

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 20 years. I was the first to report that mast cells: (a) can secrete specific mediators selectively without degranulation, that (b) can regulate blood-brain-barrier permeability, (c) can be activated by corticotropin-releasing hormone (CRH) to release VEGF selectively, (d) can be activated by synergistic action of CRH and neurotensin under stress, (e) can be activated by IL-33 and substance P synergistically, and (f) can secrete prestored TNF, accompanied by mitochondrial fission, translocation to the cell surface and release of mitochondrial DNA. I have been placed in the top 1% of authors most cited in pharmacological and in the top 5% of immunological journals.

B. Positions and Honors

1968-71 Assistant in Research, Department of Biology, Yale University, New Haven, CT
 1971-78 Assistant in Research, Department of Pharmacology, Yale University, New Haven, C
 1978-83 Research Associate, Allergy & Clin. Immunology, Dept. Internal Med, Yale
 1984-86 Associate in Clinical Immunology, Tufts University School of Medicine, Boston, MA
 1986-93 Training in Internal Medicine, Dept. of Internal Medicine, NEMC, Center, Boston,
 1985-92 Director of Medical Pharmacology, Tufts University School of Medicine, Boston,
 1983-88 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
 1975-77 *Advisory Committee to the Dean*, Yale University Graduate School
 1977 *G. Papanicolaou Graduate Research Award*, Hellenic University Club of New York
 1979,83 *Medical Award*, Hellenic Medical Society of New York
 1980 *Winternitz Prize* "for the best work in Pathology," Yale Univ. School of Medicine

- 1981,82 *Research Fellowship*, International Inst. of Cellular & Molecular Pathology, Brussels
 1986,89 *Chairman - Neuroimmunology*, 2nd & 3rd World Conf on Inflammation, Monte Carlo
 1986 *Distinguished Service Citation* for faculty excellence, Tufts University
 1987,88 *Special Faculty Recognition Award*, Tufts University School of Medicine
 1987 *Member, Alpha Omega Alpha National Medical Honor Fraternity*, USA
 1989-96 *Citation for Excellence in Teaching*, Tufts University School of Medicine
 1993 *Medical Awareness and Patient Support Award*, Interstitial Cystitis Association, NY
 1994 *Diocesan Award for Humanitarian Health Care*, Greek Orthodox Diocese of Boston
 1995 *Chairman*, International Committee to Upgrade Medical Education in Greece
 1997-01 *Supreme Scientific Advisory Health Council*, Secretary of Health, Hellenic Republic
 1998 *Community Service Award*, Mayor Thomas Menino of Boston, MA
 1999-02 *Supreme Health Board*, Instit of Social Welfare, Sec. of Labor & Human Res,
 1999 *Oliver Smith Award* "recognizing excellence, compassion and service", NEMC
 2000 *Archon of the Ecumenical Patriarchate of Constantinople*, Greek Orthodox Church
 2002 *Dr. George Papanicolaou Gold Medal* for contributions in humanism and medicine
 2003-08 *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

- 1986-18 Massachusetts Drug Formulary Commission
 2001-02 NSF Div. Integrative Biology and Neuroscience
 2000-02 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 DOD Autism Discovery grant applications

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; 12/534,571 (Allowed). 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

C. Contribution to Science (publications selected from 374 in Pubmed.gov; 21,930 citations; h-index 72).

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
- Kandere-Grzybowska K, Letourneau R, Kempuraj D, Donelan J, Poplawski S, Boucher W, Athanassiou A, Theoharides TC. L-1 induces vesicular secretion of IL-6 without degranulation from human mast cells. **J Immunol.** 2003; 171(9):4830-6. PMID:14568962
- 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
- Theoharides TC, Kempuraj D, Tagen M, Conti P, Kalogeromitros D. Differential release of mast cell mediators and the pathogenesis of inflammation. **Immunol Rev.** 2007; 217:65-78. PMID: 17498052

