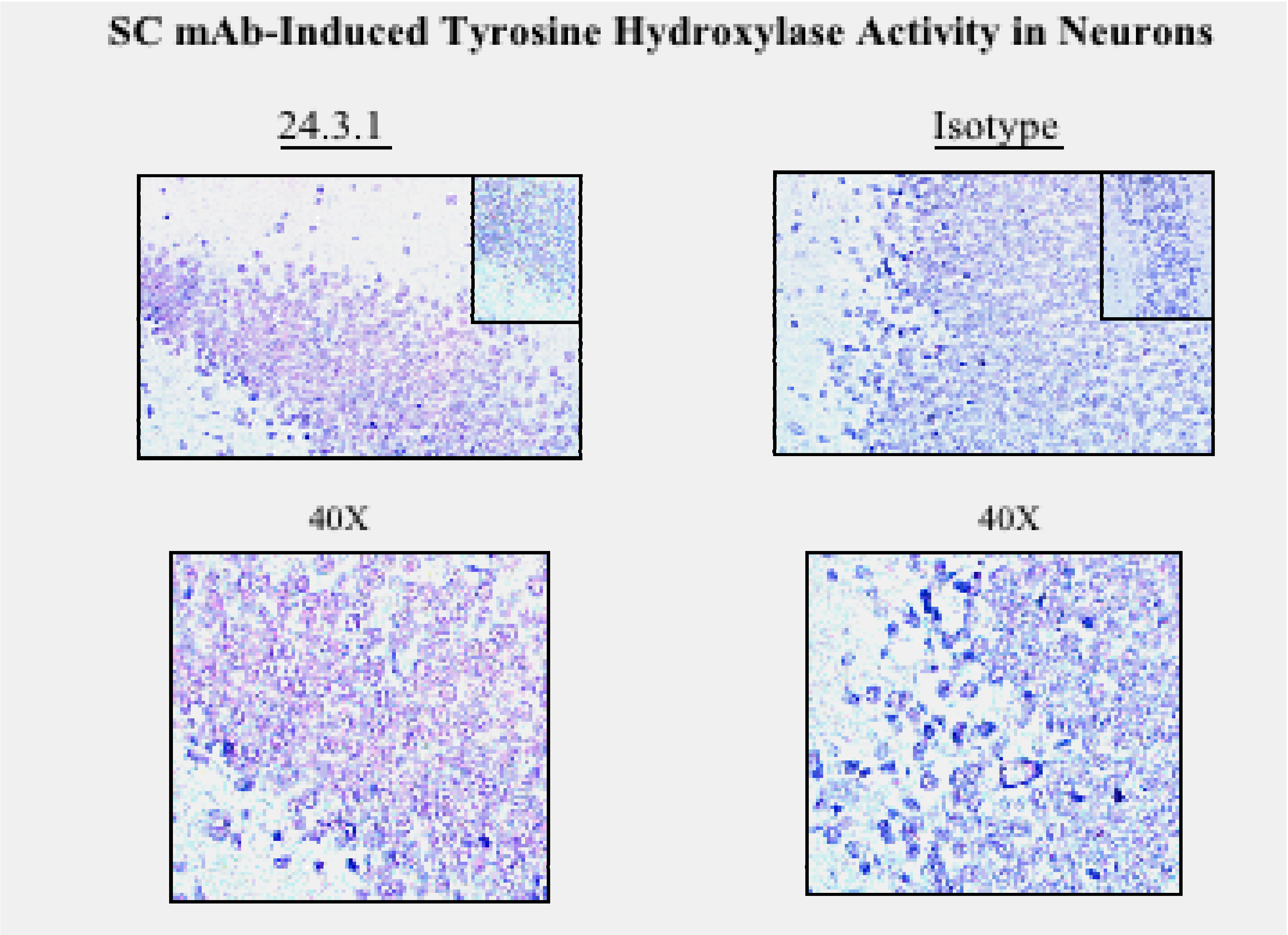
Activation of CaM Kinase II in PANDAS



Kirvan, et al, J. Neuroimmunol. 179: 173-179


CaM Kinase
Tyrosine Hydroxylase
Dopamine
Synaptic Vesicle
Dopamine
Autoreceptor
SC Autoantibody
Dopamine
Antibody-Mediated Imbalance
Sydenham Chorea

Intrathecal adminstration of human SC mAb

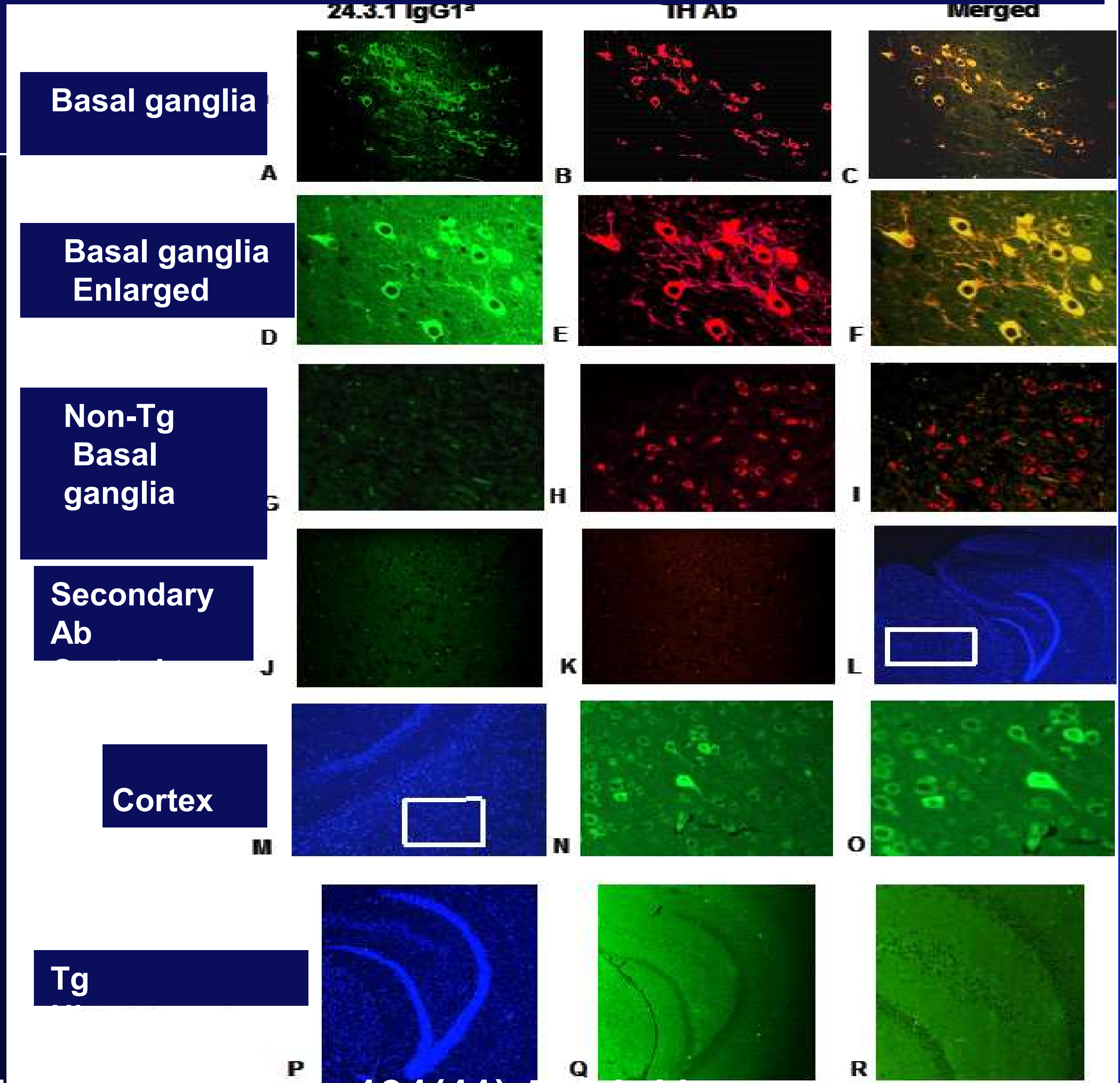


Cunningham, Current Opinion in Rheumatology July 2012

Transgenic Expression of Human Chorea mAb 24 in Mice Targets Dopaminergic Neurons In Vivo in Basal Ganglia

