BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Osborne, Barbara A.	Professor of Veterinary and Animal Science
eRA COMMONS USER NAME (credential, e.g., agency login) Barbara_Osborne	

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
Moravian College, Bethlehem, PA	B.A.	1970	English
Stanford University, Stanford, CA	Ph.D.	1979	Genetics/Immunology
National Institutes of Health/NCI, Bethesda, MD	Postdoctoral	1979-82	Immunology

A. Personal Statement

My laboratory has studied a variety of aspects of CD4 and CD8 T cell biology over the past several years and has made several seminal observations regarding the both the activation and death of T cells and these are outlined below in my Contributions to Science. Most recently, my lab addressed the role of Notch signaling in the activation of both CD4 and CD8 T cells. Another current active area of investigation is based on the role of a bacterial exopolysaccharide in blocking T cell inflammatory responses. In collaboration with Dr. Katherine Knight at Loyola University, Chicago, we have discovered that this polysaccharide effectively blocks inflammation in several mouse models of inflammatory based diseases.

In addition to my scientific endeavors, I have been actively involved in graduate education. I was the Director of the interdisciplinary Molecular & Cellular Biology Program at UMass for five years and was, until recently, the PI of an NIH T32 Training Grant in Biotechnology from NIGMS. Importantly, I have been involved in the creation of a new Institute of Applied Life Sciences (IALS) at UMass and am Co-Chair of the Center for Bioactive Delivery, one of the three centers created in IALS.

Additionally, in 1999, I co-founded a biotech company, Hematech, LLC, that grew from 3 to over 30 employees by 2005 when we sold the company to Kirin Pharmaceuticals. I also co-founded HasenTech Inc with Professors Katherine Knight and Richard Goldsby. In 2019, University of Massachusetts was awarded a patent (US 10,383,888) entitled “Exopolysaccharide for Inflammatory Disease” and this patent forms the basis of the work described in this application.

B. Positions and Honors

Positions and Employment

1977-1979 Graduate Student, Stanford University, Stanford, CA
1979-1981 Damon Runyon-Walter Winchell Postdoctoral Fellow, National Institutes of Health
1981-1983 Staff Fellow, National Institutes of Health
1983-1985 Five Colleges Research Associate, Amherst College, Amherst, MA
1985-1989 Assistant Professor, Department of Veterinary and Animal Sciences, University of Massachusetts, Amherst, MA
1989-1995 Associate Professor, Department of Veterinary and Animal Sciences, University of Massachusetts, Amherst, MA
1995-Present Professor, Department of Veterinary and Animal Sciences, University of Massachusetts, Amherst, MA
2019-Present Distinguished University Professor, University of Massachusetts, Amherst, MA.
1998-2005 Co-Founder and Senior Consultant, Hematech, LLC (www.hematech.com)

1992	Visiting Associate Professor, Laboratory of Dr. Robert Horvitz, Department. of Biology, Massachusetts Institute of Technology, Cambridge, MA
1995	Visiting Scientist, Laboratory of Dr. Robert Weinberg, Whitehead Institute, Cambridge, MA
1999-2000	Visiting Professor, Laboratory of Dr. Robert Weinberg, Whitehead Institute, Cambridge, MA

Other Experience and Professional Memberships

1996-	Whitehead Institute Board of Associates, Cambridge, MA
1993 - 2002	Senior Editor, East Coast Office of *Cell Death & Differentiation*
1998 - 2003	Editorial Board, Journal of Immunology
2002	Chancellor's Distinguished Lecturer, University of Massachusetts
2000 - 2004	Member, Damon Runyon-Walter Winchell Board of Scientific Advisors
2000 - 2005	Member, National Institute of Allergy and Infectious Diseases Board of Scientific Counselors
2002 - 2005	Chair, National Institute of Allergy and Infectious Diseases Board of Scientific Counselors
2008 - 2010	Member, National Institute on Aging, Board of Scientific Counselors
2010 - 2013	Chair, National Institute on Aging, Board of Scientific Counselors
2010 -	Director, Molecular and Cellular Biology Program, University of Massachusetts
2012-present	Member, Massachusetts Life Sciences Center, Scientific Advisory Board
2013-present	Co-Chair, Center for Bioactive Delivery, Institute for Applied Life Sciences, UMass

