Dry Eye Disease: A Modern History

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Introduction

The ocular condition in which dryness of the ocular surface is both a symptom and a clinical finding has been known for many centuries, but the nature of the normal functions of the ocular surface and the pathophysiology of the disease have only recently yielded new concepts, findings, and therapeutic approaches to this widespread problem. These discoveries have fundamentally altered our understanding of the disease and opened a new opportunity to diagnose the disease, and its subtypes, judge its severity, and approach the management of dry eye disease (DED) with new and more effective treatments. As we continue the expansion of our research, it is likely that analysis of the contents of tears may well reveal not only ocular diseases but systemic conditions as well.

The term *dry eye* was introduced by *de Roetth in 1950* to supplant the use of *Sjogren syndrome*, which was in general use for eyes with evidence of lacrimal hyposecretion [1]. The latter term is now recognized as appropriate for a subset of patients with evidence of a systemic inflammatory disease, one characteristic of which is dry eye. Several terms including keratoconjunctivitis sicca have been in use, but recently, there is general agreement that DED is a well-recognized designation familiar to scientists, clinicians, and the general public.

DED is by far the most common malady affecting the ocular surface and this story will be limited to DED; other conditions of the ocular surface will only be mentioned as they relate to DED. The principal themes which we think have had the greatest impact on our understanding of DED and new concepts of the approach to successful management of the disease will each be presented.

Theme I: Structure and Function of Components of the Tear Film and Ocular Surface

A major advance originating in the 1960s but coming to fruition in the mid-to-late 1970s was the delineation of the roles of the component ocular structures in the formation and maintenance of the precorneal tear film in health and disease. Most of the advances were related to clinical experiences and the relationship of dry eye to systemic illnesses such as Sjogren syndrome, rheumatoid arthritis, Steven Johnson syndrome, and other conditions affecting the ocular surface. It was noted that mucus secretion was decreased

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in patients with DED as opposed to other conditions. The roles for each of the components of the tear film and the ocular surface cells were beginning to be discerned in a series of experiments.

The ocular surface epithelium covering the cornea and conjunctiva are morphologically and functionally linked and it was long thought that healthy conjunctival epithelium could cover and replace severely damaged corneal epithelium. Thoft and Friend [2–4], however, demonstrated that there were significant biochemical differences between conjunctival and corneal epithelium and that transformation of conjunctival epithelium into corneal epithelium required considerable biochemical alteration including development of significant glycogen stores and hexose monophosphate shunt metabolism. Such transformation occurred in healthy conjunctiva but not in chemically damaged conjunctival epithelium. Further studies [5] confirmed the transition of conjunctival to corneal epithelium but with subtle changes in goblet cell populations. Subsequent studies identified the limbal epithelium as a critical source of corneal stem cells. It is now accepted that limbal cornea is the predominant site of corneal stem cells that are important in maintaining the integrity of the corneal epithelium [5–7].

Also important in recent research is the role of the mucin-containing glycocalyx which provides a protective covering for surface corneal epithelium [8]. Breakdown in the complete coverage allows for introduction of certain dyes, e.g., sodium fluorescein. This is a commonly employed diagnostic test for corneal damage in DED [9]. Although this is a useful test for identifying patients with positive staining and assumed disease, it is now recognized that small punctate staining in the corneal periphery is a common finding in normal subjects. This is thought to be due to an uncovering of new underlying epithelial cells as part of the normal cellular turnover prior to the generation of a new glycocalyx covering [10]. This is important particularly in qualifying subjects for inclusion in clinical trials and interpretation of possible effects of therapy.

Theme II: The Lacrimal Functional Unit

A basic understanding of the normal physiological roles played by elements of the ocular surface and their interrelations has represented a major step forward and has proved essential for further studies. The interrelated actions of the different components of the tears were first proposed by Stern, Pflugfelder, and Beuerman in 1998 [11] and subsequently validated by others [12]. The premise is that the cornea, conjunctiva, lacrimal glands, lids with the meibomian glands, and the drainage pathways are linked by a neural network which permits structures to react to changes in the environment or other components which compensate. The most obvious example of this is the compensation seen between the lacrimal glands and the meibomian glands of the lids. In early stage evaporative tear deficiency, there is an accompanying increase in aqueous tear production [13]. As DED develops, there is a breakdown in the stability of the tear film, and evidence of both subtypes of DED is seen, i.e., both aqueous tear deficiency and evaporative tear deficiency are characteristic.

