

BIOGRAPHICAL SKETCH

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NAME THEOHARIDES, THEOHARIS C.		POSITION TITLE Professor of Pharmacology and Internal Medicine (Allergy & Clinical Immunology)	
eRA COMMONS USR NAME (credential, e.g. agency login) THEOHAR			
EDUCATION/TRAINING (<i>Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.</i>)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Yale University, New Haven, CT	B.A.	1972	Biology & Hist. Medicine
Yale University, New Haven, CT	M.S.	1975	Neuroimmunology
Yale University, New Haven, CT	M.Phil.	1975	Immunopharmacology
Yale University, New Haven, CT	Ph.D.*	1978	Pharmacology
Yale University, New Haven, CT	M.D.	1983	Medicine
Tufts University, Fletcher School Law & Diplomacy	Certificate	1999	Leadership & Management
Harvard Univ, J.F. Kennedy School of Government	M.P.A.	Deferred	Biomedical Res Policy

*Doctoral Thesis advisors: W.W. Douglas, M.D.-Royal Acad. Sciences; Paul Greengard, Ph.D.-2000 Nobel Laureate in Physiol & Med; Doctoral Thesis examiner, George E. Palade, M.D.- 1974 Nobel Laureate in Physiology & Medicine

A. Personal Statement

I have been studying the regulation of mast cell activation and its role in neuroinflammatory diseases for over 30 years. I was the first to report that mast cells can: (a) secrete specific mediators selectively without degranulation; (b) regulate blood-brain-barrier permeability; (c) stimulate microglia; (d) be activated by corticotropin-releasing hormone (CRH) secreted under stress to release VEGF selectively; (e) be activated by synergistic action of CRH and neurotensin; (f) can be activated by IL-33 and substance P synergistically to secrete the pro-inflammatory cytokine TNF; (g) secrete mitochondrial DNA extracellularly that is mistaken by the body as a pathogen resulting in inflammatory reactions; (h) communicate with microglia and are involved in inflammation of the brain; (i) are inhibited by certain natural flavonoids, especially luteolin and tetramethoxyluteolin. I have published over 400 peer-reviewed papers (h-index 81) and have been placed in the top 5% of authors most cited in pharmacological and immunological journals. I, therefore, believe I am well qualified to contribute substantially to the proposed application.

- Angelidou A, Asadi S, Alysandratos KD, Karagkouni A, Kourembanas S, Theoharides TC. Perinatal stress, brain inflammation and risk of autism-review and proposal. **BMC Pediatr.** 2012;12:89. PMID:22747567
- Tsilioni I, Taliou A, Francis K, Theoharides TC. Children with autism spectrum disorders, who improved with a luteolin-containing dietary formulation, show reduced serum levels of TNF and IL-6. **Translational Psychiatry.** 2015;5:e647. PMID:26418275
- Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis and related disorders. **New Engl J Med.** 2015; 373(2):163-72. PMID:26154789
- Theoharides TC, Stewart JM, Panagiotidou S, Melamed I. Mast cells, brain inflammation and autism. **Eur J Pharmacol.** 2016;778:96-102. PMID:25941080

B. Positions and Honors

1968-1971 Assistant in Research, Department of Biology, Yale University, New Haven, CT
 1971-1978 Assistant in Research, Department of Pharmacology, Yale University, New Haven, C
 1978-1983 Research Associate, Allergy & Clin. Immunology, Dept. Internal Med, Yale

1984-1986 Associate in Clinical Immunology, Tufts University School of Medicine, Boston, MA
 1986-1993 Training in Internal Medicine, Dept. of Internal Medicine, NEMC, Center, Boston,
 1985-1992 Director of Medical Pharmacology, Tufts University School of Medicine, Boston,
 1983-1988 Assistant Professor of Pharmacology, Biochemistry and Psychiatry, Tufts University
 1989- Associate Professor of Pharmacology (1989-1994), Biochemistry and Psychiatry, Tufts
 1995- Professor of Pharmacology, and Biochemistry (2002-), Tufts U (tenured 11/2/91)
 1995- Professor of Internal Medicine (Allergy Section), Tufts Univ & Tufts Medical Center
 2004- Director, Molecular Immunopharmacology and Drug Discovery Laboratory, Tufts