Honors

1997	John Amos Comenius Alumni Award for Outstanding Achievement, Moravian College, Bethlehem, PA
1999 - 2000	Samuel Conti Award for Excellence in Research, University of Massachusetts, Amherst, MA
2005	Dean's Award, College of Natural Resources & the Environment, University of Massachusetts, Amherst, MA
2006	Chancellor's Award for Outstanding Research, University of Massachusetts, Amherst, MA
2023	Elected as Fellow of the National Academy of Inventors

C. Contributions to Science

1. **First report of T cell hybrids:** My first major contribution to science came during my PhD research at Stanford University conducted in the laboratory of Leonard Herzenberg. I came to the Herzenberg lab, pre-Kohler and Milstein, interested in making hybrids that secreted immunoglobulin and ended up instead producing the first characterized T cell hybrids. These data were first published in 1977 in *Nature*.

a. Goldsby RA, **Osborne BA**, Simpson E, Herzenberg LA. Hybrid cell lines with T-cell characteristics. Nature. 1977 Jun 23;267(5613):707-8. PubMed PMID: 301614.
b. **Osborne BA**, Goldsby RA, Herzenberg LA. Selective expression of loci in the I—J region on T cell hybrids. Curr Top Microbiol Immunol. 1978;81:217-20. PubMed PMID: 80306.
c. Goldsby RA, **Osborne BA**, Suri D, Mandel A, Williams J, Gronowicz E, Herzenberg LA. Production of specific antibody without specific immunization. Curr Top Microbiol Immunol. 1978;81:149-51. PubMed PMID: 308436.

2. **First report of isolation and characterization of cell death genes expressed in the mouse thymus.** After establishing my own laboratory at UMass in 1985, I became interested in the process of cell death. In the late 1980's essentially all of the research in cell death was conducted in either *C. elegans* or *Drosophila,* however it was becoming apparent that cell death was also an important process in shaping the immune repertoire. My laboratory decided to follow the lead of invertebrate biologists who had identified genes important in cell death in model organisms and to attempt to clone genes that mediated apoptosis in the thymus during negative selection. We were successful in this approach and reported, in *Nature*, the isolation of Nur77, a gene that regulates apoptosis in T cells. We were amongst the first who cloned and identified genes that regulate apoptosis in vertebrates. We went on to collaborate with Tyler Jacks to demonstrate that p53, a well known tumor suppressor gene, also is important in driving apoptosis in T cells. This paper, published in *Nature*, was the first to describe a role for p53 in regulating apoptosis. Over the next 10 years, my lab focused on the process of apoptosis in lymphocytes.

a. Liu ZG, Smith SW, McLaughlin KA, Schwartz LM, **Osborne BA**. Apoptotic signals delivered through the T-cell receptor of a T-cell hybrid require the immediate-early gene nur77. Nature. 1994 Jan 20;367(6460):281-4. PubMed PMID:8121494.
b. Lowe SW, Schmitt EM, Smith SW, **Osborne BA**, Jacks T. p53 is required for radiation-induced apoptosis in mouse thymocytes. Nature. 1993 Apr 29;362(6423):847-9. PubMed PMID: 8479522.
c. Schwartz LM, Smith SW, Jones ME, **Osborne BA**. Do all programmed cell deaths occur via apoptosis? Proc Natl Acad Sci U S A. 1993 Feb 1;90(3):980-4. PubMed PMID: 8430112; PubMed Central PMCID: PMC45794.
d. Grimm LM, Goldberg AL, Poirier GG, Schwartz LM, **Osborne BA**. Proteasomes play an essential role in thymocyte apoptosis. EMBO J. 1996 Aug 1;15(15):3835-44. PubMed PMID: 8670888; PubMed Central PMCID: PMC452071.