Theme III: Tear Instability and Hyperosmolarity – Hallmarks of DED

The two most characteristic features of DED are tear film instability and tear hyperosmolarity. Both of these characteristic properties are seen as early stage events which lead to other damaging events seen most commonly with inflammation. Evidence of inflammation is seen in most cases of moderate to severe DED and leads to extensive damage to the ocular surface (see Theme IV).

The initial stimulus for upsetting the normal function and interactions between the components of the lacrimal functional unit remains unclear and may differ for each of the main subtypes of DED – aqueous tear deficient and evaporative (most commonly associated with meibomian gland dysfunction). The latter is

thought to be hormonally (androgen insufficiency) influenced and is by far the most common form of DED although with increasing severity of disease, as noted above, these two characteristics – instability of the tear film and tear hyperosmolarity – are uniformly present and act as precursors to the damage to the ocular surface and events such as inflammation.

The effects of instability of the tear film are seen in variability of a number of measures of disease, e.g., tear breakup time. The normal extent of continuous covering of the cornea between blinks is reduced. The normal interblink inteval lasts at least 7 seconds, and in normal subjects the tear film should continue as an intact covering of the cornea [14]. Measurement of tear film breakup time with classical observation and timing has an inherent variability, but recent studies with ocular coherence tomography (OCT) of tear instability have demonstrated a very close relationship between elevated tear osmolarity levels and abnormal tear breakup [15].

Pioneers in the studies of tear film osmolarity in the 1980s and 1990s were Farris and Gilbard [16, 17]. Working with a laboratory methodology (freezing point depression), they demonstrated the centrality of hyperosmolarity in identifying DED. Subsequently, Tomlinson described the range and diagnostic reference levels of elevated tear osmolarity [18]. Although their technology was not suitable for routine in-office clinical use, they charted the path for the subsequent development of clinically useful instruments. Hyperosmolarity has been shown to lead to the development of inflammation of the ocular surface [19]. In addition, elevated tear osmolarity has been shown to have direct deleterious effects on the corneal and conjunctival epithelial cells [20, 21]. In a study of about 300 subjects with DED employing a new small volume methodology of electrical impedance (TearLab Corp), it has been shown that in normal subjects tear osmolarity as measured in the inferior lacrimal lake is highly stable between eyes and over time. Subjects with DED have elevated tear osmolarity (see diagnostic values in Table 3.1) with significant variability which responds to effective treatment by returning to normal levels [22–25]. This study differs from early reports of use of a 50 nl sample of tears (TearLab), wherein multiple readings were then averaged which failed to recognize the importance of the variability of osmolarity in DED subjects not only in tear osmolarity but also in other diagnostic tests, e.g., corneal staining, tear breakup time, and Schirmer testing [26].

Table 3.1 Referent values for the diagnosis of DED

Screening questionnaires	
OSDI [58].	>13
DEQ-5 [59]	>6
Tear breakup time [54]	<10 seconds
Tear osmolarity [22]	>308 mOsm/l or variance of >8 mOsm/l between eyes
Tear volume	
Tear meniscus height	<0.2 mm
Schirmer test [61]	<10 mm/5 mm [5]
(without anesthetic)	
Ocular surface staining [9, 31]	>2
(NEI scale 0–15)	

Normal subjects have similar results in both eyes, but the differences seen between dry eyes are a clinically useful measure of the diagnostic variability with a positive predictive average of 90% for correctly identifying DED. In addition, tear osmolarity was the only diagnostic test that reflected DED severity with increasing values [24, 25]. A comprehensive review of the literature published in 2014 identified over 160 papers evaluating tear hyperosmolarity of which 72% were positive, 21% neutral, and 7% negative [27]. Of the last category, major flaws in correctly identifying subjects for inclusion as normal versus disease, and failure to follow published study design accounted for the negative findings. This comprehensive review concluded that "the literature broadly supports the use of tear film osmolarity as an objective numerical measure for diagnosing, grading severity, and managing treatment of DED."

