

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.  
Follow the sample format on preceding page for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Theoharis C. Theoharides	POSITION TITLE Professor of Pharmacology and Internal Medicine		
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. of Medicine
Yale University, New Haven, CT	M.S.	1975	Neuropharmacology
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 of Law and Diplomacy	Certificate	1999	Leadership & Management
Harvard University, J.F. Kennedy School of Government	M.P.A.	Deferred	Biomedical Research Policy

\*Thesis advisors: W.W. Douglas, M.D.-Royal Acad. Sci.; Paul Greengard, Ph.D.-2000 Nobel Laureate in Physiology & Medicine

**Academic Appointments**

- 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, CT  
 1978-83 Research Associate, Clin. Immunology, Dept. Internal Med, Yale Uni & Bioch. Res. Lab. UAMC, CT  
 1983-88 Assistant Professor of Pharmacology, Biochemistry and Psychiatry, Tufts University, MA  
 1985-92 Director of Medical Pharmacology, Tufts University School of Medicine, Boston, MA  
 1989-93 House Staff, Dept. of Internal Medicine, New England Medical Center, Boston, MA  
 1989- Associate Professor of Pharmacology (1989-1994), Biochemistry and Psychiatry, Tufts University  
 1995- Professor of Pharmacology and Internal Medicine, Tufts University (tenured 11/2/91)  
 2002- Professor of Biochemistry, Tufts University

**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 *Travel Award*, American Society for Cell Biology  
 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  
 1984 *Chairman - Immunopharmacology*, 9th Int'l Congress of Pharmacology, London  
 1984 *Travel Award*, American Society for Pharmacology and Experimental Therapeutics  
 1986 *Chairman - Neuroimmunology*, 2nd World Conference 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 *Honorary Member, Alpha Omega Alpha National Medical Honor Fraternity*, USA  
 1989 *Chairman - Neuroimmunomodulation*, 3rd World Conference on Inflammation, Monte Carlo  
 1989,90 *Citation for Excellence in Teaching*, Tufts University School of Medicine  
 1991,93 *Advisory Committee*, 4th & 5th World Conferences on Inflammation, Geneva  
 1991-94 *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  
 1995,97 *Advisory Committee*, 6th & 7th World Conference on Inflammation, Geneva  
 1995 *Chairman*, International Committee to Upgrade Medical Education in Greece, Secretary of Health  
 1996 *Citation for Excellence in Teaching*, Tufts University School of Medicine  
 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*, Institute of Social Welfare, Sec. of Labor & Human Resources, Hellenic Republic  
 1999 *Oliver Smith Award* "recognizing excellence, compassion and service", New Engl. Med. Center, Boston  
 2000 *Archon of the Ecumenical Patriarchate of Constantinople*, Greek Orthodox Church, Instambul, Turkey  
 2001 *Plenary Speaker*, National Minority Research Symposium (USA), Cancun, Mexico  
 2002 *Dr. George Papanicolaou Gold Medal* for contributions in humanism and medicine

