BIOGRAPHICAL SKETCH

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NAME: Dartt, Darlene, Ann

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

POSITION TITLE: Professor of Ophthalmology (Cellular and Molecular Physiology)

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
Wells College, Aurora, New York	OTH	06/1969	Biology
Barnard College of Columbia University, New York City, New York	AB	06/1971	Biology
University of Pennsylvania, Philadelphia, PA	PhD	06/1978	Physiology

A. Personal Statement

The overall goal of my research has been the neural regulation of tear production and is currently focused on the cellular signaling pathways that nerves and growth factors use to stimulate lacrimal gland protein secretion and mucin secretion from conjunctival goblet cells under normal conditions and then to determine the dysfunction of these pathways in dry eye syndrome, allergy, refractive surgery, and during aging. For lacrimal gland secretion, we have described the steps of the many redundant signaling pathways activated by neurotransmitters and growth factors to induce lacrimal gland protein secretion. With Dr. Masli we have also investigated a new model of dry eye syndrome, the thrombospondin (TSP)-1 knockout mouse, and detailed the dysfunction of stimulated lacrimal gland protein secretion. Our work revolutionized the area of conjunctival goblet cell function, as we found that nerves responding to the external environment stimulate goblet cell secretion to protect the ocular surface from deleterious changes in the external world. We are the only laboratory to culture both rat and human goblet cells and to investigate the regulation of proliferation and secretion in a purified culture. We found that conjunctival goblet cells are a direct target of allergic and inflammatory mediators and that pro-resolution mediators can return the goblet cell response to normal. We also discovered that toxigenic gram-positive bacteria can activate the NLRP3 inflammasome to secrete the cytokine IL-1 beta, thereby terminating the infection and protecting the ocular surface from bacterial infection.

Dartt DA, Baker AK, Vaillant C, Rose PE. Vasoactive intestinal polypeptide stimulation of protein secretion from rat lacrimal gland acini. Am J Physiol. 1984 Nov;247(5 Pt 1):G502-9. PubMed PMID: 6093581.

Chen L, Hodges RR, Funaki C, Zoukhri D, Gaivin RJ, Perez DM, Dartt DA. Effects of alpha1D-adrenergic receptors on shedding of biologically active EGF in freshly isolated lacrimal gland epithelial cells. Am J Physiol Cell Physiol. 2006 Nov;291(5):C946-56; PubMed Central PMCID: PMC2151204.

Dartt DA, Hodges RR, Li D, Shatos MA, Lashkari K, Serhan CN. Conjunctival goblet cell secretion stimulated by leukotrienes is reduced by resolvins D1 and E1 to promote resolution of inflammation. J Immunol. 2011 Apr 1;186(7):4455-66; PMCID: PMC3532815.

McGilligan VE, Gregory-Ksander MS, Li D, Moore JE, Hodges RR, Gilmore MS, Moore TC, Dartt DA. Staphylococcus aureus activates the NLRP3 inflammasome in human and rat conjunctival goblet cells. PLoS One. 2013;8(9):e74010.; PubMed Central PMCID: PMC3769353.

B. Positions and Honors

Positions and Employment

1978 - 1978 Research Associate, Department of Physiology, University of Pennsylvania, Philadelphia, PA
1978 - 1979 Postdoctoral Fellow, Department of Physiology, University of Pennsylvania, Philadelphia, PA
1979 - 1981 Postdoctoral Fellow, Department of Physiology, Tufts University School of Medicine, Boston, MA
1981 - 1985 Research Assistant Professor of Physiology, Tufts University School of Medicine, Boston, MA
1985 - 1987 Instructor of Ophthalmology, Harvard Medical School, Boston, MA
1985 - 1992 Associate Scientist, Schepens Eye Research Institute, Boston, MA
1987 - 1992 Assistant Professor of Ophthalmology (Cellular and Molecular Physiology), Harvard Medical School, Boston, MA
1992 - Senior Scientist, Schepens Eye Research Institute, Boston, MA
1992 - 2014 Associate Professor of Ophthalmology (Cellular and Molecular Physiology, Harvard Medical School, Boston, MA
2012 - 2012 Visiting Scientist, Department of Optometry, University of California, Berkeley, CA
2014 - Professor of Ophthalmology (Cellular and Molecular Physiology), Harvard Medical School, Boston, MA
2015 Professor II, Oral Biology, University of Oslo, Oslo Norway