Of the two major subtypes of DED, evaporative DED is the most common; as disease severity increases, evidences of both types of DED are seen presumably as a compensatory response [28, 29] (see above).

Theme IV: The Role of Inflammation in the Pathogenesis of DED

It is intriguing to note that one of the earliest descriptions of DED was of keratoconjunctivitis sicca which has a clinical presentation of marked inflammation as part of the disease process [30]. The subsequent emphasis on inadequate aqueous tear production as the underlying cause of DED was probably due to the much larger number of patients with DED who did not express prominent clinical signs of inflammation. As knowledge of the extent and importance of DED advanced, it was clear that guidelines were needed for the classification and study of the disease. This was provided in the 1995 Report of the NEI/Industry Workshop on Dry Eye which highlighted the major categories of aqueous deficient versus evaporative dry eye and proposed guidelines for evaluation of both categories of aqueous deficiency and excess evaporation [31]. With more intense study of the ocular surface, particularly the identification of inflammatory cells and cytokines in the conjunctiva and the lacrimal glands, both primary and secondary, attention turned to the role of inflammation in the pathogenesis of DED [32, 33]. A comprehensive review of the role of inflammation in DED is available from the Reza Dana team at the Massachusetts Eye and Ear Infirmary which have been leaders is this field of inquiry [34].

Numerous studies have identified contributing inflammatory cells, cytokines, and chemokines in the inflammation cascade that is part of the pathogenesis of DED [35, 36]. Systemic immune disease such as Sjogren disease can be a cause of inflammation, but elevated tear osmolarity has also been identified as a stimulating factor [20, 37]. Determination of levels of most of the inflammatory molecules in the tears or in the ocular surface requires special laboratory measurement, but a point-of-care test for MMP9 is available for use in the clinic (InflammaDry®, Quidel, San Diego, CA) [38]. This assay provides a dichotomous outcome, with levels above 40 ng/ml producing a positive result, but is not specific to any source of ocular surface inflammation.

Theme V: The Important Role of Neurobiologic Aspects of the Ocular Surface and DED

The complexity of the neurobiology of the ocular surface has been expertly reviewed in the TFOS DEWS II Pain and Sensation Report [39]. The cornea is the most highly innervated portion of the eye and has highly specialized nerve fibers and receptors to detect mechanical, chemical, and thermal heat sensations (polymodal and mechanical nociceptors), while thermal cold sensors detect changes in cold temperature and high osmolarity [39]. The polymodal and mechanonociceptors perceive potential discomfort and cold receptors control blinking and tear secretion via sensory pathways in the trigeminal ganglion. Many of the environmental exposures which the ocular surface encounters produce no overt discomfort, but in ocular surface disease, such as DED, nociceptive receptors can signal discomfort severe enough to qualify as pain, which is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [40]. Therefore the TFOS DEWS II Pain and Sensation Report advocates that the “dryness” described by patients with DED should be considered a form of pain [39].

As noted previously, inflammation of the ocular surface is an integral part of the pathophysiology of DED and such inflammation can cause both sensitization of corneal nerves and damage to those nerves [41, 42]. The peripheral neural sensitization can further induce central neural sensitization that may lead to chronic pain [39]. Neurological changes in the ocular surface could explain the dissociation of signs and symptoms that has long been recognized in DED and which complicates clinical trial results [43]. The early hypersensitivity that has been described in early dry eye disease (and the loss of sensation with advancing disease) may lead to this discrepancy in signs and symptoms [44–46].

A further complicating feature of neurosensory dysfunction affecting the eye is neuropathic pain that occurs in the absence of clinical signs of DED. This condition can be disabling and

difficult to treat but it is not caused by and should not be confused with DED [39, 47, 48]. A questionnaire developed specifically for neurologic aspects of ocular pain has been validated as reliable [49]. Future studies evaluating specific anatomical features of the corneal nerves such as in vivo confocal microscopy [49] or the presence of nerve growth factors in the tears or tissue may help define the differences between the two conditions [50–52].