Cox, et al; J Immunology 2013

Transgenic(Tg) IgG1a Antibody 24.3.1 Targets Dopaminergic Neurons in Vivo in Tg Mouse Br



Cox, et al, J Immunology 191(11):5524-41

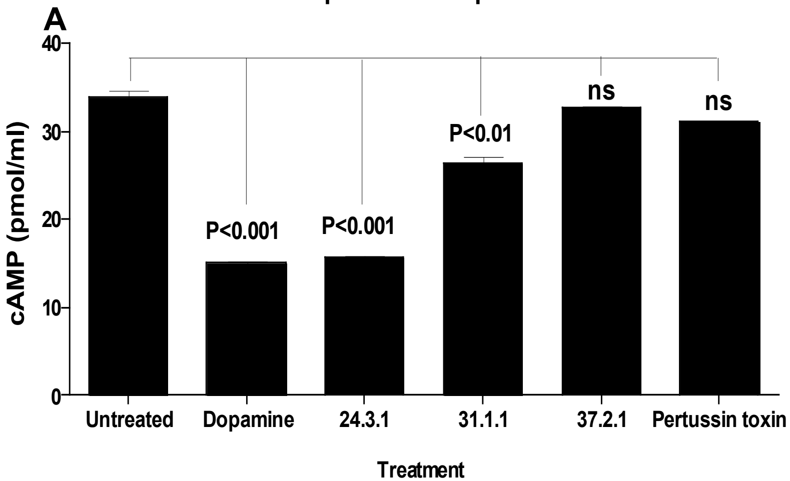
Is there evidence for a role for Dopamine Receptors in Sydenham chorea and PANDAS?

Hypothesis:

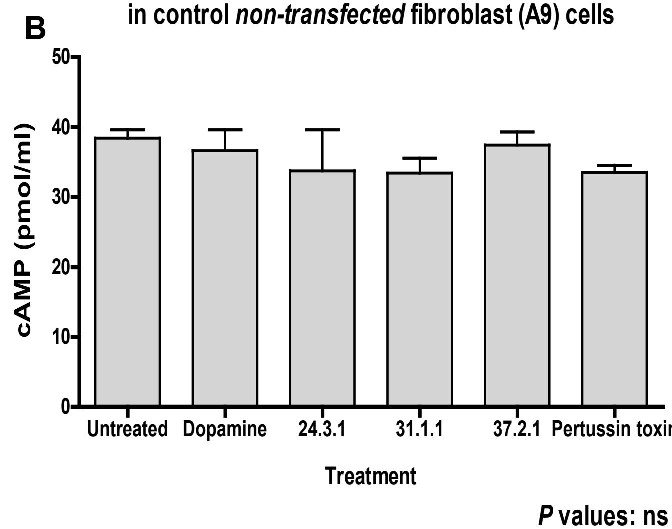
Dopamine receptors present on the surface of neuronal cells react with and respond to Abs as if they were neurotransmitters such as dopamine

Human Chorea Mab 24.3.1 Signals Dopamine D2 Receptor

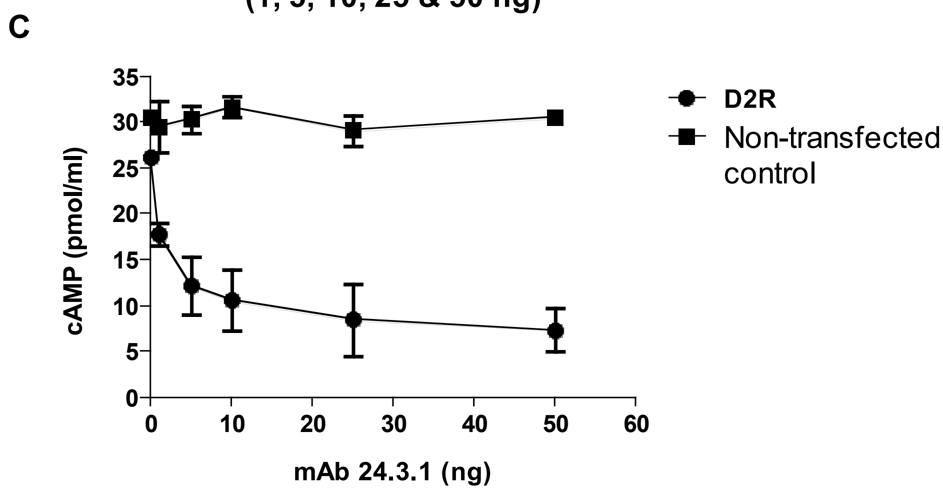
Human mAb 24.3.1 activates dopamine D2R
comparable to dopamine



cAMP levels unaffected by mAb 24.3.1
in control *non-transfected* fibroblast (A9) cells

