BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Marilyn L. Thoman	Research Professor
eRA COMMONS USER NAME (credential, e.g., agency login) MTHOMAN	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of California, Santa Barbara, CA	B.A.	1974	Biology
University of California, Berkeley, CA	Ph.D.	1978	Molecular Biology
Scripps Clinic & Research Foundation, La Jolla, CA	Postdoc	1978-1982	Immunology

A. Personal Statement

I have over 30 years of experience in the study of immunology; immunosenescence, lymphocyte development, lymphocyte/macrophage activation, inflammation, and innate immunity. My research efforts have focused on senescence in systemic immunity and thymic function. More recently my work has focused on innate immunity and host pathogen interactions utilizing viral and bacterial models.

B. Positions and Honors

Positions and Employment

1982 – 1983	Research Associate, Department of Immunology, Scripps Clinic and Research Foundation, La Jolla, CA
1983 – 1991	Assistant Member, Department of Immunology, Scripps Clinic and Research Foundation, La Jolla, CA
1991 – 1997	Assistant Member, Department of Immunology, The Scripps Research Institute, La Jolla, CA
1997 – 2009	Associate Professor, Sidney Kimmel Cancer Center, San Diego, CA
2009 – present	Research Professor, San Diego State University, Donald P. Shiley BioScience Center
2009 – present	Adjunct Research Professor, Department of Biology, San Diego State University

Other Experience and Professional Memberships

1974-1977	National Science Foundation, Graduate Fellow
1977-1978	University of California at Berkeley, Regents Fellowship
1980-1983	U.S. Public Health Service National Research Service Award
1984-1986	American Federation for Aging Research (AFAR), Inc., Research Award
1984-1987	Arthritis Foundation Investigator Award
1987-1992	U.S. Public Health Service Research Career Development Award
1984-present	American Association of Immunologists

C. Contributions to Science

1. Impact of advancing age on the peripheral T cell compartment

Elderly individuals are at significant risk for infectious disease and the development of chronic inflammatory pathologies. This risk stems in part from alterations in the function of cells comprising the innate and adaptive immune systems and in the coordination between these two branches. Many of my contributions to science have involved dissecting the impact of age on T cell differentiation and function and in approaches to regenerate this compartment.

Advancing age is associated with alterations in the capacity of the T lymphocyte compartment to adequately respond to antigenic stimulus. We now understand the immunosenescence of T cells to be due to shifts in the repertoire, intrinsic changes in cellular function as well as to extrinsic changes that alter the microenvironment, shaping the response outcome. I have made several contributions to the understanding of T lymphocyte immunosenescence. Included amongst my contributions are; I was amongst the first to report that production of Th1 cytokines is impaired in the aged and that supplementation of various immune responses by the addition of IL-2 could largely compensate for the deficiency and restore immune-vigor. Our group was one of the earliest to identify the compositional changes occurring in the of the aged peripheral T cell compartment, that shifts over time to one with an increased percentage of memory-phenotype cells at the expense of naïve populations. Assessment of the capacity of the aged thymus to regenerate depleted T cell populations revealed that advanced age lowers the number of newly emergent T cells, the kinetics of T cell differentiation do not change with age. Further, the regenerated population retains the memory-enriched proportion that was seen prior depletion. The mechanisms supporting the re-emergence of a preponderance of memory T cells is not fully understood, but likely to be due largely to peripheral expansion.

A. Timm J.A., and **Thoman, M.L.** (1999). Maturation of CD4+ lymphocytes in the aged microenvironment results in a memory-enriched population. J. Immunol. 162:711.

B. Thoman, M.L. (1999). Aging affects the regeneration of the $CD8^+$ T cell compartment in bone marrow transplanted mice. Mech Aging Dev. 112:113-124.