Theme VI: The Vicious Cycle of DED

In the arena of many newly described aspects and manifestations of DED, perhaps one of the most important advances is that of linking the key elements of DED and their interactions. This concept was introduced by Baudouin and associates in 2007 [53, 54]. This is presented also in the DEWS I Report [55]. The design identifies the *Core Mechanisms* of tear instability and tear hyperosmolarity. In addition to direct damage to the ocular surface from these, the latter has been shown to induce inflammation of the ocular surface. In a subset of systemic inflammatory disease, e.g., Sjogren syndrome and graft-versus-host disease, an early involvement in inflammation in the lacrimal glands is seen [56].

Theme VII: Recent Advances in the Diagnosis and Treatment of DED and Novel Concepts

The challenge of establishing a diagnosis in a disease with great variability in the correlation of signs and symptoms, such as DED, has recently been discussed in the TFOS DEWS II Workshop Report and a sequence of screening and clinical testing to establish the diagnosis and categorization of DED has been recommended [48]. These recommendations include identification of symptoms of ocular surface disturbance through validated questionnaires (OSDI, DEQ, IDEEL, SANDE) prior to further testing. If screening questionnaire confirms that a patient might have DED, it triggers diagnostic testing of noninvasive tear breakup time, tear osmolarity [measured prior to breakup time if FBUT used], and ocular surface staining with fluorescein and lissamine green [observing the cornea, conjunctiva, and eyelid margin]. Categorization of the subtype of DED is made based upon features of MGD [57], tear lipid thickness or dynamics, and tear volume assessment, as predominantly evaporative or predominantly aqueous deficient. Referent values for diagnosis are listed in Table3.1 [58–61]. It is important to note that other conditions that provoke ocular surface disease need to be excluded and that discomfort in the absence of disturbed homeostasis of the tear film, such as neuropathic cornea, must also be excluded.

In addition to the traditional management approach to DED of educating the patient in ways to minimize the environmental activities that stress the tear film and use of topical artificial tear preparations, there are new options for therapy, including topical anti-inflammatory agents. Topical cyclosporin was FDA approved in 2003 to treat reduced tear production thought due to inflammation [62]. In 2017, topical lifitegrast was approved for the treatment of signs and symptoms of DED [63]. Although not all patients tolerate the stinging upon instillation, those who can use the drugs often see improvement in symptoms and signs of DED [64]. Recent clinical trials demonstrate that topical KPI-121 lotoprednol preparation also reduces signs and symptoms of DED [65].

Novelty in non-anti-inflammatory therapy is also apparent in some approaches to improved lubrication of the ocular surface with Lubricin,™ a lubricant naturally occurring in joint articular surfaces [66] and with another biologic, Lacripep™, a peptide derived from the lacritin molecule that is present in normal tears but deficient in DED [67].

Novel devices to treat other aspects of DED have been FDA-cleared and commercially marketed. The LipiFlow™ system is available to treat refractory MGD by controlled application of heat and pressure to the eyelids [68]. TruTear™ has recently been introduced as a stimulant to tear secretion by intranasal application of

an electrical current with evidence that such stimulation increases tear production, meibomian gland secretion, and goblet cell activation [69, 70]. There remains intense interest in these areas of research which augurs well for further understanding of the processes operative in DED and newer forms of management.