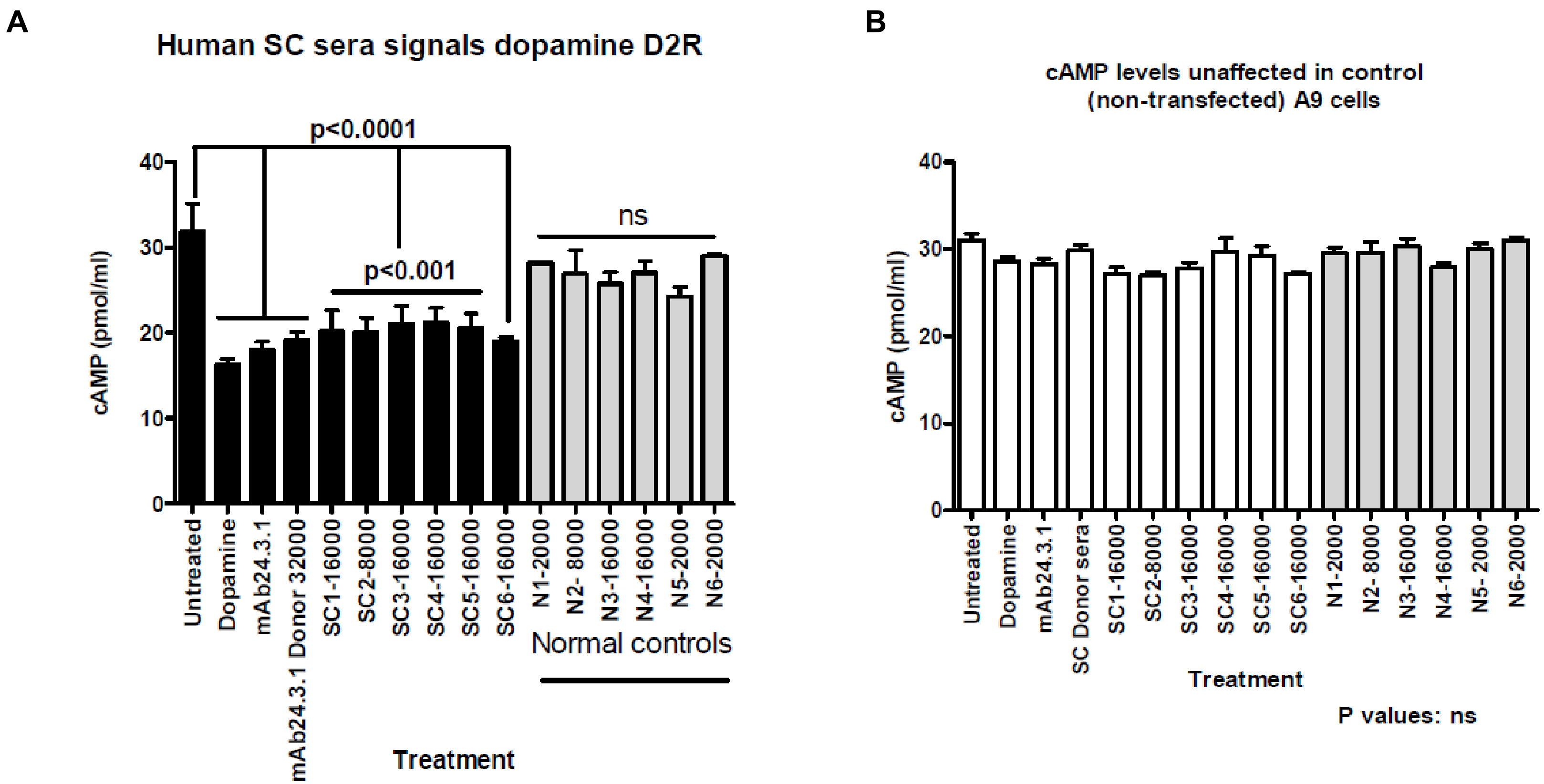


Dose-response (cAMP) of D2R transfected
and control cells treated with mAb 24.3.1
(1, 5, 10, 25 & 50 ng)



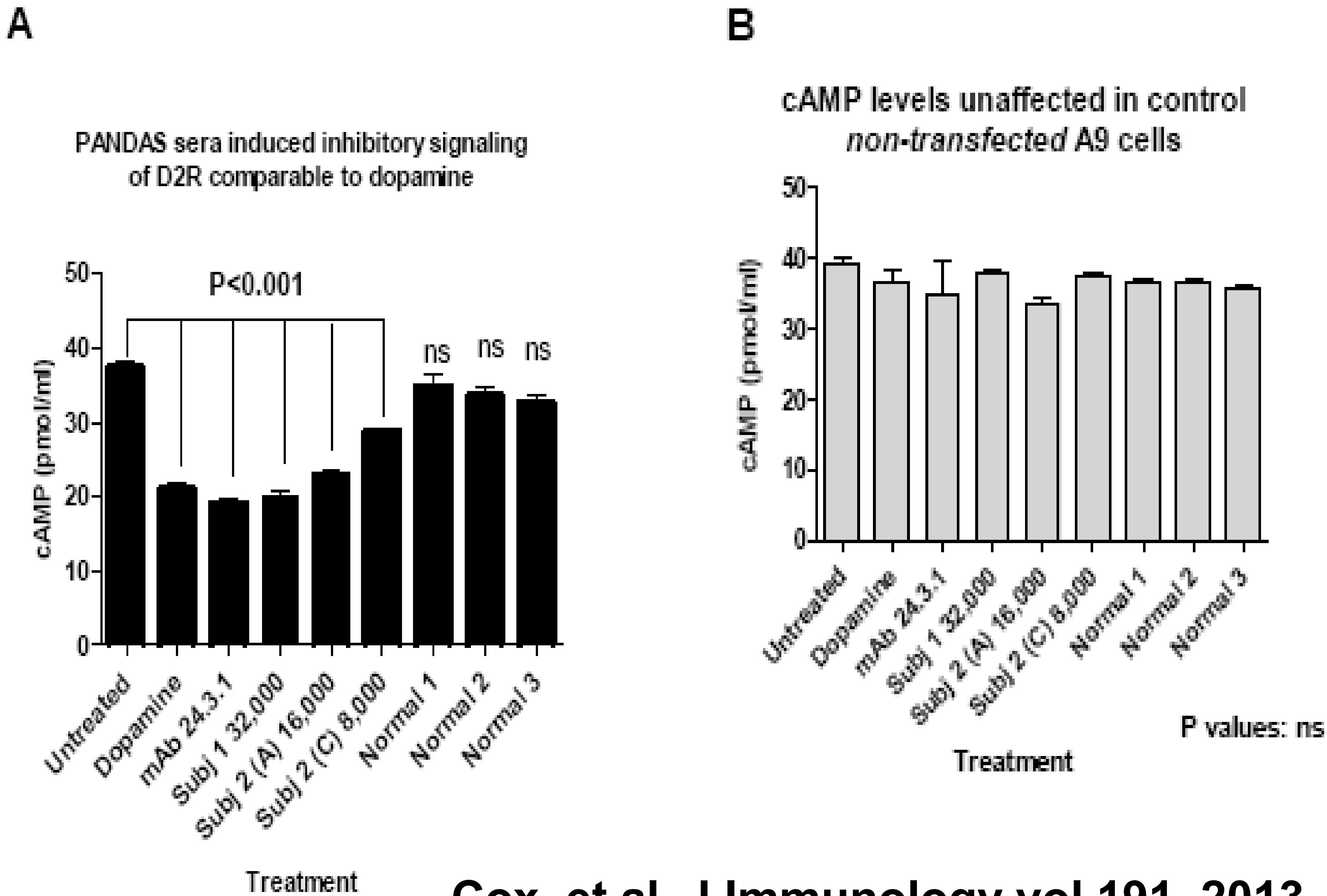
Cox, et al, J Immunology vol 191, 2013

Sydenham Chorea Sera Signals Dopamine D2 Receptor



Cox, et al, J Immunology vol 191, 2013

PANDAS Sera Signal the Dopamine D2 Receptor



Cox, et al, J Immunology vol 191, 2013

Antibody Recognition of Human Dopamine D1R

D1R and D2R may reside on neuronal cells as a heterodimer

ANTIBODIES AGAINST THE DOPAMINE D1 AND D2 RECEPTORS

Our Evidence for Autoantibodies against the Streptococcus and Brain in Sydenham chorea and PANDAS (Acute Onset)

- 1. **Kirvan et al. 2003. Mimicry and autoantibody neuronal cell signaling in Sydenham chorea. Nature Medicine 9:914-920.**
- 2. **Kirvan, et al. Autoantibody neuronal cell signaling in behavior and movement disorders J. Neuroimmunol. 179: 173-179.**
- **3. Kirvan et al. 2006. Antibodies lead to increased dopamine release from neuronal cell line. Autoimmunity 39: 21-29.**
- 4**. Kirvan, et al. 2007. Tubulin is a neuronal target in Sydenham's chorea. J Immunology 178:7412–7421**
- **5. Ben-Pazi, et al. 2013. Dopamine receptor autoantibodies correlate with symptoms in Sydenham's chorea. PLOS ONE vol 8, issue 9, Sept: e73516.**
- **6. Cox, et al. 2013. Brain human monoclonal autoantibody from Sydenham chorea targets dopaminergic neurons in transgenic mice and signals dopamine D2 receptor: Implications in human disease. J. Immunol. 191:5524-41.**

Evidence for autoantibodies in more chronic tics and OCD >1 year symptoms Two Studies

- 1. Cox, et al. 2015. Antineuronal antibodies in a heterogeneous group of youth and young adults with chronic tics and obsessive compulsive disorder. **Journal of Child and Adolescent Psychopharmacology 2015.**

- Our study suggested a significant correlation of streptococcal-associated tics and OCD with elevated anti-D1R and antilysoganglioside antineuronal antibodies in serum concomitant with higher activation of CaMKII in human neuronal cells.