Other Experience and Professional Memberships

1980 - Member, Association for Research in Vision and Ophthalmology
1982 - Member, American Physiological Society
1983 - Member, American General Physiology Society
1999 - Member, American Society for Cell Biology
2000 - Member, International Society for Contact Lens Research
2001 - 2001 Councilor, International Society of Contact Lens Research
2001 - 2007 Member, Special Study Section (2001, 2005, 2007), National Eye Institute of National Institutes of Health
2002 - Member, International Society for Eye Research
2005 - 2009 Vice President for North America, International Society for Eye Research
2009 - 2009 Member, Special Study Section, Stimulus Grants, National Eye Institute of National Institutes of Health
2009 - 2009 Grant Reviewer, Singapore Eye Research Institute
2011 - 2012 Member, AED Study Section, National Eye Institute of National Institutes of Health
2012 - Member, DPVS Study Section, National Eye Institute of National Institutes of Health

Honors

1978 Fellowship, George G. Marshall, Scandinavian-American
1979 Postdoctoral Fellowship, National Institutes of Health
2001 Lew R. Wasserman Award, Research to Prevent Blindness
2004 Spirit Award, Schepens Eye Research Institute
2009 Best Oral Presentation, Third and Fourth Military Refractive Surgery Meetings (2009, 2010)

C. Contribution to Science

1. Elucidated the cellular signaling pathways in the lacrimal gland that can be activated to stimulate protein secretion into the aqueous layer of the tear film: Prior to my work, it was only known that lacrimal gland secretion was stimulated by the parasympathetic agonist acetylcholine. I developed a method to obtain lacrimal gland acini that allowed measurement of protein secretion independent of fluid secretion, and biochemical measurements of cellular signaling pathways in these cells. I described the signaling pathways activated by cholinergic agonists, VIP, alpha1-adrenergic agonists, and EGF, providing a basis for developing topical stimuli of lacrimal gland secretion to treat dry eye and to determine how the signaling pathways in the lacrimal gland could go awry. I conceived of and directed all of this work.

Dartt DA, Baker AK, Vaillant C, Rose PE. Vasoactive intestinal polypeptide stimulation of protein secretion from rat lacrimal gland acini. Am J Physiol. 1984 Nov;247(5 Pt 1):G502-9. PMID: 6093581.

Dartt DA, Baker AK, Rose PE, Murphy SA, Ronco LV, Unser MF. Role of cyclic AMP and Ca2+ in potentiation of rat lacrimal gland protein secretion. Invest Ophthalmol Vis Sci. 1988 Nov;29(11):1732-8. PMID: 2846462.

Zoukhri D, Dartt DA. Cholinergic activation of phospholipase D in lacrimal gland acini is independent of protein kinase C and calcium. Am J Physiol. 1995 Mar;268(3 Pt 1):C713-20. PMID: 7900776.

Hodges RR, Dartt DA. Regulatory pathways in lacrimal gland epithelium. Int Rev Cytol. 2003;231:129-96. PMID: 14713005.