**Selected Publications** (from over 200)

- Theoharides TC and Canellakis ZN. Spermene inhibits induction of ornithine decarboxylase by cAMP but not by dexamethasone in rat hepatoma cells. **Nature** 255:733-734, 1975.
- Sieghart W, Theoharides TC, Alper LS, Douglas WW, Greengard P. Calcium dependent protein phosphorylation during exocytotic release of mast cell secretory granules. **Nature** 275:329-331, 1978.
- Theoharides TC, Douglas WW. Secretion in mast cells induced by calcium entrapped within phospholipid vesicles. **Science** 201:1143-5, 1978.
- 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** 207:80-82, 1980.
- Theoharides TC, Bondy PK, Tsakalos ND, Askenase PW. Differential release of serotonin and histamine from mast cells. **Nature** 297:229-231, 1982.
- Theoharides TC. Mast cells: the immune gate to the brain. **Life Sciences** 46:607-617, 1990.
- Lambracht-Hall M, Dimitriadou V, Theoharides TC. Migration of mast cells in the rat brain. **Brain Res** 56:151-9, 1990.
- Lambracht-Hall M, Konstantinidou AD, Theoharides TC. Serotonin release from brain mast cells. **Neuroscience** 39:199-207, 1990.
- Dimitriadou V, Lambracht-Hall M, Reichler J, Theoharides TC. Histochemical and ultrastructural characteristics of rat brain perivascular mast cells stimulated with compound 48/80 and carbachol. **Neuroscience** 39:209-224, 1990.
- Dimitriadou V, Buzzi MG, Moskowitz MA, Theoharides TC. Trigeminal sensory fiber stimulation induces morphologic changes reflecting secretion in rat dura mater mast cells. **Neuroscience** 44:97-112, 1991.
- Dimitriadou V, Buzzi MG, Theoharides TC, Moskowitz, MA. Ultrastructural evidence for neurogenically mediated changes in blood vessels of the rat dura mater and tongue following antidromic trigeminal stimulation. **Neuroscience** 48:187-203, 1992.
- Theoharides TC, Dimitriadou V, Letourneau R, Rozniecki JJ, Vliagoftis H, Boucher W. Synergistic action of estradiol and myelin basic protein on mast cell secretion and brain demyelination. **Neuroscience** 57:861-871, 1993.
- El-Mansoury M, Boucher W, Sant GR, Theoharides TC. Increased urine histamine and methylhistamine in interstitial cystitis. **J Urol** 152:350-353, 1994.
- Rozniecki JJ, Hauser SL, Stein M, Lincoln R, Theoharides TC. Elevated mast cell tryptase in cerebrospinal fluid of multiple sclerosis patients. **Ann Neurol** 37:63-66, 1995.
- Theoharides TC, Sant GR, El-Mansoury M, Letourneau RJ, Ucci A, Meares E. Activation of bladder mast cells in interstitial cystitis - a light and electron microscopic study. **J Urol** 153:629-636, 1995.
- Pang X, Cotreau-Bibbo MM, Sant GR, Theoharides TC. Bladder mast cell expression of high affinity estrogen receptors in interstitial cystitis. **Br J Urol** 75:154-161, 1995.
- Pang X, Marchand J, Sant GR, Kream RM, Theoharides TC. Increased number of substance P positive nerve fibers in interstitial cystitis. **Br J Urol** 75:744-750, 1995.
- Boucher W, El-Mansoury M, Pang X, Theoharides TC. Elevated mast cell tryptase in the urine of interstitial cystitis. **Br J Urology** 76:94-100, 1995.
- Theoharides TC, Spanos C, Pang X, Alferes L, Ligris K, Letourneau R, Rozniecki JJ, Webster E, Chrousos GP. Stress-induced intracranial mast cell degranulation: A CRH-mediated effect. **Endocrinology** 136:5745-5750, 1995.
- Letourneau, R, Sant, GR and Theoharides TC. Intragranular activation of bladder mast cells and their association with nerve processes in interstitial cystitis. **Br J Urol** 77:41-54, 1996.
- Pang X, Letourneau R, Rozniecki JJ, Wang L, Theoharides TC. Definitive characterization of rat brain mast cells. **Neuroscience** 73:889-902, 1996.
- Spanos C, El-Mansoury M, Letourneau R, Minogiannis P, Greenwood J, Siri P, Sant GR, Theoharides TC. Carbachol-induced bladder mast cell activation. Augmentation by estradiol and implications for interstitial cystitis. **Urology** 48:809-816, 1996.
- Pang X, Sant GR, Theoharides TC. Altered expression of bladder mast cell growth factor receptor (c-kit) expression in interstitial cystitis. **Urology** 51:939-944, 1998.
- Theoharides TC, Singh L, Boucher W, Pang X, Letourneau R, Webster E, Chrousos G. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability: a possible explanation for its pro-inflammatory effects. **Endocrinology** 139:403-413, 1998.
- Pang X, Alexacos N, Letourneau R, Seretakis D, Gao W, Boucher W, Cochrane DE, Theoharides TC. A neurotensin receptor antagonist inhibits acute immobilization stress-induced cardiac mast cell degranulation, a corticotropin-releasing hormone-dependent process. **J Pharmacol Exp Therap** 287:307-314, 1998.
- Conti P, Reale M, Barbacane RC, Letourneau R, Theoharides TC. Intramuscular injection of hrRANTES causes mast cell recruitment and increased transcription of histidine decarboxylase in mice. Lack of effects in genetically mast cell-deficient W/W<sup>v</sup> mice. **FASEB J** 12:1693-1700, 1998.
- Singh L, Boucher W, Pang X, Letourneau R, Seretakis D, Green M, Theoharides TC. Potent mast cell degranulation and vascular permeability triggered by urocortin through CRH receptors. **J Pharmacol Exp Therap** 288:1349-1356, 1999.
- 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 78kD protein phosphorylated in response to the mast cell "stabilizer" cromolyn. **J Pharmacol Exp Therap** 294:810-821, 2000.