- 2. Singer, et al. 2015. Neuronal antibody biomarkers for Sydenham's chorea identify a group fo children with chronic recurrent exacerbations of tic and obsessive compulsive symptoms following a streptococcal infection. **PLOS One.**

- Found Increased anti-D1R and anti-lysoganglioside antibodies and antibody mediated CaMKII activation in the chronic tics

Lewis Rat and Mouse Models of Streptococcal Induced Behavioral Changes

And Autoimmunity :

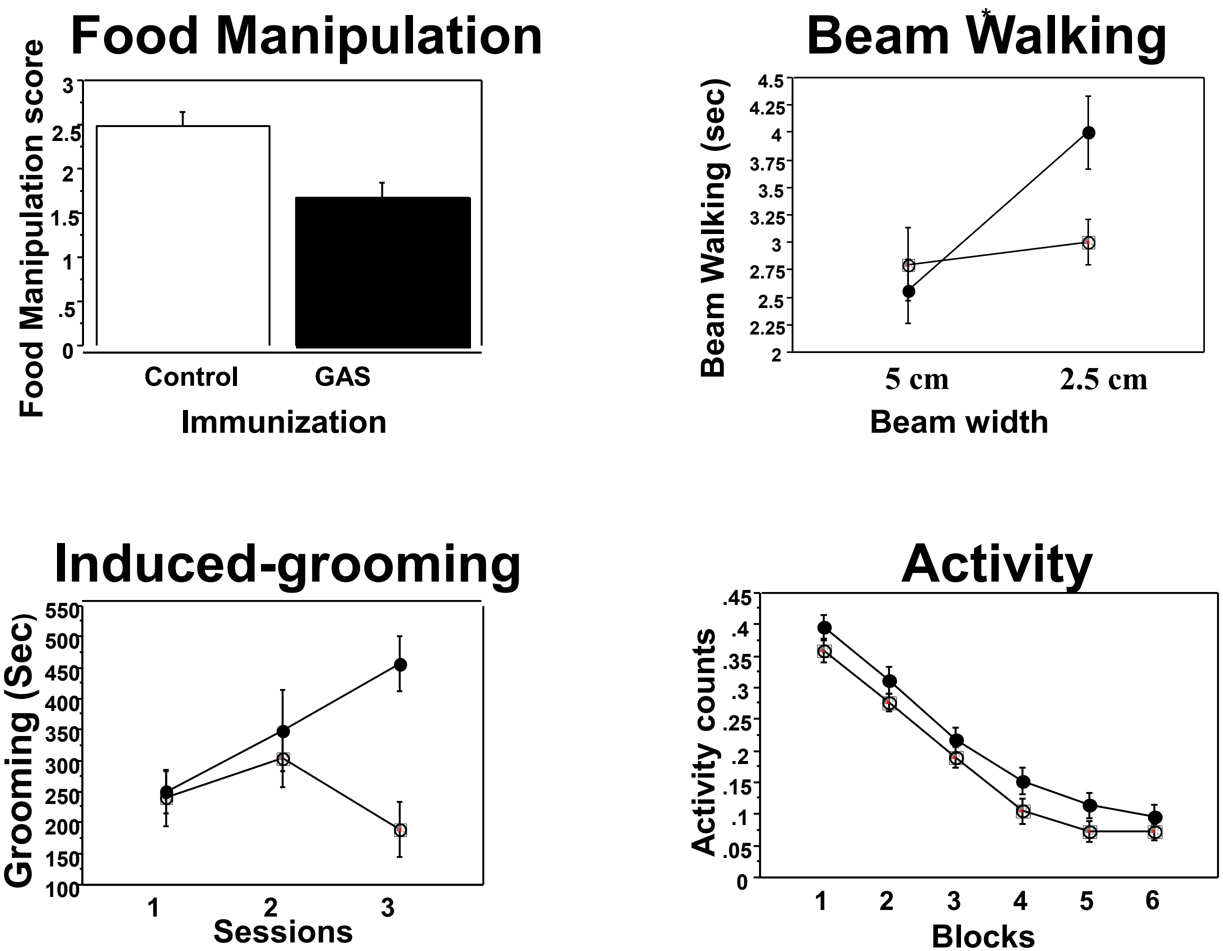
A Potential Model for

Human Disease

Collaborators:
Dr. Daphna Joel,
Dr. Lior Brimberg,
Dr. Dafna Lotan
Tel Aviv University

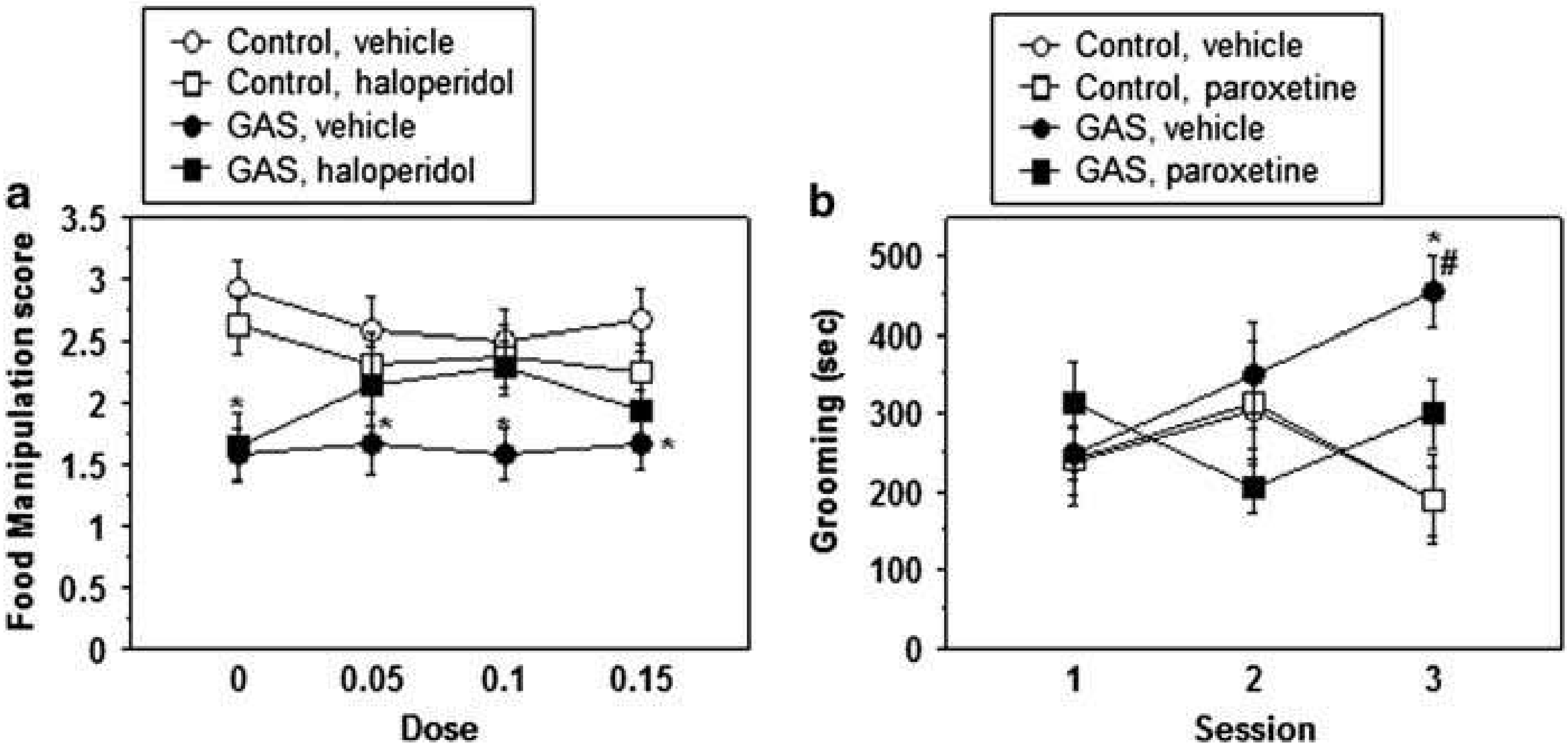
Brimberg, et al, Neuropsychopharmacology (2012) 37, 2076-87

