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, Medford, MA	Certificate	1999	Leadership & Managem
Harvard Univ, J.F. Kennedy School of Government, Boston, MA	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 am a Professor of Immunology, and my research is focused on the mechanism of selective secretion of cytokines and other pro-inflammatory molecules from mast cells. I have a broad background in immunology, and I have been studying the regulation of mast cells and their role in allergic and inflammatory diseases for over 30 years. My research efforts were the first to reveal 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 vascular endothelial growth factor (VEGF) selectively, (d) be activated by synergistic action of corticotropin-releasing hormone (CRH) and neurotensin, (e) can be activated by IL-33 and substance P (SP) synergistically to secrete the pro-inflammatory cytokines IL-1β and TNF, (f) secrete mitochondrial DNA (mtDNA) extracellularly that is mistaken by the body as a pathogen resulting in inflammatory reactions, and (g) communicate with microglia involved in inflammation of the brain. We have shown that secretion of mast cell and microglia mediators is inhibited by the natural flavonoids luteolin and methoxyluteolin, as well as by the cytokine IL-38. My laboratory has been committed to uncovering ways to regulate secretion of pro-inflammatory and vasoactive mediators from mast cells and microglia, as they may contribute to the pathogenesis of Autism Spectrum Disorders (ASD), Post-Acute Sequalae SARS-CoV-2 infection (PASC, also known as Long-COVID syndrome (L-COVID)), Mast Cell Activation Syndrome, and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), diseases that are often comorbid and affect multiple organs without effective treatment. I have published over 470 peer-reviewed papers (h-index 97) and have been placed in the world's top two percent of most cited scientists by Stanford University, and the top-rated expert in the world on mast cells by Expertscape. I, therefore, believe I am well qualified to contribute substantially to the proposed application. For this study, I will serve as the principal investigator (PI) of the Center and Project #1, as well as Co-PI of the Administrative Core. I, together with Dr. Klimas will be responsible for all aspects of the Center, will communicate with all participants and the Advisory Committee, as well review all experiments, the interpretation of the results and their publication.

Ongoing and recently completed projects that I would like to highlight include:

Anonymous donation
Theoharides (PI)
1/1/21-12/31/2023
Neuroimmune priming of human mast cells

BioTechne
Theoharides (PI)
1/1/19-8/30/2021
Effect of IL-38 on human microglia activation

Solve ME/CFS Initiative 2018 Ramsay Award
Theoharides (PI)
11/1/18-12/31/2019
Role of extracellular vesicles in Myalgic Encephalomyelitits/Chronic Fatigue Syndrome

Citations:

1. Hatziagelaki E, Adamaki M, Tsilioni I, Dimitriadis G, **Theoharides TC.** Myalgic Encephalomyelitis/Chronic Fatigue Syndrome-Metabolic disease or disturbed homeostasis due to focal inflammation in the hypothalamus? *J Pharmacol Exp Ther*. 2018 Oct;367(1):155-167. PMID: 30076265.
2. Tsilioni I, Pantazopoulos H, Conti P, Leeman SE, **Theoharides TC**. IL-38 inhibits microglial inflammatory mediators and is decreased in amygdala of children with autism spectrum disorder. *Proc Natl Acad Sci U S A.* 2020;117(28):16475-16480. PMID: 32601180
3. **Theoharides TC**. In Search of Effective Treatments for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Clin Ther.* 2019;41(5):796-797. PMID: 31030992.
4. Tziastoudi M, Cholevas C, Stefanidis I, **Theoharides TC**. Evidence of Overlap in Immunity-Associated Genes involving COVID-19 and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome based on genetic association and cohort studies: *Annals Clin Transl Neurol,* 2022. in press.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

7/1/2022 Professor, INIM and Director, Center of Excellence for Neuroinflammation Research, NSU
2021-2022 Visiting Professor, Institute of Neuro-Immune Medicine (INIM), Nova Southeastern Univer (NSU), FL
2018-2022 Chief Advisor and Chair, Health Education and Research Advisory Committee, The American College of Greece (part-time), Athens, Greece
2004-2022 Director, Molecular Immunopharmacology and Drug Discovery Laboratory, Tufts Univ, Boston, MA
1995- Professor of Internal Medicine (Allergy Section), Tufts Univ & Tufts Medical Center, Boston, MA
1995- Professor of Pharmacology, and Biochemistry (tenured 11/2/91), Tufts University, Boson, MA
1989-1994 Associate Professor of Pharmacology, Biochemistry and Psychiatry, Tufts University, Boston, MA
1983-1988 Assistant Professor of Pharmacology, Biochemistry and Psychiatry, Tufts University, Boston, MA
1985-1992 Director of Medical Pharmacology, Tufts University School of Medicine, Boston, MA
1986-1993 Training in Internal Medicine, Dept. of Internal Medicine, NEMC, Center, Boston, MA
1984-1986 Associate in Clinical Immunology, Tufts University School of Medicine, Boston, MA
1978-1983 Research Associate, Allergy & Clin. Immun., Dept. Internal Med, Yale University, New Haven, CT
1971-1978 Assistant in Research, Department of Pharmacology, Yale University, New Haven, CT
1968-1971 Assistant in Research, Department of Biology, Yale University, New Haven, CT