- Deliargyris EN, Raymond RJ, Theoharides TC, Boucher W, Tate D, Dehmer GJ. Sites of interleukin-6 release in patients with acute coronary syndromes and in patients with congestive heart failure. **Am J Cardiol** 86:913-918, 2000.
- Theoharides T.C., Patra P, Boucher W, Letourneau R., Kempuraj D, Chiang G., Jeudy S. Hesse L, Athanasiou A. Chondroitin sulfate inhibits connective tissue mast cells. **Brit J Pharmacol** 131:1039-1049, 2000.
- Dimitriadou V, Pang X, Theoharides TC. Hydroxyzine inhibits experimental allergic encephalomyelitis (EAE) and associated brain mast cell activation. **Intl J Immunopharmacol** 22:673-684, 2000.
- Chiang G, Patra P, Letourneau R, Jeudy S, Boucher W, Green M, Sant GR, Theoharides TC. Pentosanpolysulfate inhibits mast cell histamine secretion and intracellular calcium ion levels: an alternative explanation of its beneficial effect in interstitial cystitis. **J Urology** 164: 2119-2125, 2000.
- Middleton E, Kandaswami C, Theoharides TC. The effect of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. **Pharmacol Rev** 52:673-751, 2000.
- Esposito P, Georghe D, Pang X, Kandere K, Connolly R, Jacobson S, Theoharides TC. Acute stress increases permeability of the blood-brain-barrier through activation of brain mast cells. **Brain Res** 888:117-127, 2001.
- Esposito P, Connolly R, Jacobson S, Gheorghe D, Theoharides TC. Gamma camera demonstration of <sup>99m</sup>Tc gluceptate extravasation in rat brain by acute stress. **Brain Res Protocols** 8:143-149, 2001.
- Reuter U, Bolay H, Jansen-Olesen I, Chiarugi A, Sanchez del Rio M, Letourneau R, Theoharides TC, Waeber C, Moskowitz, MA. Delayed inflammation in rat meninges: implications for migraines. **Brain** 124:2490-2502, 2001.
- Katsarou-Katsari A, Singh LK, Theoharides TC. Alopecia areata and affected skin CRH receptor upregulation induced by acute emotional stress. **Dermatology** 203:157-161, 2001.
- Boucher WS, Letourneau R, Huang M, Kempuraj D, Green M, Sant GR, Theoharides TC. Intravesical sodium hyaluronate inhibits the rat urinary mast cell mediator increase triggered by acute immobilization stress. **J Urol** 167:380-384, 2002.
- Theoharides TC. Mast cells and stress - A psychoneuroimmunological perspective. **J Clin Psychopharm** 22:103-108, 2002.
- Chandler N, Jacobson S, Esposito P, Connolly R, Theoharides TC. Acute stress shortens the time of onset of experimental allergic encephalomyelitis (EAE) in SJL/J mice. **Brain, Behavior, Immunity** 13:225-239, 2002.
- Esposito P, Chandler N, Kandere K, Basu S, Jacobson S, Connolly R, Tutor D, Theoharides TC. Corticotropin-releasing hormone (CRH) and brain mast cells regulate blood-brain-barrier permeability induced by acute stress, **J Pharmacol Exp Therap** 303:1061-1066, 2002.
- Huang M, Pang X, Letourneau R, Boucher W, Theoharides TC. Acute stress induces cardiac mast cell activation and histamine release that are increased in apolipoprotein E knockout mice. **Cardiovascular Res** 55:150-160, 2002.