Streptococcal immunization affected behavior



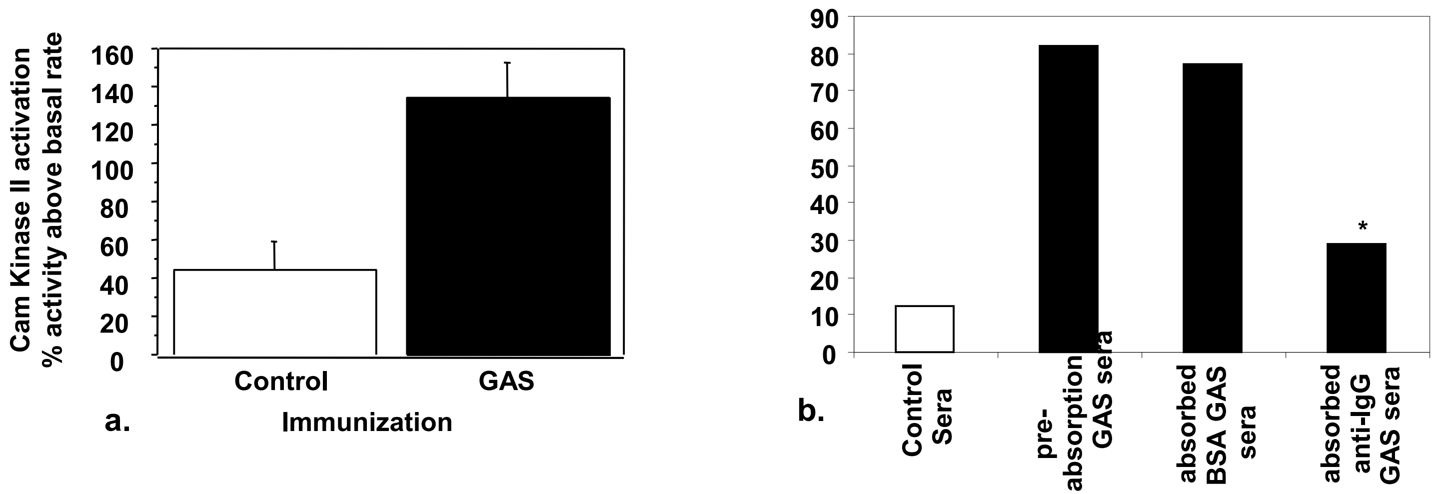
Brimberg, et al, Neuropsychopharmacology (2012) 37, 2076-87

Treatment of immunized rats with haloperidol or paroxetine abrogated behavioral changes

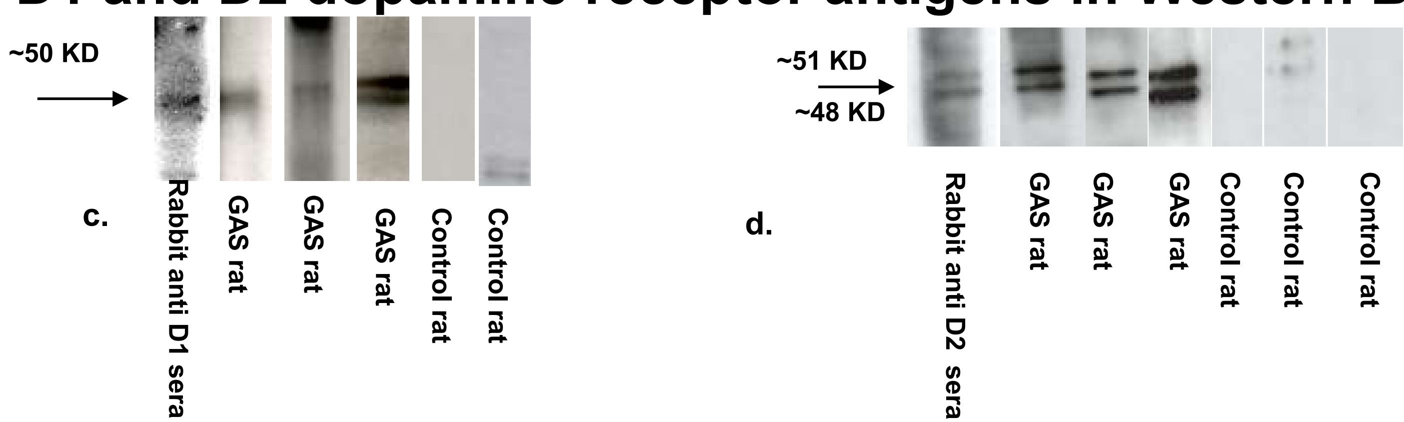


Brimberg, et al, Neuropsychopharmacology (2012) 37, 2076-87

IgG antibodies from streptococcal immunized rats activated CaM kinase II and were absorbed with anti-IgG