C. Thoman, ML. (1997) Effects of the aged microenvironment on CD4+ T cell maturation. Mech. Age. Dev. 96:75.

D. Thoman, M.L. (1997) Early steps in T cell development are affected by aging. Cell. Immunol. 178:117.

E. Hobbs. M.V., Ernst, D.N., Glasebrook A.L., Rehse M.A., McQuitty, D. N., **Thoman M.L.,** etal. (1991). Cell proliferation and cytokine production by CD4+ from old mice. J. Cell. Biochem. 46:312Mu X.Y., and

2.T Lymphocyte Differentiation- Thymic Involution and Regeneration

A hallmark feature of vertebrate aging is the loss of thymic mass and reduced production of T lymphocytes. It is believed that the loss of T cell differentiation contributes to the skewing of the repertoire and supports the gradual accumulation of memory at the expense of naïve populations. During T cell differentiation within the thymus, bone marrow-derived progenitors enter at the cortico-medullary boundary and undergo a precise program of cell differentiation and migration through the thymic parenchyma. During the aging process, a combination of fewer cells transiting key maturation steps as well as diminished expansion of thymocyte subsets results in the dramatic diminution in the production and release of mature T cells to the periphery. I have had a long-term interest in T cell differentiation in the involuting thymus and have made several contributions to our understanding of this process. I identified specific developmental transitions that are particularly vulnerable to aging. We established that the initial earliest progenitor transition, from the TN1 to TN2 state (characterized by the acquisition of CD25 expression) is particularly vulnerable to aging. Further, the proliferative expansion of the TN4 subset is also an age-sensitive developmental step. Age-associated limitations at these strategic points significantly diminish T cell differentiation in the aging thymus.

Our overriding interest is in understanding the mechanisms underlying the age- related changes in T cell differentiation with the goal of restoring vigorous T cell production in the elderly. To this end, our focus has been to identify how aging affects regulatory factors that control the earliest steps of T cell development. Our work has focused on the reconstitution of thymopoiesis by means of increasing thymic epithelial cell functionality in the aged as well as identifying other regulatory molecules involved with restricting T cell differentiation. To assess the impact on thymopoiesis, a novel somatic cell gene therapy approach was developed. Thymic stromal cells were genetically engineered to express the protein of interest, then implanted into the thymus of variously aged mice. Utilizing the known deficiencies in signaling molecules produced by the thymic epithelial cells with age our group was able to engineer a stromal cell line to produce IL-7 and transplant these lines into the thymic rudiment of adult mice. The implanted cells stably integrated into the

thymic architecture. Implantation of IL-7 producing stromal epithelial cells promoted the progenitor DN1 to DN2 transition in the aging thymus, but did not correct the loss of T cell production. Other proteins known to be involved with epithelial cell signaling, including Wnt 4 and sonic hedgehog were also investigated.
In order to further investigate the regulation of T cell differentiation during age, we initiated an analysis of of miRNA expression in the major DN subsets, comparing populations purified from young and aged animals. This miRNA profiling revealed that a significant overexpression of multiple miRNA species characterized the aged DN1 population. Several hundred miRNA species were overexpressed relative to expression in the same population derived from young mice. With each successive differentiative step, there were decreasing differences in the relative expression of the panel of miRNA species.

A. Virts, E.L., **Thoman M.L.** (2010). Age-associated changes in miRNA expression profiles in thymopoiesis. Mech. Ageing Dev. 131:743-8. PMCID: PMC3005860

B. Virts, E.L., Phillips, J.A., **Thoman, M.L.** (2006). A novel approach to the thymic rejuvenation in the aged. Rejuvenation Res. 9(1):134-42.

C. Phillips, J.A., Bronstetter, T.I., English, C.A., Virts, E.L., and **Thoman, M.L.** (2004). IL-7 gene therapy in aging rescues thymic lineage commitment without reversing involution. J Immunol. 173:4867-4874.

D. Thoman, M.L. (1997) Early steps in T cell development are affected by aging. Cell. Immunol. 178:117.

E. Thoman, M.L. (1995). The pattern of T lymphocyte differentiation is altered during thymic involution. Mech.Age.Devel. 82:155.

3. Immunoregulatory Properties of Immunoglobulin and Complement Proteins

Two effector mechanisms of humoral immunity are those mediated by secreted antibodies and those mediated by the proteins comprising the complement system (also is an important effector of innate immunity). Cells of both the adaptive and innate immune compartments bear receptors that bind portions of immunoglobulin molecules (Fc receptors) or various complement protein fragments that upon ligation of results in important immunoregulatory responses. My contribution to the understanding of these regulatory responses includes: 1. The first description and characterization of a secreted T cell product induced by stimulation with Fc fragments. This material possesses B cell stimulatory activity and is integral to the Fc fragment induction of polyclonal immunoglobulin synthesis in both humans and mice: 2. The identification of IL-1 and IL-6 as macrophage products triggered by Fc binding to these cells and: 3. The identification of a tetrapeptide sequence (residues 351-355) in the Fc region that possesses B cell differentiation-inducing activity.