3. **First report of the induction of Notch activation through TCR signaling:** While investigating the mechanism of how Nur77 induces apoptosis, we conducted a yeast two-hybrid screen to identify protein interaction partners with Nur 77. This screen yielded the murine Notch1 protein as an interactor with Nur77. We went on to show that Notch1 expression blocks apoptosis in T cells. These data were published in the Cutting Edge section of Journal of Immunology. This observation led us to the demonstration that TCR stimulation induces Notch1 activity and over the last 10-12 years, we have shown that Notch1 expression is critically important in many functions of $CD4^+$ T cells. Most notably, we were the first to demonstrate that Notch1 expression is necessary for the induction of Th1 cells and blockade of Notch1 activation can block the development of a Th1 regulated disease, EAE, and these data were published in *Nature Immunology*. In an attempt to determine the mechanism by which Notch regulates $CD4^+$ T cell function, we were the first to find that Notch signaling in T cells leads to activation of NF-kB. Others have subsequently found that Notch signaling activates NF-kB in many other cell types. Additionally, we have demonstrated unique functions for Notch signaling in driving differentiation of Th17 cells, iTreg cells and CTL maturation. Taken together these findings suggest Notch signaling plays a critical role in many aspects of $CD4^+$ T cell activation and function. Most recently, we have explored the mechanisms by which Notch influences T cell function and surprisingly have found that much of Notch signaling in T cells occurs through non-canonical Notch signaling pathways and our current focus is defining these non-canonical pathways. Our goal in this research is to identify targets of Notch that may prove useful in regulating Notch function in disease.

    a. Jehn, B., Bielke, W., Pear, W., & **Osborne, B.A**. (1999). Nur77 and Notch-1 cooperate in the regulation of cell death. Cutting Edge/J. Immunol., 162:635-38
    b. Palaga, T., Miele, L., Golde,T.E., & **Osborne, B.A**. (2003) TCR-mediated Notch signaling regulates proliferation and IFN-gamma production in peripheral T cells. J Immunol. Sep 15;171(6):3019-24. PMID: 12960327.
    c. Minter, L.M., Turley, D.M., Das, P., Shin, H.M., Joshi, I., Lawlor, R.G, Cho, O.H., Palaga, T., Telfer, J.C., Kostura, L., Fauq, A.H., Simpson, K., Such, K.A., Miele, L., Golde, T.E., Miller, S.D. & **Osborne, B.A.** (2005). Inhibitors of γ–secretase inhibitors block in vivo and in vitro Th1 polarization by preventing Notch upregulation of Tbx21. Nat Immunol. Jul; 6(7):680-8. PMID: 15991363.
    d. Shin, H.M., Minter, L.M., Cho, O.H., Gottipati, S., Fauq, A.H., Golde, T.E., Sonenshein, G.E., and **Osborne B.A.** (2006) Notch1 Augments NF-γB Activity by Facilitating its Nuclear Retention. EMBO J., 125:129-38.

4. **Formation of the first biotech company to clone cows expressing human antibodies:** In addition to the more traditional contributions to science listed above, I was involved in starting a biotech company, Hematech LLC, in 1999. Hematech was formed by three scientists, Jim Robl, Richard Goldsby and myself along with a lawyer, Jim Barton. Our goal was to create genetically engineered cows that produce human inmmunoglobulin. Since antibodies are broadly neutralizing for many viruses and bacteria, we reasoned that a large animal producing human polyclonal antibodies could serve as a valuable source of human IVIG and ultimately protection against a number of important human pathogens. We took advantage of the cloning technology developed by Jim Robl and produced cows through cloning that lack bovine Ig loci and express human Ig genes. This was accomplished through genetic deletion of the bovine Ig loci as well as deletion of the gene that encodes susceptibility to BSE. Three patents resulted from these accomplishments and Hematech, LLC was sold to Kirin Pharmaceuticals in 2005. Each of the partners in this venture had unique contributions. Jim Robl was the inventor of the cloning technology, Richard Goldsby and myself provided the

immunology expertise and knowledge of the bovine Ig loci and Jim Barton provided the business and legal experience necessary to run a company. During this period, I wrote and was awarded three SBIRs that supported the research.