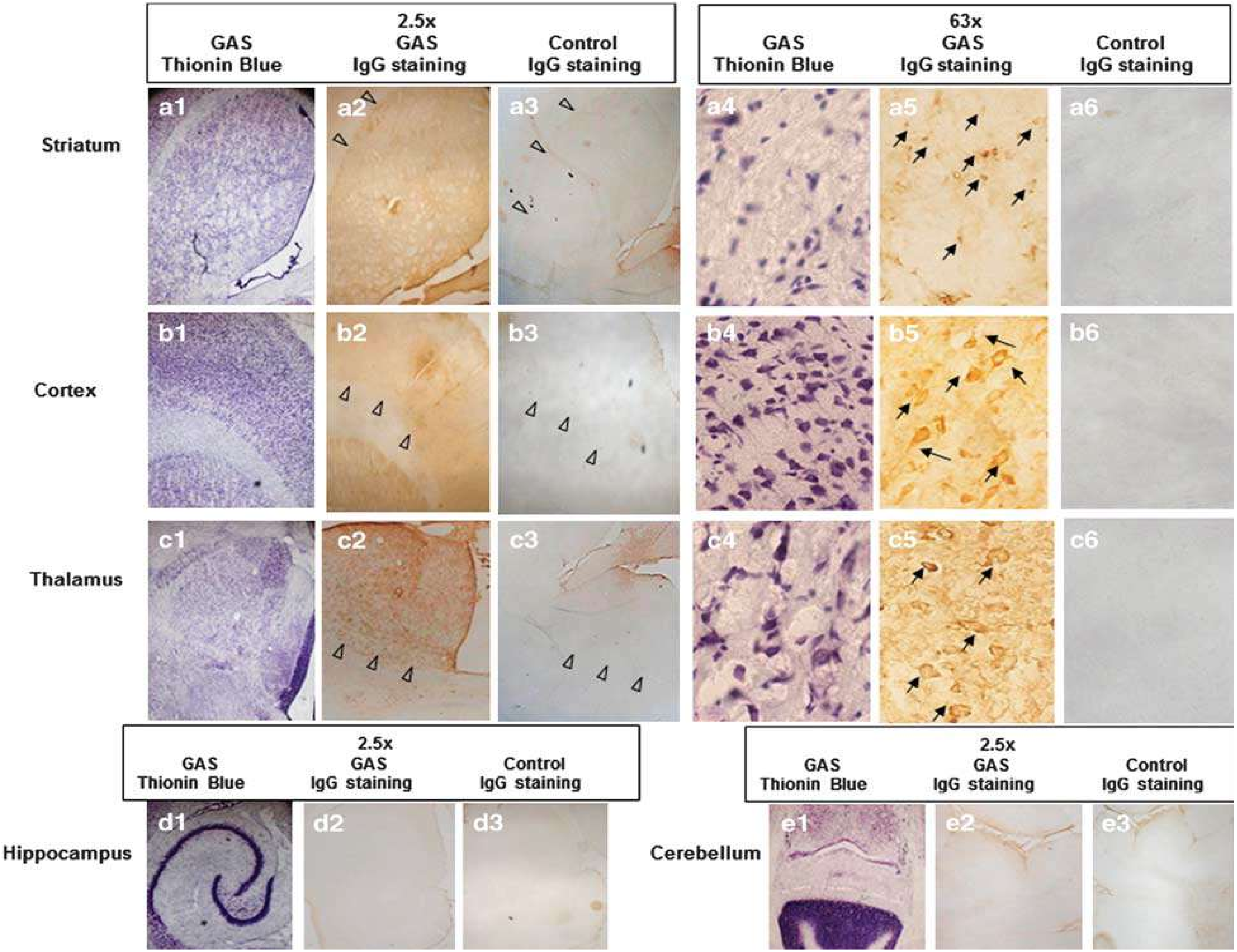


Streptococcal immunization induced antibodies against D1 and D2 dopamine receptor antigens in Western Blot



Brimberg, et al, Neuropsychopharmacology (2012) 37, 2076-87

Lewis rat streptococcal immunization model of SC/PANDAS : Antibody deposits in the striatum, cortex and thalamus but <u>NOT</u> the hippocampus or cerebellum



Brimberg, et al, Neuropsychopharmacology (2012) 37, 2076-87

Evidence That Antibodies and Group A Streptococci Lead to Behavioral Alterations in an Animal Model

- 1. **Hoffman,K.L., Hornig,M. et al. 2004.** A murine model for neuropsychiatric disorders associated with group A beta-hemolytic streptococcal infection. J Neuroscience 24: 1780–1791.

- 2**. Yaddanapudi, K Hornig, M *et al*. 2009.** Yaddanapudi K, Hornig M, et al. Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of PANDAS. **Molecular Psychiatry**15:712–726

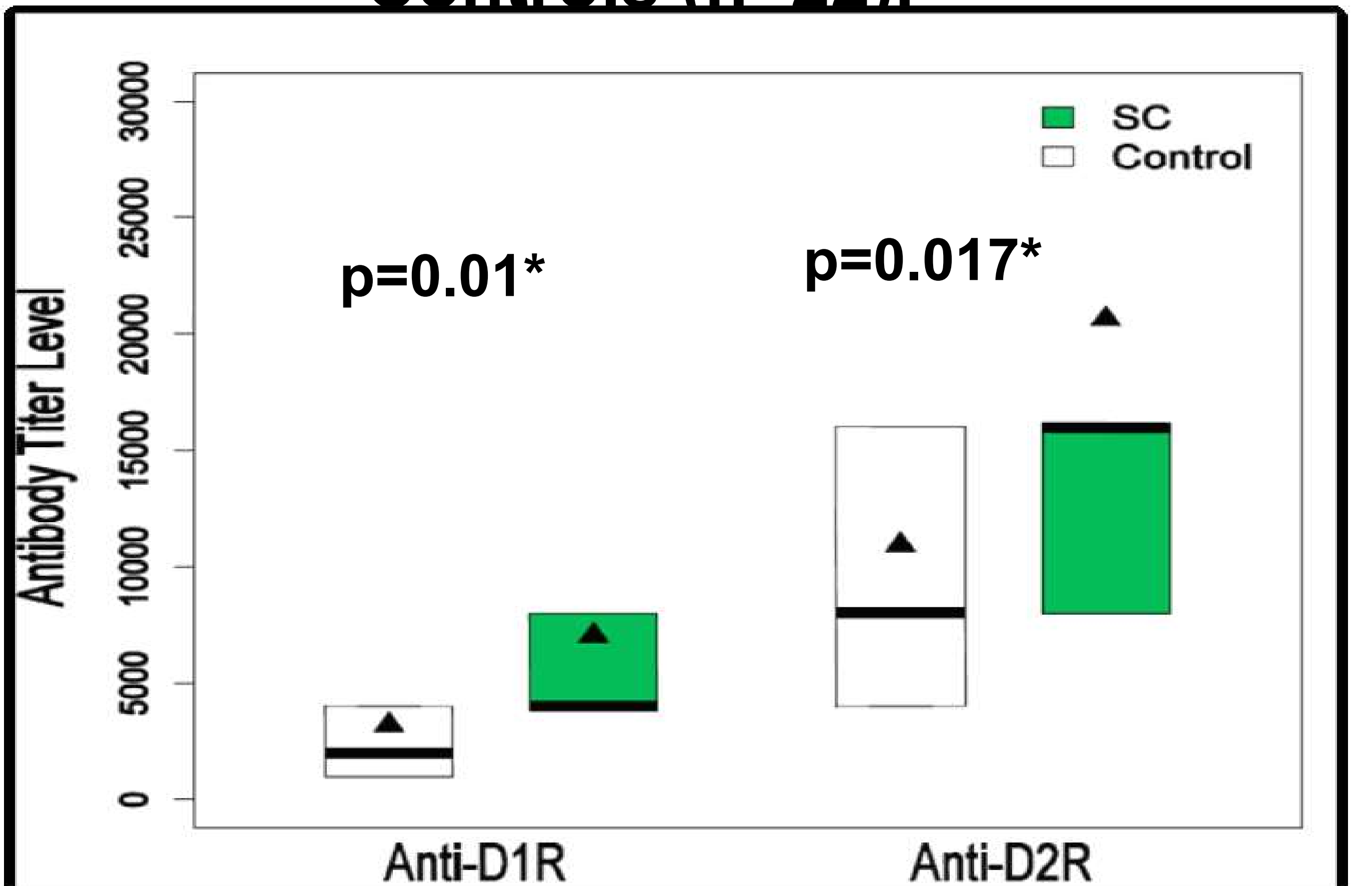
- 3. **Brimberg, et al.2012.** Behavioral, pharmacological and immunological abnormalities rafter streptococcal exposure: A novel model of Sydenham chorea and related neuropsychiatric disorders. **Neuropsychopharmacology** 37:2076-2087.1–12.