2. Used animal models of dry eye disease to determine the mechanisms of lacrimal gland dysfunction in this disease: Previous to my work, models to study the dysfunction of the lacrimal gland in dry eye disease and to develop treatments were limited. Jeffrey Gilbard, MD developed a dry eye rabbit model to test different artificial tear formulations and the method to determine tear osmolarity as a measure of tear secretion. I suggested that we use this model to determine topical compounds that could increase tear secretion--compounds that my previous work indicated (see Contribution 1) stimulated lacrimal gland secretion. We found that compounds that increased cellular cAMP levels were effective in decreasing tear osmolarity and increasing tear production. A small clinical trial showed the efficacy of our treatment. Although our drug was never taken to a larger clinical trial, similar topical secretagogues have been accepted for use in Japan. I have used two mouse models to study dry eye disease. First, the MLR/lpr model—With Driss Zoukhri, PhD, I found that the lacrimal gland dysfunction that lead to disease was the prevention of neurotransmitter release from efferent nerves by the increase in IL-1 beta produced by infiltrating inflammatory cells. For a second model, with Sharmila Masli, I used the thrombospondin-1 (TSP-1) knockout mouse in which TGF-beta-induced inflammation o ccurs, which causes a decrease in lacrimal gland protein secretion along with an increase in tear volume, leading to an alteration in tear composition that damages the ocular surface. Treatment with portions of the thrombospondin-1 molecule is now being explored to rescue the dysfunction in this model. We also discovered that a polymorphism of TSP-1 predisposed individuals to chronic dry eye after refractive surgery, suggesting a potential treatment for dry eye in a readily identifiable population. I conceived of the approach and directed the experiments for these models except those in collaboration with Dr. Masli.

Gilbard JP, Rossi SR, Heyda KG, Dartt DA. Stimulation of tear secretion and treatment of dry-eye disease with 3-isobutyl-1-methylxanthine. Arch Ophthalmol. 1991 May;109(5):672-6. PMID: 1709002.

Zoukhri D, Hodges RR, Rawe IM, Dartt DA. Ca2+ signaling by cholinergic and alpha1-adrenergic agonists is up-regulated in lacrimal and submandibular glands in a murine model of Sjögren's syndrome. Clin Immunol Immunopathol. 1998 Nov;89(2):134-40. PMID: 9787115.

Turpie B, Yoshimura T, Gulati A, Rios JD, Dartt DA, Masli S. Sjögren's syndrome-like ocular surface disease in thrombospondin-1 deficient mice. Am J Pathol. 2009 Sep;175(3):1136-47.; PMCID: PMC2731132.

Contreras-Ruiz L, Ryan DS, Sia RK, Bower KS, Dartt DA, Masli S. Polymorphism in THBS1 gene is associated with post-refractive surgery chronic ocular surface inflammation. Ophthalmology. 2014
Jul;121(7):1389-97; PMCID: PMC4197802.

3. Demonstrated that conjunctival goblet cells were neurally innervated and that stimulation of neural receptors induced conjunctival goblet cell secretion: Until I entered the field, conjunctival goblet cells were thought to be basic secretors into the tear film. That is, their secretion was not regulated but occurred at a constant low level to make up the “basal” tear film, in contrast to the lacrimal gland that secreted in response to stimuli and produced “overflow” tears. We found that efferent nerves surrounded the goblet cells, and that stimuli from sensory nerves activated the efferent nerves to cause goblet cell mucin secretion especially MUC5AC, the goblet cell mucin. In a very innovative step, we were able to culture conjunctival goblet cells and study the cellular pathways activated by neurotransmitters, growth factors, lipid mediators, and cytokines to stimulate secretion. We found that activation of phospholipases C, D, and A2 by increasing the intracellular [Ca2+], activating protein kinase C, and stimulating p42/p44 MAPK activity caused secretion. As conjunctival goblet cell mucin

secretion is critical to the health of the ocular surface, stimulating these cells in dry eye and other inflammatory diseases, is a potential treatment. We participated in generating pre-clinical evidence in cultured goblet cells showing that two potential dry eye treatments, rebamipide and NGF peptides, were effective. Rebamipide is now used in Japan to treat dry eye. NGF peptides are currently in clinical trial. I conceived of and directed the experiments.