2. **Ornithine decarboxylase, polyamines and moesin regulate cell growth.**

- 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
- Canellakis ZN, Theoharides TC. Stimulation of ornithine decarboxylase synthesis and its control by polyamines in regenerating rat liver and cultured rat hepatoma cells. **J Biol Chem.** 1976; 251(14):4436-41. PMID:180026
- Theoharides TC, Canellakis ZN. Antiserum monospecific to hepatic ornithine decarboxylase. **J Biol Chem.** 1976; 251(6):1781-4. PMID:815261
- Correia I, Wang L, Pang X, Theoharides TC. Characterization of the 78 kDa mast cell protein phosphorylated by the antiallergic drug cromolyn and homology to moesin. **Biochem Pharmacol.** 1996; 52(3):413-24. PMID:8687495
- Theoharides TC, Wang L, Pang X, Letourneau R, Culm KE, Basu S, Wang Y, Correia I. Cloning and cellular localization of the rat mast cell 78-kDa protein phosphorylated in response to the mast cell "stabilizer" cromolyn. **J Pharmacol Exp Ther.** 2000; 294(3):810-21. PMID:10945828

3. **Corticotropin-releasing hormone (CRH) has pro-inflammatory effects through 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, Papaliodis 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](#)
- Theoharides TC, Petra AI, Stewart JM, Tsilioni I, Panagiotidou S, Akin C. High serum corticotropin-releasing hormone (CRH) and bone marrow mast cell CRH receptor expression in a mastocytosis patient. **J Allergy Clin Immunol.** 2014; 134(5):1197-9. PMID: 24985398

4. **Activated mast cells secrete mitochondrial components (ATP, DNA) outside the cells where they are misconstrued as innate pathogens mounting a strong auto-inflammatory response.**

- Zhang BD, Angelidou A, Alysandratos KD, Vasiadi M, Francis K, Asadi. S, Theoharides A, Sideri K, Lykouras L, Kalogeromitros D, Theoharides TC, Mitochondrial DNA and anti-mitochondrial

antibodies in serum of autistic children. *J Neuroinflammation*. 2010. 7(1):80. PMID: 21083929; PMCID: PMC3001695

- Zhang B, Alysandratos KD, Angelidou A, Asadi S, Sismanopoulos N, Delivanis D-A, Weng Z, Miniati A, Vasiadi M, Katsarou-Katsari A, Miao B, Leeman S, Kalogeromitros D, Theoharides TC. Human mast cell degranulation and granule-stored TNF secretion requires mitochondrial translocation to sites of exocytosis. *J Allergy Clin Immunol*. 2011; 127(6):1522-1531.e8. PMID: 21453958; PMCID: PMC3381794
- Asadi S, Theoharides TC. Corticotropin-releasing hormone and extracellular mitochondria augment IgE-stimulated human mast-cell vascular endothelial growth factor release, which is inhibited by luteolin. *J Neuroinflammation*. 2012; 9(1):85. PMID: 22559745; PMCID: PMC3464732
- Theoharides TC, Asadi S, Panagiotidou S, Weng Z. The "missing link" in autoimmunity and autism: extracellular mitochondrial components secreted from activated live mast cells. *Autoimmun Rev*. 2013; 12(12):1136-42. PMID:23831684

5. We have identified potential objective biomarkers for autism spectrum disorders.

- Angelidou A, Francis K, Vasiadi M, Alysandratos KD, Zhang B, Theoharides A, Lykouras L, Sideri K, Kalogeromitros D, Theoharides TC. Neurotensin is increased in serum of young children with autistic disorder. *J Neuroinflammation*. 2010; 7:48. PMID: 20731814; PMCID: PMC2936302
- Theoharides TC, Asadi S, Patel AB. Focal brain inflammation and autism. *J Neuroinflammation*. 2013; 10:46. PMID: 23570274; PMCID: PMC3626551.
- 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
- Petra AI, Panagiotidou S, Hatzigelaki E, Stewart JM, Conti P, Theoharides TC. Gut-Microbiota-Brain Axis and Its Effect on Neuropsychiatric Disorders With Suspected Immune Dysregulation. *Clin Ther*. 2015;37(5):984-995. doi: 10.1016/j.clinthera.2015.04.002. PMID:26046241
- Theoharides TC, Stewart JM, Panagiotidou S, Melamed I. Mast cells, brain inflammation and autism. *Eur J Pharmacol*. 2015 May 1. [Epub ahead of print]. PMID: 25941080
- 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. *Transl Psychiatry*. 2015 Sep 29;5:e647

6. IL-33 has strong synergistic effect with the peptide substance P inducing production of VEGF that disrupts both skin and brain protective barriers.