References

1. de Roetth A. The dry eye. Acta XVI Concilium Ophthalmologicum (Britannia). Br Med Assoc London. 1950;1:456–64.
2. Thoft RA, Friend J. Biochemical transformation or regenerating ocular surface epithelium. Invest Oph Vis Sci. 1977;16:14–20.
3. Thoft RA, Friend J. The X, Y, Z hypothesis of corneal epithelial aintenance. Invest Ophthalmol Vis Sci. 1983;24:1442–3.
4. Shapiro MS, Friend J, Thoft RA. Corneal re-epithelialization from the conjunctiva. Invest Ophthalmol Vis Sci. 1981;21(1 Pt 1):135–42.
5. Kinoshita S, Kiorpes TC, Friend J, Thoft RA. Limbal epithelium in ocular surface wound healing. Invest Ophthalmol Vis Sci. 1982;24:1442–3.
6. Schirmer A, Galvn S, Sun TT. Differentiation-related expression of a major 64k corneal keratin in vivo and in culture suggests limbal location of corneal epithelial stem cells. J Cell Biol. 1986;103:49–62.
7. Pellegrini G, De Luca M. Eyes on the prize: limbal stem cells and corneal restoration. Cell Stem Cell. 2014;15:121.
8. Gipson IK, Hori Y, Argüeso P. Character of ocular surface mucins and their alteration in dry eye disease. Ocul Surf. 2004;2:131–48.
9. Methodologies to diagnose and monitor dry eye disease: report of the diagnostic methodology subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5:108–52.
10. Bron AJ, Argüeso P, Irkec M, Bright FV. Clinical staining of the ocular surface: Mechanism and interpretations. Prog Retin Eye Res. 2015;44:36–61.
11. Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. Cornea. 1998;17:584–9. Review
12. Pflugfelder SC, de Paiva CS. The pathophysiology of dry eye disease: what we know and future directions for research. Ophthalmol. 2017;124(11S):S4–S13.
13. Arita R, Morishige N, Shirakawa R, Kawashima M, Sakimoto T, Suzuki T, Tsubota K. Increased tear fluid production as a compensatory response to meibomian gland loss: a multi-center cross-sectional study. Ophthalmol. 2015;122:925–33.
14. Godfrey KJ, Wilsen C, Satterfield K, Korn BS, Kikkawa DO. Analysis of spontaneous eyelidblink dynamics using a 240 frames per second smartphone camera. Ophthalmic Plast Reconstr Surg. 2019. https://doi.org/10.1097/IOP.0000000000001356. [Epub ahead of print]
15. Deinema LA, Vingrys AJ, Chinnery HR, Downie LE. Optical coherence tomography reveals changes to corneal reflectivity and thickess in individuals with tear hyperosmolarity. Transl Vis Sci Technol. 2017;6:6.
16. Gilbard JP, Farris RL, Santamaria J 2nd. Osmolarity of tear microvolumes in keratoconjunctivitis sicca. Arch Ophthalmol. 1978;96:677–81.
17. Farris RL. Tear osmolarity-a new gold standard? Adv Exp Med Biol. 1994;350:495–503.
18. Tomlinson A, McCann LC, Pearce EI. Comparison of human tear film osmolarity measured by electrical impedance and freezing point depression techniques. Cornea. 2010;29(9):1036–41.
19. Liu H, Begley C, Chen M, Bradley A, Bonanno J, McNamara NA, Nelson JD, Simpson T. A link between tear instability and hyperosmolarity in dry eye. Invest Ophthalmol Vis Sci. 2009;50:3671–9.
20. Igarashi T, Fujimoto C, Suzuki H, Ono M, Iijima O, Takahashi H, Takahashi H. Short-time exposure of hyperosmolarity triggers interleukin-6 expression in corneal epithelial cells. Cornea. 2014;33:1342–7.
21. Gilbard JP, Carter JB, Sang DN, Refojo MF, Hanninen LA, Kenyon KR. Morphologic effect of hyperosmolarity on rabbit corneal epithelium. Ophthalmol. 1984;91:1205–12.
22. Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. Am J Ophthalmol. 2011;151:792–8.
23. Sullivan BD, Whitmer D, Nichols KK, et al. An objective approach to dry eye disease severity. Invest Ophthalmol Vis Sci. 2010;51:6125–30.
24. Sullivan BD. Challenges in using signs and symptoms to evaluate new biomarkers of dry eye disease. Ocul Surf. 2014;12:2–3.
25. Sullivan BD, Crews LA, Sonmez B, et al. Clinical utility of objective tests for dry eye disease: variability over time and implications for clinical trials and disease management. Cornea. 2012;31:1000–8.
26. Khanal S, Millar TJ. Barriers to clinical uptake of tear osmolarity meaurements. Br J Ophthalmol. 2012;96:341–4.
27. Potvin R, Makar S, Rapuano CJ. Tear film osmolarity and dry eye disease: a review of the literature. Clin Ophthalmol. 2015;(9):2039–47.
28. Viso E, Rodriguez-Ares MT, Abelenda D, et al. Prevalence of asymptomatic and symptomatic meibomian gland dysfunction in the general population of Spain. Invest Ophthalmol Vis Sci. 2012;53:2601–6.
29. Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. Cornea. 2012;31:472–8.
30. Sjogren HSC. Zur kenntnis der keratoconjunctivitis sicca (Keratitis filiformis bei Hypofuncktion

