BIOGRAPHICAL SKETCH

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NAME: **Theoharides, Theoharis C.,**

eRA COMMONS USER NAME (credential, e.g., agency login): **THEOHAR**

POSITION TITLE: **Professor of Immunology**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	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 Physiology & Medicine; 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 cells and their role in allergic and inflammatory 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) be activated by corticotropin-releasing hormone (CRH) secreted under stress to release VEGF selectively; (d) be activated by synergistic action of CRH and neurotensin; (e) can be activated by IL-33 and substance P (SP) synergistically to secrete the pro-inflammatory cytokines IL1β and TNF; (f) secrete mitochondrial DNA (mtDNA) extracellularly that is mistaken by the body as a pathogen resulting in inflammatory reactions; (g) communicate with microglia and are involved in inflammation of the brain especially as they may relate to n the pathogenesis of Autism Spectrum Disorders, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Mastocytosis, diseases that are often comorbid and affect multiple organs without effective treatment. We have shown that secretion of mast cell mediators is inhibited by the natural flavonoids luteolin and methoxyluteolin. My laboratory has been committed to uncovering ways to regulate secretion of mast cell mediators for which there is no clinically effective drug since the only “mast cell blocker” cromolyn in weakly effective and shows rapid tachyphylaxis. I have published over 449 peer-reviewed papers (h-index 91) 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.

a. Theoharides TC, Valent P, Akin C. Mast Cells, Mastocytosis, and Related Disorders. ***N Engl J Med***. 2015;373(2):163-72. PMID:26154789

b. 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; PMCID: PMC5441798

c. Patel AB, Theoharides TC. Methoxyluteolin Inhibits Neuropeptide-stimulated Proinflammatory Mediator Release via mTOR Activation from Human Mast Cells. ***J Pharmacol Exp Ther***. 2017 Jun;361(3):462-471. PMID: 28404689

d. Taracanova A, Tsilioni I, Conti P, Norwitz ER, Leeman SE, Theoharides TC. Substance P and IL-33 administered together stimulate a marked secretion of IL-1β from human mast cells, inhibited by methoxyluteolin. ***Proc Natl Acad Sci USA***. 2018;115(40):E9381-E9390. PMID:30232261

B. Positions and Honors

Positions

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, CT
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 T*heodore 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 C*hairman,* 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,* Inst. of Social Welfare, Sec. of Labor & Human Res, Hellenic Rep
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
2010 *Inductee*, Rare Diseases Hall of Fame
2011 *Honorary Doctor of Medicine,* Athens University (conferred January, 2011)
2013 *Honorary Doctor of Science,* HellenicAmerican University (conferred October, 2013)
2018 *Albert Nelson Marquis Lifetime Achievement Award* (Marquis Who is Who)
2018 *Albert Nelson Marquis Distinguished Humanitarian Award* (Marquis Who is Who)
2020 Inductee, World Academy of Sciences

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 (50) Myalgic Encephalopathy/Chronic Fatigue Syndrome SEP
2019 ZRG1 CFS-N (80) S Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
2020 ZRG1 CFS-N (80) S Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

C. Contributions to Science (selected from 452 papers in Pubmed.gov; 35,150 citations; *h-index 91*).

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

Ever since I was a graduate student, I was fascinated by the ability of the mast cells to store or synthesize as many as 100 different biologically active mediators. As part of doctoral thesis, I showed that mast cells can secrete either the content of individual granules, without compound exocytosis, or individual mediators without degranulation. I further showed that there may be an internal mechanism regulating stimulus-secretion coupling and degranulation involving the phosphorylation of a particular protein we later cloned.The ability of mast cells to secrete individual mediators could explain their involvement in numerous pathophysiological processes and inflammatory diseases.

a. 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
b. Theoharides TC, Douglas WW. Secretion in mast cells induced by calcium entrapped within phospholipid vesicles. ***Science*** 1978; 201:1143-1145. PMID: 684435
c. 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
d. 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.

Allergic and inflammatory diseases are known to worsen with emotional and physical stress, but they has been historically considered to be of psychosomatic origin. We showed for the first time that the key hormone secreted under stress, corticotropin-releasing hormone (CRH) can be secreted outside the hypothalamic-pituitary adrenal axis and stimulate mast cells to selectively secrete pro-inflammatory mediators without degranulation, as well augment allergic triggers leading to degranulation. These findings extend out previous reports of the ability of mast cells to secrete individual mediators and expand the ability of mast cells to

participate in the pathogenesis of diseases that worsen with stress, including the disruption of the blood-brain barrier, which is involved in multiple sclerosis and other inflammatory diseases of the brain.

a. 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
b. 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
c. 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; PMC2840132
d. 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 are involved in inflammatory conditions.