The observation that mammalian leukocytes possess receptors for various components of complement prompted speculation that the complement system might influence adaptive immune function. In particular both the third and fifth complement components (C3 and C5) and their cleavage products have been demonstrated to regulate aspects of innate and adaptive immunity. We have had a long-standing interest in the immunoregulatory properties of the anaphylatoxins. We described the suppression of human polyconal anitboty secretion by C3a and identified that one mode of action was through the activation of a CD8+ suppressor T cell. Conversely, the anaphylatoxin, C5a displays immunoenhancing activity that potentiates specific and non-specific human humoral immune responses and T cell proliferative responses. The carboxyterminal arginine of C5a was found not to be required for these activities. Further work identified the induction of various pro-inflammatory cytokines as important mediators of the C5a activity. Our identification of the peptide sequences possessing regulatory activity allowed the development of response-selective peptide mimetics of C3a and C5a.

A. Morgan, E.L., Morgan, B.N., Stein, E.A., Virts, E.L., **Thoman, M.L.**, Sanderson, S.D., and Phillips, J.A. (2010). Enhancement of In Vivo and In Vitro Immune Functions by a Conformationally-Biased, Response-Selective Agonist of Human C5a: Implications for a Novel Adjuvant in Vaccine Development. Vaccine 28: 463-

469. PMCID: PMC2789185

B. Morgan, E.L., Hobbs, M.V., **Thoman, M.L**., Janda, J., Noonan, D.J., Kadar, J., and Weigle, W.O. (1990). Induction of Human B Cell differentiation by Fc Region Activators. II. Stimulation of IL-6 Production. J. Immunol. 144: 2499-2505.

C. Morgan, E.L., Hobbs, M.V. **Thoman, M.L**. and Weigle, W.O. (1986) Lymphocyte Activation by the Fc Region of Immunoglobulins. Immunol. Invest. 15:625-687.

D. Morgan, E.L., **Thoman, M.L**., Hobbs, M.V., Weigle, W.O. and Hugli, T.E. (1985). Human C3a-Mediated Suppression of the Immune Response. II. Suppression of Human *in Vitro* Polyclonal antibody Responses Occurs through the Generation of Nonspecific OKT8+ Suppressor T Cells. Clin. Immunol. Immunopath. 37:114-123.

E. Morgan, E.L., **Thoman, M.L**., Weigle, W.O., and Hugli, T. E. (1983). Anaphylatoxin-Mediated Regulation of the Immune Response. II. C5a-Mediated enhancement of Human Humoral and T Cell-Mediated Immune Responses. J. Immunol. 130: 1257-1261.

4. Development of a C5a-peptido-mimetic with unique immunoenhancing activity

We have developed several peptido-mimetics of C5a that activate macrophages and dendritic cells but are not capable of driving mast cell degranulation. These peptide-mimetics (EP67/EP54) conjugated to various antigens, possess a profound adjuvant activity that enhances both Th1/Th2 type immunoglobulin synthesis, likely due to enhancement of antigen processing and pro-inflammatory cytokine release. We have extended these observations on EP67 adjuvant activity into the aged mouse model, demonstrating that EP67 is more effective than either Complete Freund's adjuvant or the Toll-like Receptor ligand, CpGs, for the induction of immunoglobulin responses to protein antigens in older animals. Recently we have developed a mucosal vaccine incorporating EP67 and antigenic peptides derived from influenza that can be administered by insufflation to the nasal-associated mucosal tissue. In early preliminary tests it has been shown to reduce morbidity to influenza infection in a mouse model.

In addition to the adjuvant activity that requires physical association of the EP67 and antigenic determinant, EP67 alone triggers potent immunoprotective innate immune responses against several bacterial, fungal and viral pathogens. Subcutaneous administration of EP67 shortens the duration and severity of Staphyloccocal skin infections, and cervical administration reduces Group B streptococcal infections of the female genital tract. Insufflation of the lungs with EP67 within 24 hours of influenza infection (either pre- or post-infection), limits the morbidity of a sub-lethal viral dose. Very recently we have demonstrate that an effectiveRemarkably, administration of EP67 within this time period, can prevent mortality. EP67 is also able to effectively induce similar protective responses in the skin and lungs of aged mice.