der Tranendreusen). Acta Ophthalmol (Kbh). 1933;(Supp2):1–151.
31. Lemp MA. Report of the National Eye Institute/Industry Workshop on clinical trials in dry eye. CLAO J. 1995;21:221–32.
32. Luo L, Li DQ, Doshi A, Farley W, Corrales RM, Pflugfelder SC. Experimental dry eye stimulates production of inflammatory cytokines and MMP-9 and activates MAPK signaling pathways on the ocular surface. Invest Ophthalmol Vis Sci. 2004;45:4293–301.
33. Pflugfelder SC, de Paiva CS, Li D-Q, Stern ME. Epithelial–immune cell interaction in dry eye. Cornea. 2008;27:S9–11. (1-7).
34. Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017;15:438–510.
35. Stevenson WG, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. Arch Ophthalmol. 2012;130:90–100.
36. Rosette C, Karin M. Ultraviolet light and osmotic stress: activation of the JNK cascade through multiple growth factor and cytokine receptors. Science. 1996;274:1194–7.
37. Stern ME, Schaumburg CS, Pflugfelder SC. Dry eye as a mucosal autoimmune disease. Int Rev Immunol. 2013;32:19–41.
38. Kaufman HE. The practical detection of mmp-9 diagnoses ocular surface disease and may help prevent its complications. Cornea. 2013;32:211–6.
39. Belmonte C, Nichols JJ, Cox SM, Brock JA, Begley CG, Bereiter DA, Dartt DA, Galor A, Hamrah P, Ivanusic JJ, Jacobs DS, McNamara NA, Rosenblatt MI, Stapleton F, Wolffsohn JS. TFOS DEWS II pain and sensation report. Ocul Surf. 2017;15:404–37.
40. IASP. The International Association for the Study of Pain: https://www.iasp-pain.org.
41. Quallo T, Vastani N, Horridge E, Gentry C, Parra A, Moss S, et al. TRPM8 is a neuronal osmosensor that regulates eye blinking in mice. Nat Commun. 2015;6:7150.
42. Benowitz LI, Popovich PG. Inflammation and axon regeneration. Curr Opin Neurol. 2011;24:577–83.
43. Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. Cornea. 2004;23:762–70.
44. De Paiva CS, Pflugfelder SC. Corneal epitheliopathy of dry eye induces hyperesthesia to mechanical air jet stimulation. Am J Ophthalmol. 2004;137:109–15.
45. Xu KP, Yagi Y, Tsubota K. Decrease in corneal sensitivity and change in tear function in dry eye. Cornea. 1996;15:235–9.
46. Versura P, Frigato M, Cellini M, Mulè R, Malavolta N, Campos EC. Diagnostic performance of tear function tests in Sjogren's syndrome patients. Eye (Lond). 2007;21:229–37.
47. Geber C, Baumg€artner U, Schwab R, Müller H, Stoeter P, Dieterich M, et al. Revised definition of neuropathic pain and its grading system: an open case series illustrating its use in clinical practice. Am J Med. 2009;122(10 Suppl):S3–12.
48. Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II diagnostic methodology report. Ocul Surf. 2017;15:539–74.
49. Qazi Y, Hurwitz S, Khan S, Jurkunas UV, Dana R, Hamrah P. Validity and reliability of a novel ocular pain assessment survey (OPAS) in quantifying and monitoring corneal and ocular surface pain. Ophthalmology. 2016;123:1458–68.
50. Stave J, Zinser G, Grummer G, Guthoff R. Modified Heidelberg Retinal Tomograph HRT. Initial results of in vivo presentation of corneal structures. Ophthalmologe. 2002;99:276–80.
51. Kheirkhah A, Dohlman TH, Amparo F, Arnoldner MA, Jamali A, Hamrah P, et al. Effects of corneal nerve density on the response to treatment in dry eye disease. Ophthalmology. 2015;122:662–8.
52. Lambiase A, Micera A, Sacchetti M, Cortes M, Mantelli F, Bonini S. Alterations of tear neuromediators in dry eye disease. Arch Ophthalmol. 2011;129:981–6.
53. Baudouin C. A new approach for better comprehension of diseases of the ocular surface. J Fr Ophtalmol. 2007;30:239–46.
54. Baudouin C, Messmer EM, Aragona P, Geerling G, Labetoulle M. Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction. Br J Ophthalmol. 2016.
55. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5:75–92.
56. Shikari H, Antin JH, Dana R. Ocular graft-versus-host disease: a review. Surv Ophthalmol. 2013;58:233–51.
57. Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, O'Brien T, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2011;52:2050–64.
58. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. Arch Ophthalmol. 2000;118:615–21.
59. Chalmers RL, Begley CG, Caffery B. Validation of the 5-Item Dry Eye Ques- tionnaire (DEQ-5): discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. Cont Lens Anterior Eye. 2010;33:55–60.
60. Sullivan BD, Whitmer D, Nichols KK, Tomlinson A, Foulks GN, Geerling G, Khanal S, Ramaesh K, Diaper C, McFadyen A. Tear film osmolarity: determination of a referent for dry eye diagnosis. Invest Ophthalmol Vis Sci. 2010;47:4309–15.
61. de Monchy I, Gendron G, Miceli C, Pogorzalek N, Mariette X, Labetoulle M. Combination of the Schirmer I and phenol red thread tests as a rescue strategy for diagnosis of ocular dryness associated