Increasing evidence supports the involvement of mast cells not only in allergic, but also in inflammatory diseases. In order for the mast cells to play such an important role, they should be able to not only release pro-inflammatory mediators selectively, but do so in pathological quantities. We showed that when human mast cells are stimulated by the neuropeptide substance P together with the cytokine IL-33, they secrete impressive amounts of VEGF, TNF and IL-1β without degranulation. These results indicate that mast cells can respond to neuroimmune triggers with selective release of key mediators that could contribute to the development of neuroinflammation and may explain the pathogenesis of diseases such as Autism Spectrum Disorders, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Mastocytosis, diseases that are often comorbid and affect multiple organs without effective treatment.

a. 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
b. 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: 2840132I
c. 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 May 16;114(20):E4002-E4009. PMID: 28461492; PMCID: PMC5441798
d. Taracanova A, Tsilioni I, Conti P, Norwitz ER, Leeman SE, Theoharides TC. Substance P and IL-33 administered together stimulate a marked secretion of IL-1β from human mast cells, inhibited by methoxyluteolin. ***Proc Natl Acad Sci U S A***. 2018 Oct 2;115(40):E9381-E9390. PMID:30232261

4. Mast cells, microglia and objective biomarkers in autism spectrum disorder (ASD).

Autism is still classified as a psychiatric diseases and, in spite of the discovery of numerous mutations, the pathogenesis remain unknown and there are no objective biomarkers hampering its effective treatment. We showed that the peptide neurotensin, found in the brain and the gut, is uniquely increased in the serum of children with ASD as compared to normotypic controls. We further showed that neurotensin can stimulate human cultured microglia, the innate brain immune cells, to release pro-inflammatory mediators, possibly enclosed inside extracellular microvesicles that would protect them from degradation and allow them to reach the brain. These results support the presence of inflammation in the brain of children with ASD, possibly in the amygdala where microglia have been shown to be activated, and indicate that neurotensin could serve both as a biomarker and as a target for novel therapies. Two patents have been awarded to me as follows: US 9,050,275 (issued 06/09/15), entitled, “Methods of treating autism spectrum

disorders and compositions for same" and US 9,176,146 (issued 11/3/15) entitled, " Methods of screening for and treating autism spectrum disorders and compositions for same."

a. 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; PMCID: PMC5190146
b. Theoharides TC, Tsilioni I, Patel AB, Doyle R. Atopic diseases and inflammation of the brain in autism spectrum disorders. ***Translational Psychiatry***. 2016 Jun 28;6(6):e844. PMID:27351598; PMICD: PMC4931610
c. 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; PMCID: PMC5111711
d. Tsilioni I, Patel A, Pantazopoulos H, Barretta S, Conti P, Leeman SE, Theoharides TC. IL-37 is increased in brains of children with autism spectrum disorder and inhibits human microglia stimulated by neurotensin. ***Proc Natl Acad Sci USA.*** 2019;116(43):21659-21665. PMID:31591201.

5. Luteolin and methoxyluteolin have potent anti-oxidant and anti-inflammatory actions.

In spite of the involvement of mast cells in allergic and inflammatory diseases, there is no clinically effective inhibitors of the secretion of mast cell mediators, except for the "mast cell blocker" cromolyn, which is a weak inhibitor of histamine secretion and shows rapid tachyphylaxis. My lab has been committed to uncovering ways to regulate secretion of mast cell mediators for which there is no clinically effective drug since only the "mast cell blocker" cromolyn in weakly effective and shows rapid tachyphylaxis. We have shown that secretion of mast cell mediators is inhibited by the natural flavonoids luteolin and methoxyluteolin. The US patent no. 8,268,365 (issued 9/18/12) entitled, " Anti-inflammatory compositions for treating brain inflammation" has been awarded to me and involves flavonoid combinations now available in unique dietary supplements.

a. 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
b. 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 May;148(2):208-15. PMID:16532021; PMCID: PMC1617055
c. 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
d. Patel AB, Theoharides TC. Methoxyluteolin Inhibits neuropeptide-stimulated proinflammatory mediator release via mTOR activation from human mast cells. ***J Pharmacol Exp Ther***. 2017 Jun;361(3):462-471. PMID:28404689

For a full list of my publications, please copy and paste into a browser the following link:
https://www.ncbi.nlm.nih.gov/pubmed/?term=theoharides

D. Additional Information: Research Support

Ongoing Research Support

BioTechne, PI: Theoharides Duration 1/1/19-12/31/20
Effect of IL-38 on human microglia activation

Completed Research Support

Anonymous donation, PI: Theoharides Duration 1/1/17-12/31/19
Expression of neurotensin and its receptors in brains of children with autism

Anonymous donation, PI: Theoharides Duration 1/1/17-12/31/19
Identification of exosomes in serum of children with autism and effect on cultured human microglia

Solve ME/CFS Initiative 2018 Ramsay Award, PI: Theoharides Duration 11/1/18-12/31/19
Studied the role of extracellular vesicles in myalgic encephalomyelitits/chronic fatigue syndrome

Veritas Grants, PI: Theoharides Duration 1/1/17-12/31/18
Studied the effect of mycotoxins on human microglia