- Theoharides TC, Kandere, K. Mast cell involvement in neurogenic inflammation. In **Migraine: a Neuroinflammatory Disease?** (E.L.H. Spierings and M. Sanchez del Rio, eds.), pp.115-132, Birkhäuser verlag:basel, Switzerland, 2002.
- Esposito P, Basu S, Letourneau R, Jacobson S, Theoharides, TC. Corticotropin-releasing factor (CRF) can directly affect brain microvessel endothelial cells. **Brain Res** 968:192-198, 2003.
- Lytinas M, Kempuraj D. Huang M, Boucher W, Esposito P, Theoharides TC. Acute stress results in skin CRH secretion, mast cell activation and vascular permeability, an effect mimicked by intradermal corticotropin-releasing hormone and inhibited by histamine –1 receptor antagonists. **Intl Arch Allergy Immunol** 130: 224-231, 2003.
- Madhappan B, Kempuraj D, Christodoulou S, Boucher W, Tsapikidis S, Karagiannis V, Athanassiou A, Theoharides TC. High levels of intrauterine corticotropin-releasing hormone, urocortin, tryptase and interleukin-8 in spontaneous abortions. **Endocrinology** 144:2285-2290, 2003.
- Huang M, Pang X, Karalis K, Theoharides TC. Stress-induced interleukin-6 release in mice is mast cell-dependent and more pronounced in Apolipoprotein E knockout mice. **Cardiovascular Res** 59:241-249, 2003.
- Kandere-Grzybowska K, Georghe D, Esposito P, Huang M, Gerard NP and Theoharides TC. Stress-induced dura vascular permeability does not develop in mast cell-deficient and neurokinin-1 receptor knockout mice. **Brain Res** 980:213-220, 2003.
- Alexandrakis M, Letourneau R, Kempuraj D, Kandere-Grzybowska K, Huang M, Christodoulou S, Boucher W, Seretakis D, Theoharides TC. Flavones inhibit proliferation and increase mediator content in human leukemic mast cells (HMC-1). **Eur J Hematol** 71:1-7, 2003.
- Maurer M, Theoharides TC, Granstein RD, Bischoff SC, Bienenstock J, Henz B.M., Kovanen, P.T., Piliponsky, A.M., Kambe, N., Vliagoftis, H., Levi-Schaffer, F., Metz, M., Miyachi, H., Befus, D., Forsythe, P., Kitamura, Y., Galli, S. What is the physiological function of mast cells? **Exp. Dermatol** 12:1-24, 2003.
- Kandere-Grzybowska K, Letourneau R, Kempuraj D, Donelan J, Paplawski S, Boucher W, Athanassiou A, Theoharides, TC. IL-1 induces vesicular secretion of IL-6 without degranulation from human mast cells. **J Immunol** 171:4830-4836.
- Letourneau R, Rozniecki JJ, Dimitriadou V, Theoharides TC. Ultrastructural evidence of brain mast cell activation without degranulation in monkey experimental allergic encephalomyelitis (EAE). **J Neuroimmunol**, in press.
- Kempuraj D, Basu S, Huang M, Kandere-Grzybowska K, Boucher W, Letourneau R, Athanassiou A, Theoharides TC. Azelastine inhibits secretion of IL-6, TNF- $\alpha$  and IL-8 as well as NF- $\kappa$ B activation and intracellular calcium ion levels in normal human mast cells. **Intl Arch Allergy Immunol**, in press.
- Kempuraj D, Papadopoulou N, Lytinas M, Huang M, Kandere-Grzybowska K, Madhappan B, Boucher W, Christodoulou S, Athanassiou A. Theoharides TC. Corticotropin-releasing hormone (CRH) and its structurally related urocortin (Ucn) are synthesized and secreted by human mast cells. **Endocrinology**, in press.