Public Advisory Committees

2022 ZRG1 MOSS-S (04) S-Musculoskeletal, Oral & Skin Sciences, Innate Immunity
2022 ZRG1 ETTN-U (82) S USU Intramural High Priority Research
2021 NIAID Clinical Trial Implementation Cooperative Agreement-Special Emphasis Panel
2020 ZRG1 CFS-N (80) S Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
2019 ZRG1 CFS-N (80) S Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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
2016 ZRG1 MOSS-C (02) Skin Immunology
2015 ZRG1 MOSS-V (02) M Special Emphasis Panel
2015 ZRG1 MOSS-C (02) Skin Immunology-CHAIR
2013 ZRG1 VH-D 02M Molecular and Cellular Hematology
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 & Skin Sciences
2010 NIMSD ZRG1 MOSS-D12B SBIR: Dermatology, Rheumatology and Inflammation
2009 NIH ZDK1 GRB-6 Urology Research Centers
2009 SEP, National Center for Minority Health & Disparities (NCMHD)
2008 NIH ZRG1 CFS-D
2007 ZAI1 SV-IS1 Cellular & Inflammatory Pathways
2007 NIAID Asthma & Allergic Diseases Cooperative Research Centers
2004 Italian Ministry of Universities and Research
2003 VA Neurobiology Section A
2002 NIH ZDK1 GRB-B (J2) Biol Neuroendocrine Peptides
2002 NIH ZDK11 GRB-9 Urology Research Centers
2002 NIDDK Reparative Medicine Section (SSS-M)
2001-2002 NSF Div. Integrative Biology and Neuroscience
2000-2002 NIH Biobehavioral & Behavioral Processes-SS2
1985-2022 Massachusetts Drug Formulary Commission

Honors

2020 Inductee, World Academy of Sciences
2018 Albert Nelson Marquis Distinguished Humanitarian Award (Marquis Who is Who)
2018 Albert Nelson Marquis Lifetime Achievement Award (Marquis Who is Who)
2013 Honorary Doctor of Science, Hellenic-American University (conferred October, 2013)
2011 Honorary Doctor of Medicine, Athens University (conferred January, 2011)
2010 Inductee, Rare Diseases Hall of Fame
2009 Fellow, American Academy of Allergology and Clinical Immunology
2008 Fellow, American Academy of Allergy, Asthma, Immunology
2007 Science and Medicine Award, Fed. HASNE, Boston, MA
2006 Hygeia Award, New Engl. Hellenic Medical & Dental Society, Boston, MA
2003-2008 National Public Health Council, Secretary of Health, Hellenic Republic
2002 Dr. George Papanicolaou Gold Medal for contributions in humanism and medicine
1999 Archon of Ecumenical Patriarchate of Constantinople, Greek Orthodox Church
1999 Oliver Smith Award “recognizing excellence, compassion and service”, NEMC
1999-2002 Supreme Health Board, Inst. of Social Welfare, Sec. of Labor & Human Res, Hellenic Rep
1998 Community Service Award, Mayor Thomas Menino of Boston, MA
1997-2001 Supreme Scientific Advisory Health Council, Secretary of Health, Hellenic Republic
1995 Chairman, International Committee to Upgrade Medical Education in Greece
1994 Diocean Award for Humanitarian Healthcare, Greek Orthodox Diocese of Boston
1994-2000 Member, Board of Directors, Institute of Pharmaceutical Research and Technology, Athens
1993 Medical Awareness and Patient Support Award, Interstitial Cystitis Association, NY
1989-1996 Citation for Excellence in Teaching, Tufts University School of Medicine
1987 Inductee, Alpha Omega Alpha National Medical Honor Fraternity, USA
1987-1988 Special Faculty Recognition Award, Tufts University School of Medicine
1986 Distinguished Service Citation for faculty excellence, Tufts University
1986-1989 Chairman - Neuroimmunology, 2nd & 3rd World Conf on Inflammation, Monte Carlo
1981-1982 Research Fellowship, International Inst. of Cellular & Molecular Pathology, Brussels
1980 Winternitz Prize "for the best work in Pathology," Yale Univ. School of Medicine
1979-1983 Medical Award, Hellenic Medical Society of New York
1977 G. Papanicolaou Graduate Research Award**,** Hellenic University Club of New York
1975-1977 Advisory Committee to the Dean, Yale University Graduate School
1972 Theodore Cuyler Award "for outstanding Yale College graduates," Yale University

1972 Cum Laude & Divisional Honors for joint Bachelor of Arts, Yale College
1971 Yale College Dean's Award for senior research thesis
1971 Connecticut Commission for Undergraduate Research Award

C. Contributions to Science (selected from 470 papers in Pubmed.gov; 41,027 citations; *h-index 97*).

1. **Mast cells secrete the mediators selectively, thus participating in different biological processes.** As part of my doctoral thesis, I showed that mast cells can secrete either the content of individual granules, without compound exocytosis, or individual mediators without degranulation. In addition, I 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.** We showed for the first time that the key hormone secreted under stress, 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 expand on 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.** We showed that when human mast cells are stimulated by the neuropeptide SP 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 ASD, ME/CFS, 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;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;115(40):E9381-E9390. PMID:30232261

4. **Mast cells, microglia and objective biomarkers in ASD.** 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 United States 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;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 antioxidant and anti-inflammatory actions.** 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 is 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 United States 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;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;361(3):462-471. PMID:28404689

Complete List of Published Work in My Bibliography:
https://pubmed.ncbi.nlm.nih.gov/?term=Tehoharides&filter=dates.1968-2022&sort=date