with Sjogren's syndrome. Invest Ophthalmol Vis Sci. 2011;52:5167–73.
62. Center for Drug Evaluation and Research, approval 021023 (Oct 10, 2003).
63. Center for Drug Evaluation and Research, approval 208073 (July 12, 2017).
64. Perry HD, Solomon R, Donnenfeld ED, Perry AR, Wittpenn JR, Greenman HE, Savage HE. Evaluation of topical cyclosporine for the treatment of dry eye disease. Arch Ophthalmol. 2008;126:1046–50.
65. Personal communication, Kim Brazzell, PhD, Kala Pharmaceuticals, 2018.
66. Lambiase A, Sullivan BD, Schmidt TA, Sullivan DA, Jay GD, Truitt ER 3rd, Bruscolini A, Sacchetti M, Mantelli F. A two-week, randomized, double-masked study to evaluate safety and efficacy of Lubricin(150 μg/mL) eye drops versus sodium hyaluronate (HA) 0.18% eye drops (Vismed®) in patients with moderate dry eye disease. Ocul Surf. 2017;15:77–87.
67. Karnatia R, Laurieb DE, Laurie GW. Lacritin and the tear proteome as natural replacement therapy for dry eye. Exp Eye Res. 2013;117:39–52.
68. Lane SS, DuBiner HB, Epstein RJ, et al. A new system, the LipiFlow, for the treatment of meibomian gland dysfunction. Cornea. 2012;31:396–404.
69. Friedman NJ, Butron K, Robledo N, Loudin J, Baba SN, Chayet A. A nonrandomized, open-label study to evaluate the effect of nasal stimulation on tear production in subjects with dry eye disease. Clin Ophthalmol. 2016;10:795–804.
70. Gumus K, Schuetzle KL, Stephen C, Pflugfelder SC. Randomized, controlled, crossover trial comparing the impact of sham or intranasal neurostimulation on conjunctival goblet cell degranulation. Am J Ophthalmol. 2017;177:159–68.