Kessler TL, Mercer HJ, Zieske JD, McCarthy DM, Dartt DA. Stimulation of goblet cell mucous secretion by activation of nerves in rat conjunctiva. Curr Eye Res. 1995 Nov;14(11):985-92. PMID: 8585937.

Dartt DA, Kessler TL, Chung EH, Zieske JD. Vasoactive intestinal peptide-stimulated glycoconjugate secretion from conjunctival goblet cells. Exp Eye Res. 1996 Jul;63(1):27-34. PMID: 8983961.

Shatos MA, Ríos JD, Horikawa Y, Hodges RR, Chang EL, Bernardino CR, Rubin PA, Dartt DA. Isolation and characterization of cultured human conjunctival goblet cells. Invest Ophthalmol Vis Sci. 2003 Jun;44(6):2477-86. PMID: 12766046.

Ríos JD, Shatos MA, Urashima H, Dartt DA. Effect of OPC-12759 on EGF receptor activation, p44/p42 MAPK activity, and secretion in conjunctival goblet cells. Exp Eye Res. 2008 Apr;86(4):629-36. PMID: 18295205.

4. Discovered that conjunctival goblet cells are a direct target of allergic and inflammatory mediators that stimulate conjunctival goblet cell secretion, but that pro-resolution mediators can terminate this secretion bringing the goblet cells back to homeostasis: Normally functioning goblet cells are critical to ocular surface health. However, the role of goblet cells in ocular surface inflammatory disease was unknown. We used allergic conjunctivitis as a model to study inflammatory diseases. Using cultured conjunctival goblet cells, we found these cells to be a direct target of the mediators of allergy and inflammation and to actively participate in the disease's pathogenesis. Pro-inflammatory mediators such as histamine, leukotrienes, and prostaglandins induce conjunctival goblet cell mucin secretion. The receptors and signaling pathways for these compounds are present in the goblet cells. All contribute to mucin overproduction during allergy and inflammation. To resolve these diseases and return the goblet cells and conjunctiva to homeostasis, the overproduction of mucins must decrease. I found that the pro-resolution mediatiors the resolvins and lipxins function in this manner without depleting the cells of mucins and the cellular mechanism for this effect. My lab is currently studying the role of goblet cells in a mouse model of ocular allergy developed by Daniel Saban. This should soon form the basis for new treatments of ocular allergy and other inflammatory diseases characterized by increased mucin production. In collaboration with Charles Serhan, I conceived of and designed the experiments.

Dartt DA, Hodges RR, Li D, Shatos MA, Lashkari K, Serhan CN. Conjunctival goblet cell secretion stimulated by leukotrienes is reduced by resolvins D1 and E1 to promote resolution of inflammation. J Immunol. 2011 Apr 1;186(7):4455-66. PubMed PMID: 21357260; PMCID: PMC3532815.

Li D, Carozza RB, Shatos MA, Hodges RR, Dartt DA. Effect of histamine on Ca(2+)-dependent signaling pathways in rat conjunctival goblet cells. Invest Ophthalmol Vis Sci. 2012 Oct 5;53(11):6928-38. PMCID: PMC3466073.

Li D, Hodges RR, Jiao J, Carozza RB, Shatos MA, Chiang N, Serhan CN, Dartt DA. Resolvin D1 and aspirin-triggered resolvin D1 regulate histamine-stimulated conjunctival goblet cell secretion. Mucosal Immunol. 2013 Nov;6(6):1119-30. PMCID: PMC3742576.

Hodges RR, Dartt DA. Tear film mucins: front line defenders of the ocular surface; comparison with airway and gastrointestinal tract mucins. Exp Eye Res. 2013 Dec;117:62-78. PubMed Central PMCID: PMC4222248.