- 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, Petra A, Taracanova A, Panagiotidou S, Conti P. IL-33 targeting in autoimmune and inflammatory disorders. *J Pharm Exp Ther*. 2015; 354(1):24-31. PMID: 25906776
- Theoharides TC, Stewart JM, Hatzigelaki E, Kolaitis G. Brain "fog," inflammation and obesity: key aspects of neuropsychiatric disorders improved by luteolin. *Front Neurosci* 2015;9:225. PMID: 26190965

7. The natural flavonoids quercetin and luteolin have potent anti-oxidant and anti-inflammatory actions, while also inhibiting activation of keratinocytes, mast cells, microglia, and T-cells.

- 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
- Kempuraj D, Tagen M, Iliopoulou BP, Clemons A, Vasiadi M, Boucher W, House M, Wolfberg A, Theoharides TC. Luteolin inhibits myelin basic protein-induced human mast cell activation and mast cell-dependent stimulation of Jurkat T cells. *Br J Pharmacol*. 2008; 155(7):1076-84. PMID: 15912140; PMCID: 2597265

- Papaliadis D, Boucher W, Kempuraj D, Theoharides TC. The flavonoid luteolin inhibits niacin-induced flush. **Br J Pharmacol**. 2008; 153(7):1382-7. PMID: 18223672; PMCID: 2437911
- Weng Z, Patel AB, Vasiadi M, Therianou A, Theoharides TC. Luteolin inhibits human keratinocyte activation and decreases NF-κB induction that is increased in psoriatic skin. **PLoS One**. 2014; 28;9(2):e90739. PMID: 24587411; PMCID: 3938790
- 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

8. Mast cells are involved in inflammatory conditions that worsen with stress.

- Theoharides TC, Cochrane DE. Critical role of mast cells in inflammatory diseases and the effect of acute stress. **J Neuroimmunol**. 2004; 146(1-2):1-12. PMID: 14698841
- Theoharides TC, Sismanopoulos N, Delivanis DA, Zhang B, Hatzigelaki EE, Kalogeromitros D. Mast cells squeeze the heart and stretch the gird: their role in atherosclerosis and obesity. **Trends Pharmacol Sci**. 2011; 32(9):534-42. PMID: 21741097
- 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
- Theoharides TC, Enakuaa S, Sismanopoulos N, Asadi S, Papadimas EC, Angelidou A, Alysandratos KD. Contribution of stress to asthma worsening through mast cell activation. **Ann Allergy Asthma Immunol**. 2012;109(1):14-9. PMID: 22727152
- Theoharides TC. Atopic conditions in search of pathogenesis and therapy. **Clin Ther**. 2013; 35(5):544-7. PMID: 23642292
- Karagkouni A, Alevizos M, Theoharides TC. Effect of stress on brain inflammation and multiple sclerosis. **Autoimmun Rev**. 2013; 12(10):947-53. PMID: 23537508
- Sismanopoulos N, Delivanis DA, Mavrommati D, Hatzigelaki E, Conti P, Theoharides TC. Do mast cells link obesity and asthma? **Allergy**. 2013; 68(1):8-15. PMID: 23066905; PMCID: PMC3515712.
- Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis and related disorders. **New Engl J Med**. 2015; 373(2):163-72. PMID:26154789

D. Research Support

Ongoing Research Support

National Psoriasis Foundation Translational Award

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

PI: Theoharides

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

The Jane Botsford Johnson Foundation Research Award

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

PI: Theoharides

Environmental triggers activate mTOR in mast cells and microglia inhibited by methoxyluteolin

The Mastocytosis Society

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

PI: Theoharides

Serum levels of CRH, IL-33 and neurotensin in Mastocytosis

Autism Research Institute

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

PI: Theoharides

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

Michael S and Katherine Johnson Family Fnd.

Duration: 2/1/14-6/30/15

PI: Theoharides

Serum levels of CRH, neurotensin and IL-33 in fibromyalgia patients

Completed Research Support

1 R01 NS071361-05

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

PI: Theoharides

Brain mast cells and chronic fatigue syndrome

1 R01 NS066205-04

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

MPI: Veves and LoGerfo; Role: Subcontract

Role of neuropeptides in diabetic foot problems

2 R01 AR47652-11

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

PI: Theoharides

Stress induces skin mast cell activation and vasodilation