- 4**. Lotan, D.,et al. 2014.** Behavioral and neural effects of intra-striatal infusion of anti-steptococcal antibodies in rats. **Brain, Behavior and Immunity** 38: 249-262**.**

- **5. Lotan, D. et al. 2014.** Antibiotic treatment attentuates behavioral and neurochemical changes induced by exposure of rats to group A streptococcal antigen. **PLOS One** DOI: 10.1371/journal.pone.0101257

Is Sydenham Chorea, a streptococcal induced autoimmune sequela, a path to understanding neuropsychiatric disorders associated with

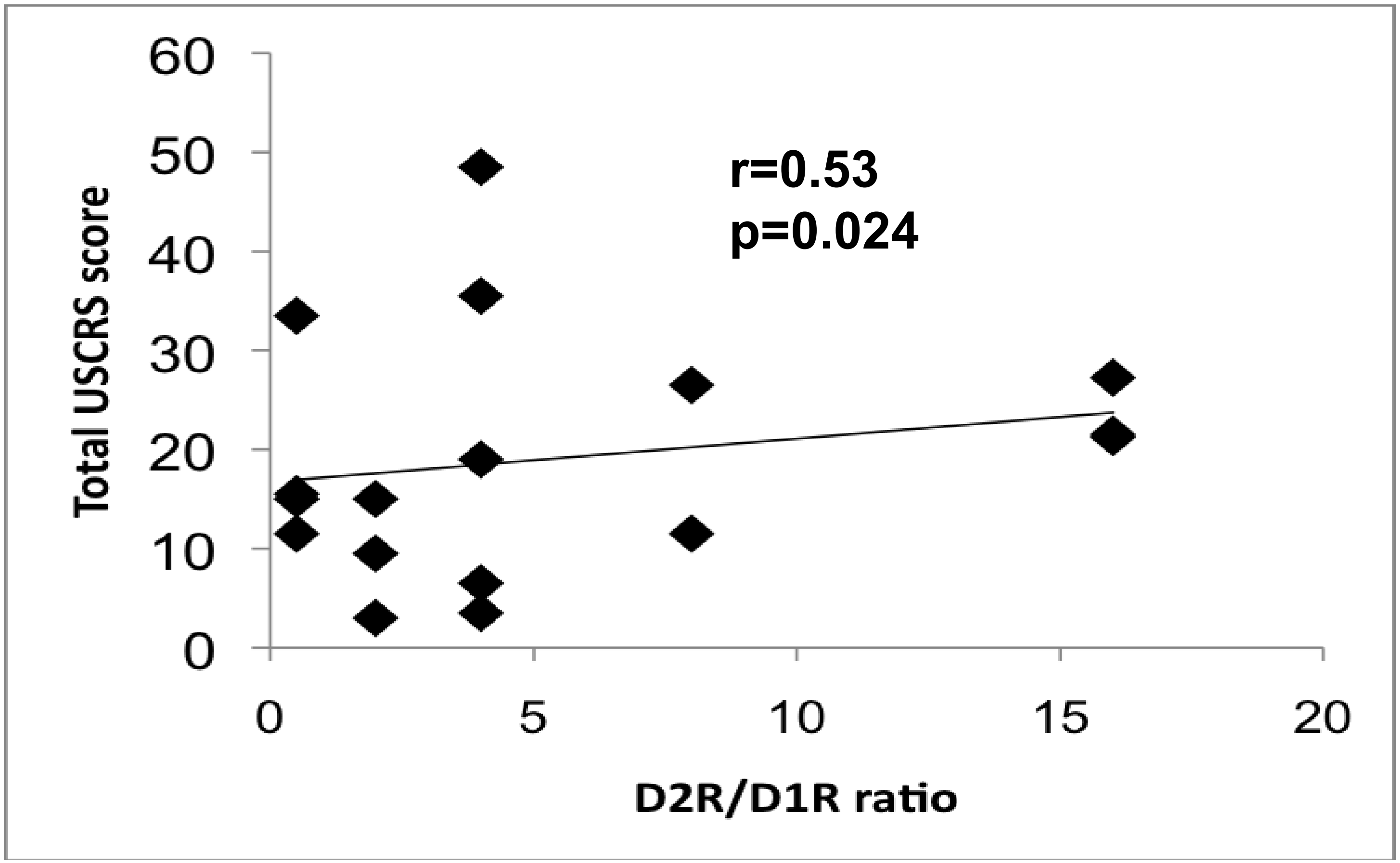
Distribution of Anti-D1R and Anti-D2R IgG antibody titers of Sydenham's chorea patients (n=22) and Controls (n=22).



*Wilcoxon Rank Sum Test

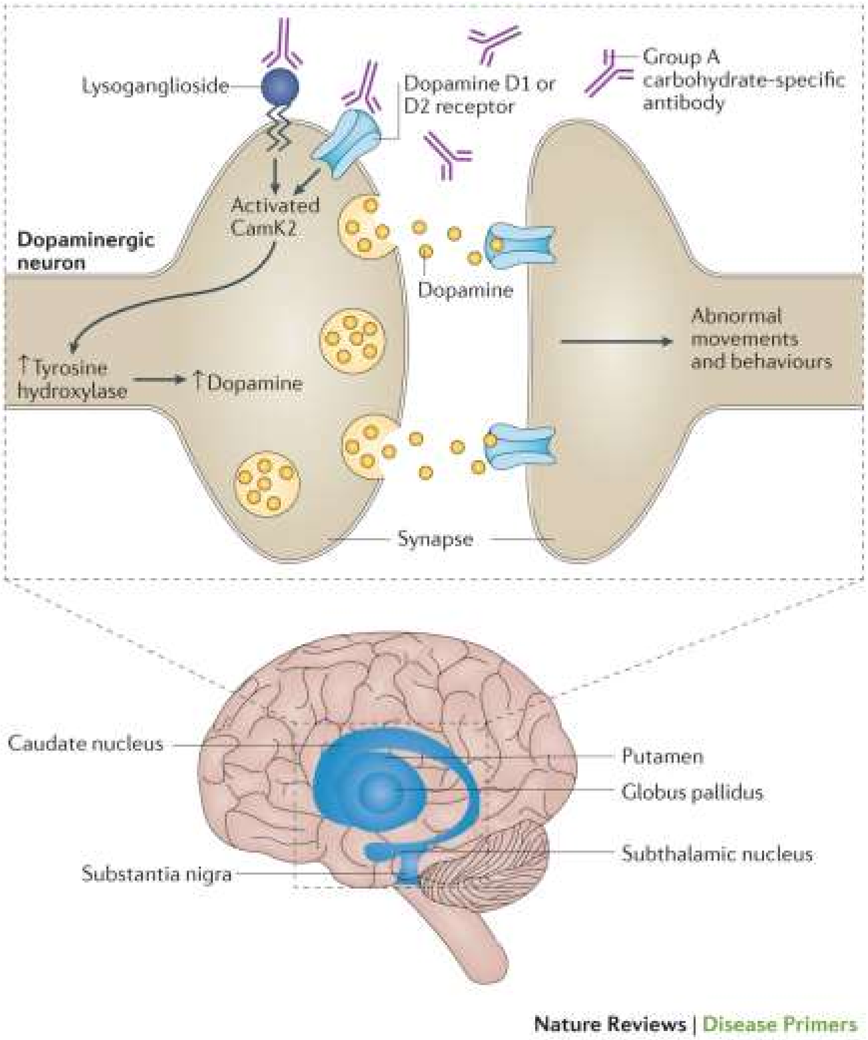
Dr Hilla Ben Pazi,et al; Shaare Zedek Med Ctr, Jerusalem, *PLoS One 9/2013*