Honors

1971 *Connecticut Commission for Undergraduate Research Award*
 1971 *Yale College Dean's Award* for senior research thesis
 1972 *Cum Laude & Divisional Honors* for joint Bachelor of Arts, Yale College
 1972 *Theodore Cuyler Award* "for outstanding Yale College graduates," Yale University
 1975-1977 *Advisory Committee to the Dean*, Yale University Graduate School
 1977 *G. Papanicolaou Graduate Research Award*, Hellenic University Club of New York
 1979-1983 *Medical Award*, Hellenic Medical Society of New York
 1980 *Winternitz Prize* "for the best work in Pathology," Yale Univ. School of Medicine
 1981-1982 *Research Fellowship*, International Inst. of Cellular & Molecular Pathology, Brussels
 1986-1989 *Chairman - Neuroimmunology*, 2nd & 3rd World Conf on Inflammation, Monte Carlo
 1986 *Distinguished Service Citation* for faculty excellence, Tufts University
 1987-1988 *Special Faculty Recognition Award*, Tufts University School of Medicine
 1987 *Member, Alpha Omega Alpha* National Medical Honor Fraternity, USA
 1989-1996 *Citation for Excellence in Teaching*, Tufts University School of Medicine
 1993 *Medical Awareness and Patient Support Award*, Interstitial Cystitis Association, NY
 1994 *Diocean Award for Humanitarian Health Care*, Greek Orthodox Diocese of Boston
 1995 *Chairman*, International Committee to Upgrade Medical Education in Greece
 1997-2001 *Supreme Scientific Advisory Health Council*, Secretary of Health, Hellenic Republic
 1998 *Community Service Award*, Mayor Thomas Menino of Boston, MA
 1999-2002 *Supreme Health Board*, Instit of Social Welfare, Sec. of Labor & Human Res,
 1999 *Oliver Smith Award* "recognizing excellence, compassion and service", NEMC
 1999 *Archon of the Ecumenical Patriarchate of Constantinople*, Greek Orthodox Church
 2002 *Dr. George Papanicolaou Gold Medal* for contributions in humanism and medicine
 2003-2008 *National Public Health Council*, Secretary of Health, Hellenic Republic
 2006 *Hygeia Award*, New Engl. Hellenic Medical & Dental Society, Boston, MA
 2007 *Science and Medicine Award*, Fed. HASNE, Boston, MA
 2008 *Fellow*, American Academy of Allergy, Asthma, Immunology
 2009 *Fellow*, European Academy of Allergology and Clinical Immunology
 2011 *Honorary Doctor of Medicine*, Athens University (conferred January, 2011)
 2013 *Honorary Doctor of Science*, HellenicAmerican University (conferred October, 2013)

Public Advisory Committees

1986-2018 Massachusetts Drug Formulary Commission
 2001-2002 NSF Div. Integrative Biology and Neuroscience
 2000-2002 NIH Biobehavioral & Behavioral Processes-SS2
 2002 NIH ZDK1 GRB-B (J2) Biol Neuroendoc Peptides
 2002 NIH ZDK11 GRB-9 Urology Research Centers
 2002 NIDDK Reparative Medicine Section (SSS-M)
 2003 VA Neurobiology Section A
 2004 Italian Ministry of Universities and Research
 2007 ZAI1 SV-IS1 Cellular & Inflammatory Pathways
 2007 NIAID Asthma & Allergic Diseases Cooperative Research Centers
 2008 NIH ZRG1 CFS-D
 2009 NIH ZDK1 GRB-6 Urology Research Centers

2009	SEP, National Center for Minority Health & Disparities (NCMHD)
2010	NIMSD ZRG1 MOSS-D12B SBIR: Dermatology, Rheumatology and Inflammation
2012	ZRG1 CFS-M (80) S-Chronic Fatigue Syndrome
2012	ZRG1 MOSS T12- Small Business: Dermatology, Rheumatology and Inflammation
2012	ZRG1 MOSS-S (04) S-Musculoskeletal, Oral a& Skin Sciences
2013	ZRG1 VH-D 02M Molecular and Cellular Hematology
2015	ZRG1 MOSS-V (02) M Special Emphasis Panel
2015	ZRG1 MOSS-C (02) Skin Immunology-CHAIR
2016	ZRG1 MOSS-C (02) Skin Immunology
2017	ZRG1 BBBP-L(40) P: RFA HD-17-009-Autism Centers of Excellence
2017	ZRG1 IFCN-N (U54) Myalgic Encephalopathy/Chronic Fatigue Syndrome CRCs
2017	ZRG1 IFCN-N (R21) Myalgic Encephalopathy/Chronic Fatigue Syndrome-CHAIR