Theoharides TC, Conti P. Mast cells: the Jekyll and Hyde of tumor growth. *Trends Immunol*, in press.

Theoharides TC, Cochrane D. Critical role of mast cells in inflammatory diseases and the effect of acute stress. *J Neuroimmunol*, in press.

### Public Advisory Committees:

1986-03	Massachusetts Drug Formulary Commission	2002	NIH ZDK1 GRB-B (J2) Biol Neuroendoc Peptid
2000-02	NIH Biobehavioral & Behavioral Processes-SS2	2002	NIDDK Reparative Medicine Section (SSS-M)
2001-02	NSF Div. Integrative Biology and Neuroscience	2002	DK ZDK11 GRB-9 Urology Research Centers
2003	VA Neurobiology Section		

### U.S. Patents:

#### **Method claims**

#5,250,529 (10/05/93)	Prevention of migraines	#6,020,305 (02/01/00)	Treating skin disorders with CRH antagonists
#5,648,350 (07/15/97)	Painful gastrointestinal syndromes	#08/67,310 (08/13/03)	CRH receptor blockers for cardiac ischemia (allowed)
#5,855,884 (01/05/99)	Stress-induced migraines	#09/056,707 (07/23/03)	Proteoglycans for mast cell conditions (allowed)
#5,821,259 (10/13/98)	Histamine-3 receptor agonists	#10/166,088 (filed 06/11/02)	Treating IL-6-mediated inflammation
#5,994,357 (11/30/99)	Hydroxyzine for interstitial cystitis		

#### **Composition claims**

#6,624,148 (issued 09/23/03)	Proteoglycan compositions for the treatment of cardiovascular inflammatory diseases (allowed)
#6,635,625 (issued 10/21/03)	Proteoglycan compositions for the treatment of bladder/prostate inflammation (allowed)
#6,641,806 (issued 11/04/03)	Proteoglycan compositions for the treatment of arthritic inflammation conditions (allowed)
#10/329367 (filed 05/20/03)	Proteoglycan compositions for the treatment of skin inflammatory diseases (allowed)
#51275/142 (filed 07/02/03)	Proteoglycan compositions for the treatment of cardiovascular inflammatory diseases (pending)
#09/711, 669 (filed 01/30/01)	Proteoglycans/flavonoids for inflammation (CIP/DIV of 09/056.707)
#09/773, 576 (filed 02/02/01)	Proteoglycans/antihistamines divisional (DIV of 09/056.707)
#10/439,139 (filed 05/16/03)	Proteoglycans/flavonoids for inflammation (CIP of 09/056.707)
#PCT/US02/00476 (filed 01/03/02)	Proteoglycans/flavonoids for inflammation (CIP of 09/771,669) EPO entered National Phases

### Research Support

#### Recent

<b>1 R01 NS38326 NINDS (PI: Theoharides)</b> CRH-induced dura mast cell activation	Duration: 7/1/99-6/30/03 Direct Cost/yr: \$153,573	40%
<b>1 U01 DK065244 NIDDK (PI: Sant; Co-I: Theoharides)</b> Interstitial cystitis clinical trials group	Duration: 7/1/98-6/30/03 Direct Cost/yr: \$140,000	10%

#### Active

<b>1 U01 DK065244 NIDDK (PI: Sant; Co-I: Theoharides)</b> Interstitial Cystitis Collaborative Research Network	Duration: 9/1/03-2/28/08 Direct Cost/yr: \$150,000	10%
<b>1 R01 AR47652 NIAMSD (PI: Theoharides)</b> Stress induces skin mast cell activation and vasodilation	Duration: 4/1/01-3/31/06 Direct Cost/yr: \$175,000	30%
<b>1 R01 DK062861 NIDDK (PI: Theoharides)</b> Acute restraint stress-induced neurogenic bladder inflammation	Duration: 5/1/03-4/30/07 Direct Cost/yr: \$175,000	30%
<b>BC024430 DOD-Concept Award (PI: Theoharides)</b> Role of mast cells in mammary gland carcinogenesis	Duration: 9/1/03-8/31/04 Direct Cost/yr: \$75,000	5%

#### Competitive Renewal

<b>1 R01 NS38326 NINDS (PI: Theoharides)</b> CRH-induced dura mast cell activation	Duration: 7/1/04-6/30/09 Direct Cost/yr: \$153,573	20%
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#### Pending

<b>RFA GM-03-009 (PI: Theoharides)</b> Center of Excellence for Complex Biomedical Systems Research	Duration 7/1/04-6/30/09 Direct Cost/yr: \$1,810,256	30%
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Principal Investigator/Program Director (Last, first, middle): Theoharides, Theoharis, C.