Dopamine receptor antibody ratio (D2R/D1R) correlates with neuropsychiatric symptoms (USCRS score)

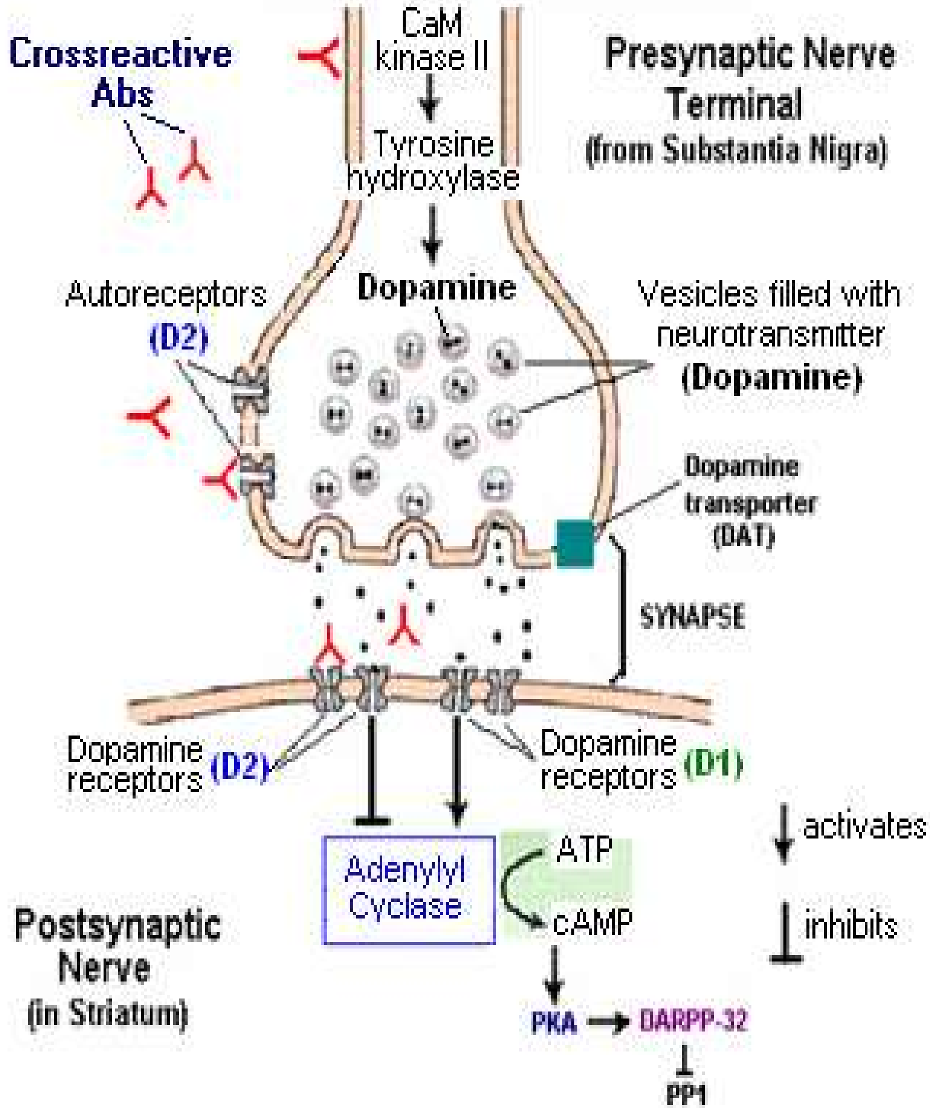


Ben-Pazi,et al; Shaare Zedek Med Ctr, Jerusalem, PLoS One 9/2013

Figure 4 Molecular and cellular basis of Sydenham's chorea



Carapetis, J. R. *et al.* (2015) Acute rheumatic fever and rheumatic heart disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.84



(adapted from http://nobelprize.org)

Dopamine neurotransmission

MODEL OF AUTOANTIBODY EFFECTS IN THE BRAIN

Binding of high avidity cross-reactive anti-neuronal Abs to lysoganglioside and dopamine receptors may cause alterations in dopamine neurotransmission.

Hypothesis: Autoantibody-mediated increases in central dopamine levels and selective activation of dopamine D2 receptors combine to produce the altered movement and neuropsychiatric symptoms of Sydenham chorea and related disorders such as PANDAS.

Concept of Autoantibodies in Autoimmune Diseases

Groups of autoantibodies against different antigens can be associated with a particular type of autoimmune disease.

Anti-neuronal antibodies have >91% sensitivity for the disease.

In PANDAS, PANS, Tics/OCD or some neuropsychiatric diseases associated with inflammation, anti-neuronal autoantibody groups against certain neuronal antigens and receptors are a characteristic feature.

Immune Complexes which persist and contain crossreactive antigens from microorganisms or host antigens may activate the immune system in exacerbations and flares.

Disease Symptoms may be a Two Step Process:

1)Immune Responses against the infectious pathogen such as antibody/T cell responses

2) Opening the Blood Brain Barrier due to infection or stress would allow Antibodies to penetrate into the brain (Th17 entering brain through olfactory bulb-Agalliu/Cleary et al)

Potential Pathogenesis of Disease

Antibodies leading to Excess dopamine → Genes mutated that degrade dopamine (catechol-o-methyl-transferase/epistasis)) → Failure to degrade dopamine → Altered Brain function

Acknowledgements for Chorea and PANDAS Studies

University of Oklahoma Health Sciences Center

Janet S. Heuser
Adita Blanco
Kathy Alvarez
Christine Kirvan, PhD
Carol Cox, PhD
Jonathan Zuccolo, PhD
Amir Zuccolo, PhD
Chandra Menendez, PhD
Sean Reim
Rebecca Benltey, MS

Natl Inst of Mental Health

Susan Swedo, MD
Lisa Snyder, MD
Paul Grant, MD

Yale University

Paul Lombroso, PhD
Jim Leckman, MD
Ivana Kawikova, MD

Tel Aviv University

Daphna Joel, PhD
Lior Brimberg, PhD
Dafna Lotan, Ph.D.

Shaare Zedek Medical Ctr Movement Disorders Clinic Jerusalem Israel

Hilla Ben-Pazi, MD

Columbia University

Brian Fallon, MD

Johns Hopkins Univ

Harvey Singer, MD

Harvard University

Michael Jenike,MD
Dan Geller, MD

Univ of Oklahoma HSC Biostatistics Dept

Julie Stoner, PhD

University of Minnesota

Ed Kaplan, MD