Patents

Methods: US No. 5,250,529; 5,648,350; 5,821,259; 5,855,884; 5,994,357; 6,020,305; 6,689,748; 7,759,307; 7,923,0431; 8,268,365; 9,050,275; 9,176,146. EPO No. 0618796; EPO No. 0748217

Compositions: US No. 6,624,148; 6,635,625; 6,641,806; 6,645,482; 6,984,667; 7,155,278; 7,906,153; 7,799,766

Administrative Experience

President, Theta Biomedical Consulting and Development Co., Inc.

President, BiomedAdvice, LLC

President, BrainGate (non-profit-Greece)

Scientific Director, AutismFreeBrain (non-profit-USA)

Scientific Director, Algonot, LLC

C. Contribution to Science (publications selected from 400 in Pubmed.gov; 27,849 citations; h-index 81).

1. Mast cells secrete the mediators selectively, thus participating in different biological processes.

- Sieghart W, Theoharides TC, Alper LS, Douglas WW, Greengard P. Calcium dependent protein phosphorylation during exocytotic release of mast cell secretory granules. **Nature** 1978; 275:329-331. PMID: 357989
- Theoharides TC, Douglas WW. Secretion in mast cells induced by calcium entrapped within phospholipid vesicles. **Science** 1978; 201:1143-1145. PMID: 684435
- Theoharides TC, Sieghart W, Greengard P, Douglas, WW. Anti-allergic drug cromolyn may inhibit histamine secretion by regulating phosphorylation of a mast cell protein. **Science** 1980; 207:80-82. PMID: 6153130
- Theoharides TC, Bondy PK, Tsakalos ND, Askenase PW. Differential release of serotonin and histamine from mast cells. **Nature** 1982; 297:229-231. PMID: 6176873

2. Stress has pro-inflammatory effects through CRH-induced mast cell activation.

- Esposito P, Chandler N, Kandere K, Basu S, Jacobson S, Connolly R, Tutor D, Theoharides TC. Corticotropin-releasing hormone and brain mast cells regulate blood-brain-barrier permeability induced by acute stress. **J Pharmacol Exp Ther.** 2002; 303(3):1061-6. PMID: 12438528
- Cao J, Papadopoulou N, Kempuraj D, Boucher WS, Sugimoto K, Cetrulo CL, Theoharides TC. Human mast cells express corticotropin-releasing hormone (CRH) receptors and CRH leads to selective secretion of vascular endothelial growth factor (VEGF). **J Immunol.** 2005; 174:7665-7675. PMID: 15944267
- Donelan J, Papadopoulou N, Marchand J, Kempuraj D, Lytinas M, Boucher W, Papaliadis D, Theoharides TC. Corticotropin-releasing hormone (CRH) induces skin vascular permeability through a neurotensin (NT)-dependent process. **Proc Natl Acad Sci USA.** 2006; 103:7759-7764. PMID: 16682628; **PMCID: 2840132**
- Vasiadi M, Therianou A, Sideri K, Smyrnioti M, Delivani D, Sismanopoulos N, Asadi S, Katsarou-Katsari A, Petrakopoulou D, Theoharides A, Antoniou C, Stavrianeas N, Kalogeromitros D, Theoharides TC. Increased serum CRH levels with decreased skin CRH-R1 gene expression in

psoriasis and atopic dermatitis. *J Allergy Clin Immunol*. 2012; 129(5):1410-3. PMID: 22360979; PMCID: PMC3340539

3. **Mast cells, microglia and objective biomarkers in autism spectrum disorders.**

- Tsilioni I, Dodman N, Petra AI, Taliou A, Francis K, Moon-Fanelli A, Shuster L, Theoharides TC. Elevated serum neurotensin and CRH levels in children with autistic spectrum disorders and tail-chasing bull terriers with a phenotype similar to autism. *Translational Psychiatry*. 2014; 4:e466. PMID: 25313509
- Theoharides TC, Asadi S, Patel AB. Focal brain inflammation and autism. *J Neuroinflammation*. 2013;10:46. PMID:23570274
- Theoharides TC, Tsilioni I, Patel AB, Doyle R. Atopic diseases and inflammation of the brain in autism spectrum disorders. *Translational Psychiatry*. 2016;6(6):e844. PMID:27351598
- Patel AB, Tsilioni I, Leeman SE, Theoharides TC. Neurotensin stimulates sortilin and mTOR in human microglia inhibitable by methoxyluteolin, a potential therapeutic target for autism. *Proc Natl Acad Sci*. 2016; 113: E7049–E7058. PMID:27663735