a. Kuroiwa Y, Kasinathan P, Choi YJ, Naeem R, Tomizuka K, Sullivan EJ, Knott JG, Duteau A, Goldsby RA, Osborne BA, Ishida I, Robl JM. Cloned transchromosomic calves producing human immunoglobulin. Nat Biotechnol. 2002 Sep;20(9):889-94.Epub 2002 Aug 12. PubMed PMID: 12172556.

b. Patent # 7,491,867 - issued 2/17/09
Expression of xenogenous (human) immunoglobulins in cloned, transgenic ungulates
Inventors: Robl; James M. (Brandon, SD), *Goldsby*; Richard A. (Leverett, MA), Ferguson; Stacy E. (Dallas, TX), Kuroiwa; Yoshimi (Sioux Falls, SD), Tomizuka; Kazuma (Gunma, JP), Ishida; Isao (Isehara, JP), **Osborne; Barbara A.** (Leverett, MA)

c. Patent # 7,414,170 - issued 8/19/08
Transgenic bovines capable of human antibody production
Inventors: Robl; James M. (Brandon, SD), Kasinathan; Poothappillai (Sioux Falls, SD), *Goldsby*; Richard A. (Leverett, MA), Kuroiwa; Yoshimi (Sioux Falls, SD), Tomizuka; Kazuma (Takasaki, JP), Ishida; Isao (Isehara, JP), **Osborne; Barbara** (Leverett, MA)

d. Patent # 7,074,983 - issued 7/11/06
Transgenic bovine comprising human immunoglobulin loci and producing human immunoglobulin
Inventors: Robl; James M. (Brandon, SD), *Goldsby*; Richard A. (Leverett, MA), Ferguson; Stacy E. (Dallas, TX), Kuroiwa; Yoshimi (Takasaki, JP), Tomizuka; Kazuma (Takasaki, JP), Ishida; Isao (Isehara, JP), **Osborne; Barbara A**. (Leverett, MA)

5. **Strategies for Targeted Drug Delivery:** During the past 4 years, UMass Amherst has created the Institute for Applied Life Sciences (IALS). There are three centers within IALS, one of which is the Center for Bioactive Delivery (CBD). I am co-chair of CBD with Thai Thayumanavan. As such, we lead a group of UMass investigators interested in developing various platforms for drug delivery. The creation of IALS and CBD has driven enhanced collaboration between drug delivery groups and labs with biological systems amenable for delivery. As an immunologist, we work with cells that can easily be manipulated ex vivo and returned to an in vivo environment. This has led to several collaborations highlighted below.

a. Prasad P, Molla MR, Cui W, Canakci M, **Osborne B**, Mager J, **Thayumanavan S**. Polyamide Nanogels from Generally Recognized as Safe Components and Their Toxicity in Mouse Preimplantation Embryos. Biomacromolecules. 2015 Nov 9;16(11):3491-8. PubMed Central PMCID: PMC4970214.

b. Gordon MR, Canakci M, Li L, Zhuang J, **Osborne B, Thayumanavan S**. Field Guide to Challenges and Opportunities in Antibody-Drug Conjugates for Chemists. Bioconjug Chem. 2015 Nov 18;26(11):2198-215. PubMed Central PMCID: PMC4933296.

c. Moyano DF, Liu Y, Ayaz F, Hou S, Puangploy P, Duncan B, **Osborne BA**, Rotello VM. Immunomodulatory effects of coated gold nanoparticles in LPS-stimulated in vitro and in vivo murine model systems. Chem. 2016;1(2):320-327. PubMedCentral PMCID: PMC5328597.

d. Ozay EI, Gonzalez-Perez G, Torres JA, Vijayaraghavan J, Lawlor R, Sherman HL, Garrigan DT Jr, Burnside AS, **Osborne BA**, Tew GN, Minter LM. Intracellular Delivery of Anti-pPKCθ (Thr538) via Protein Transduction Domain Mimics for Immunomodulation. Mol Ther. 2016 Dec;24(12):2118-2130. PubMed Central PMCID: PMC5167783.

My full list of my publications can be found at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/barbara.osborne.1/bibliograpahy/40844590/public/?sort=date&direction=ascending