A. Patras, K.A., Rosler, B., **Thoman, M.L.,** and Doran, K.S. (2015). Characterization of host immunity during persistent vaginal colonization by Group B *Streptococcus.* Mucosal Immunology. Advance online publication Apr.8 2015. doi: 10.1038/mi.2015.23.

B. Cavaco, C.K., Patras, K.A., Samal. J., **Thoman, M.L.**, Morgan, E.L., Sanderson, S.D., and Doran, K.S. (2013). A novel C5a-derived immunobiotic peptide reduces Streptococcus agalactiae colonization though targeted bacterial killing. Antimicrobial agents and Chemotherapy 57(11): 5492-5499. PMCID: PMC3811312

C. Sanderson S.D., **Thoman M.L**., Kis K., Virts EL., Herrera E.B., Widdman S., Sepulveda H., and Phillips J.A. (2012). Innate Immune Induction and Influenza Protection Elicited by a Response-Selective Agonist of Human C5a**.** PLoS ONE 7(7): e40303

D. Sheen, T.R., Cavaco, C.K., Ebrahimi, C.M., **Thoman, M.L**., Sanderson, S.D., Morgan, E.L., Doran, K.S**.** (2011). Control of Methicillin Resistant Staphylococcus aureus Infection Utilizing a Novel Immunostimulatory

Peptide. Vaccine. 30:9-13. PMCID: PMC3229650

E. Morgan, E., **Thoman, M**., Sanderson, S., and Phillips J. (2010). A Novel Adjuvant for Vaccine Development in the Aged. Vaccine 28:8275-8279. PMCID: PMC2997863

5. Pulmonary Cholinergic Anti-Inflammatory Pathway Activation During Influenza Infection

Inflammatory cytokine production can be regulated by the brain via the cholinergic anti-inflammatory pathway, or CAP. In this pathway, locally secreted acetylcholine binds to α7 nicotinic acetylcholine receptors on inflammatory macrophages, inhibiting NF-κB nuclear translocation and down-regulating synthesis of inflammatory cytokines such as TNF, IL-1β, IL-6, and HMGB1. This pathway is presumed to function in the lungs, but the source of local acetylcholine secretion in response to pulmonary inflammation is as yet unknown. We have found that acetylcholine-secreting CD4 T cells (i.e., cholinergic CD4 T cells) appear in the lungs and airways during influenza infection. These cells are antigen-specific and express surface proteins matching those expressed by CD4 T resident memory cells. They can be identified in the lungs for at least onemonth after infection and appear at a time when viral burden is very low. This is the first evidence for cholinergic lymphocyte involvement during infectious disease. Pulmonary acetylcholine concentrations increase during influenza infection, peaking on day 10 co-incident with the peak number of cholinergic CD4 T cells, before dropping to basal concentrations by day 15 post-infection. We hypothesize that cholinergic CD4 T cells are the source of the increased airway acetylcholine, that acetylcholine is secreted in response to antigen-specific stimulation, and that this acetylcholine plays a crucial role in regulating the immune response in the recovery stage of infection, possibly influencing the polarization of resident macrophages to a pro-repair state.

A full list of my published work is found at the following site:

http://www.ncbi.nlm.nih.gov/sites/myncbi/marilyn.thoman.1/bibliography/40333323/public/?sort=date&direction=ascending

Teaching Experience

Point Loma Nazarene University- Lecturer August 2014-2015
Responsibilities include: curriculum preparation and instruction of Microbiology, Microbiology Lab, Medical Microbiology and Biochemistry and Cell Biology

San Diego State University – Lecturer August 2013-Present
Responsibilities include: curriculum development and implementation for Advanced Biochemistry and Molecular Cell Biology, Advanced Cellular and Molecular Immunology, Biology of Aging

San Diego Community College District- Lecturer Spring 2016-Present
Microbiology and Lab

Completed SDSU Flexible Course Design Summer Institute
Currently enrolled in Introduction to Teaching with Canvas Self-Paced Course at SDSU & the Online Faculty Certification Program at SDCCD Mesa