4. **Luteolin and methoxyluteolin have potent anti-oxidant and anti-inflammatory actions.**

- Middleton E Jr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacol Rev*. 2000; 52(4):673-751. PMID: 11121513
- Kandere-Grzybowska K, Kempuraj D, Cao J, Cetrulo CL, Theoharides TC. Regulation of IL-1 induced selective release of IL-6 from human mast cells and inhibition by quercetin. *Br J Pharmacol*. 2006;148(2):208-15. PMID:16532021
- Weng Z, Patel AB, Panagiotidou S, Theoharides TC. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. *J Allergy Clin Immunol*. 2014; 135(4):1044-1052.e5. PMID: 25498791
- Patel AB, Theoharides TC. Methoxyluteolin Inhibits neuropeptide-stimulated proinflammatory mediator release via mTOR activation from human mast cells. *J Pharmacol Exp Ther*. 2017;361(3):462-471. PMID:28404689

5. **Mast cells are involved in inflammatory conditions.**

- Theoharides TC and Canellakis ZN. Spermine inhibits induction of ornithine decarboxylase by cAMP but not by dexamethasone in rat hepatoma cells. *Nature* 1975; 255:733-734. PMID: 49027
- Theoharides TC, Zhang B, Kempuraj D, Tagen M, Vasiadi M, Angelidou A, Alysandratos KD, Kalogeromitros D, Asadi S, Stavrianeas N, Peterson E, Leeman S, Conti P. IL-33 augments substance P-induced VEGF secretion from human mast cells and is increased in psoriatic skin. *Proc Natl Acad Sci USA*. 2010; 107(9):4448-53. PMID: 20160089; PMCID: 28401321
- Theoharides TC, Alysandratos KD, Angelidou A, Delivanis DA, Sismanopoulos N, Zhang B, Asadi S, Vasiadi M, Weng Z, Miniati A, Kalogeromitros D. Mast cells and inflammation. *Biochim Biophys Acta*. 2012; 1822(1):21-33. PMID: 21185371; PMCID: PMC3318920
- Taracanova A, Alevizos M, Karagkouni A, Weng Z, Norwitz E, Conti P, Leeman SE, Theoharides TC. SP and IL-33 together markedly enhance TNF synthesis and secretion from human mast cells mediated by the interaction of their receptors. *Proc Natl Acad Sci USA*. 2017;114(20):E4002-E4009. PMID: 28461492

For a full list of my publications, please copy and paste into a browser the following link:

<https://www.ncbi.nlm.nih.gov/sites/myncbi/1J3Voz5rx2NAq/bibliography/52767223/public/?sort=date&direction=ascending>

D. Research Support

Ongoing Research Support

Anonymous donation

PI: Theoharides

Expression of Neurotensin and its receptors in brains of children with autism

Duration 1/1/17-12/31/19

Anonymous donation

PI: Theoharides

Identification of exosomes in serum of children with autism and effect on cultured human microglia

Duration 1/1/17-12/31/19

Completed Research Support

Pfizer #WI194875

PI: Theoharides

Effect of inflammasome in psoriasis

Duration 1/1/15-12/31/16

National Psoriasis Foundation Translational Award

PI: Theoharides

The role of the novel mTOR pathway in psoriasis and the effect of methoxyluteolin

Duration: 6/1/13-5/31/15

Autism Research Institute

PI: Theoharides

Serum levels of CRH, neurotensin and mitochondrial DNA in children with autism

Duration: 7/1/14-6/30/15

1 R01 NS071361-05

PI: Theoharides

Brain mast cells and chronic fatigue syndrome

Duration: 7/1/10-6/30/15

1 R01 NS066205-04

MPI: Veves and LoGerfo; Role: Subcontract

Role of neuropeptides in diabetic foot problems

Duration: 7/1/10-6/30/15

2 R01 AR47652-11

PI: Theoharides

Stress induces skin mast cell activation and vasodilation

Duration: 9/1/07-8/31/13