5. Found that conjunctival goblet cells protect the ocular surface from infection by gram positive bacteria as these bacteria activate the NLRP3 inflammasome in goblet cells to secrete the cytokine IL-1 beta that terminates the infection: I recently discovered a new cellular mechanism by which goblet cells prevent bacterial infection—by activation of the NLRP3 inflammasome. Toxigenic gram positive bacteria bind to toll-like receptors on conjunctival goblet cells and activate the inflammasome to produce the cytokine IL-1beta. This cytokine calls in neutrophils to help destroy the bacteria. My work on the role of conjunctival goblet cells in ocular allergy, inflammatory diseases, and bacterial

infection highlight the critical role these cells have in protecting the ocular surface. My work has opened up a new field, the role of conjunctival goblet cells in protecting the ocular surface from damage preserving clear vision. I have shown that goblet cells have a plethora of mechanisms to respond to the environment. My work will identify novel treatments to preserve and enhance goblet cell function thus maintaining ocular surface health. I worked with Meredith Gregory-Ksander on this project. I conceived of the experiments and implemented them.

McGilligan VE, Gregory-Ksander MS, Li D, Moore JE, Hodges RR, Gilmore MS, Moore TC, Dartt DA. Staphylococcus aureus activates the NLRP3 inflammasome in human and rat conjunctival goblet cells. PLoS One. 2013;8(9):e74010. PMCID: PMC3769353.

Hodges RR, Dartt DA. Tear film mucins: front line defenders of the ocular surface; comparison with airway and gastrointestinal tract mucins. Exp Eye Res. 2013 Dec;117:62-78. PubMed Central PMCID: PMC4222248.

Complete List of Published Work in My Bibliography: HYPERLINK "http://www.ncbi.nlm.nih.gov/myncbi/1nqey8e6A2Ck_/bibliography/46729842/public/?sort=date&direction=asce" \h http://www.ncbi.nlm.nih.gov/myncbi/1nqey8e6A2Ck_/bibliography/46729842/public/?sort=date&direction=asce nding

D. Research Support

Ongoing Research Support

RO1 EY026202 Makarenkova (PI) 01/01/16 – 12/31/20
"Lacrimal Gland Repair Using Progenitor Cells"
The goal of this project is to analyze lacrimal gland progenitor cell populations, determine cell lineage specific changes during dry eye disease progression and to identify the optimum progenitor cells to repair the "diseased" lacrimal gland.
Role: Co-Investigator

RO1 EY019470-06 Dartt (PI) 01/01/14 – 12/31/18
"Conjunctival Goblet Cell Mucin Secretion in Inflammation and Its Resolution"
The goal of this project is to determine the cellular mechanisms by which pro-inflammatory mediators induce goblet cell secretion and anti-inflammatory, pro-resolution compounds attenuate goblet cell secretion to restore the normal, critical mucin layer to the ocular surface.
Role: PI

RO1 EY022415-03 Dartt (PI) 05/01/12 – 04/30/17
"Conjunctival Goblet Cell NLRP3 Inflammasome in Ocular Surface Bacterial Infection"
The long-term object of this project is to determine: a) if bacteria interact directly with conjunctival goblet cells, b) what cellular signaling mechanisms and functions are triggered in the goblet cells, c) if activation of these functions prevents bacterial keratitis and conjunctivitis, and d) if drugs that activate these functions can be developed to treat ocular surface infections.
Role: PI

Completed Research Support

R01 EY06177-27 Dartt (PI) 09/01/13 – 08/31/14
Dartt, Darlene (PI)
"Mechanism of Lacrimal Gland Secretion"
The long-term objective is to investigate the types of purinergic receptors activated by nucleotides in the lacrimal gland, evaluate receptor function, and determine if their dysfunction contributes to the loss of secretion that accompanies inflammation that develops with aging and in Sjogren's syndrome.
Role: PI

Corporate Sponsored Res. Dartt (PI) 01/06/14 – 06/06/14
Johnson & Johnson Vision Care
"Development of a Conjunctival Construct for Testing Solutions and Contact Lens Materials"

The goal of this project is to develop methods to culture full thickness conjunctiva for testing contact lens solutions and materials.
Role: PI