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EDITORIAL

Moving beyond lamellar keratoplasty - Are we taking our first step?

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Among the various fields of ophthalmic surgery, it is arguably corneal transplantation that has undergone the greatest evolution in recent years. The transition to selective replacement of the individual corneal layers is now established principle. What is interesting is that for the most part this transition has been driven by surgical innovation supported by basic instruments only. Endothelial keratoplasty in its various forms requires acquisition of new surgical maneuvers facilitated by inserting devices.[1] Renewed interest in anterior lamellar keratoplasty has been fuelled by the big bubble technique, which requires nothing more than a needle and air-filled syringe in its most basic form.[2] On this journey, there has not been the need for extensive pharmacologic or industry involvement to date. The question we now face as corneal surgeons are whether we are preparing to make the next leap, toward cellular surgery, with the stimulation of cell mitosis and migration, *ex vivo* expansion of cell layers, and delivery of cell lines as injectable suspensions. This will require more in-depth research and trials supported by industry. It is likely to follow a longer time course than the "demonstrate, practice, adopt" sequence that we are now used to.

The first pharmacologic agents to arise as potential tools on this journey are Rho-kinase inhibitors. They are unlikely to be the last. The Rho-kinase enzyme was first described in the mid-1990s, with two isoforms subsequently identified and located separately on the genome - ROCK 1 on chromosome 18 and ROCK 2 on chromosome 2.[3,4] Their most consistently demonstrated function is to regulate cytoskeletal modification necessary for several cellular processes, but most notably migration, with essential roles in embryogenesis.[5] They are ubiquitous in the body (although expression between isoforms differs according to location) and are especially critical in mediating smooth muscle contraction.[4-7] This has led to the exploration of their possible role as therapeutic targets in pulmonary and cardiovascular disease, and approval in three countries as agents for treating cerebral vasospasm post-subarachnoid hemorrhage (fasudil - China) and glaucoma (ripasudil - Japan and netarsudil - USA).[8-10] In glaucoma, the intraocular pressure is lowered presumably through increased trabecular outflow through a contracted trabecular meshwork. However, their potential effect on the cornea may be more dramatic, appearing to stimulate endothelial cell migration and possibly to a lesser extent mitosis.

Pioneering work by Kinoshita, Okumura, and Koizumi began the exploration of these agents as adjuvants to corneal endothelial healing.[11-16] This work coincided with surgical trials involving removal of guttata in Fuchs endothelial dystrophy without placement of a graft in several centers.[17,18] This operation seems to have a variable effect between patients, with some failing to clear their cornea for reasons yet unclear. In 2017, we described clearance of corneal edema in two patients, otherwise not appearing to resolve, after a short course of topical ripasudil.[19] This led to much enthusiasm that the combination of these ideas would lead to new, non-graft options for patients with endothelial disease. Subsequent trials are now testing that hypothesis in detail, both investigator and drug company initiated.

While browsing through the library of Massachusetts Eye and Ear Infirmary in 2018, Roberto Pineda stumbled across and forwarded to me a reference that serves as a reminder that there is nothing new under the sun. A detailed description published in 1955 by Louis Paufique of guttata removal in Fuchs' dystrophy without graft placement.[20] This idea clearly never overcame the local factors arrayed against endothelial mitosis to achieve universal adoption. The exciting question for corneal surgeons today is - can we take an old idea and combine it with new scientific innovation, to overcome its hurdles and potentially do away with the need for graft tissue in endothelial disease. A question worth asking with some patience required before we receive an answer.

References

1. Dapena I, Ham L, Melles GR. Endothelial keratoplasty: DSEK/DSAEK or DMEK – the thinner the better? Curr Opin Ophthalmol 2009;20:299-307.
2. Anwar M, Teichmann KD. Big-bubble technique to bare Descemet's membrane in anterior lamellar keratoplasty. J Cataract Refract Surg 2002;28:398-403.
3. Leung T, Chen XQ, Manser E, Lim L. The p160 rhoA-binding kinase ROK alpha is a member of a kinase family and is involved

in the reorganization of the cytoskeleton. Mol Cell Biol 1996; 16:5313-27.
4. Loirand G. Rho kinases in health and disease: From basic science to translational research. Pharmacol Rev 2015;67:1074-95.
5. Kalcheim C. Neural crest emigration: From start to stop. Genesis 2018;56:e23090.
6. Feng Y, LoGrasso PV, Defert O, Li R. Rho kinase (ROCK) inhibitors and their therapeutic potential. J Med Chem 2016; 59:2269-300.
7. Kubo T, Yamaguchi A, Iwata N, Yamashita T. The therapeutic effects of rho-ROCK inhibitors on CNS disorders. Ther Clin Risk Manag 2008;4:605-15.
8. Liu GJ, Wang ZJ, Wang YF, Xu LL, Wang XL, Liu Y, *et al.* Systematic assessment and meta-analysis of the efficacy and safety of fasudil in the treatment of cerebral vasospasm in patients with subarachnoid hemorrhage. Eur J Clin Pharmacol 2012; 68:131-9.
9. Garnock-Jones KP. Ripasudil: First global approval. Drugs 2014;74:2211-5.
10. Hoy SM. Netarsudil ophthalmic solution 0.02%: First global approval. Drugs 2018;78:389-96.
11. Nakagawa H, Koizumi N, Okumura N, Suganami H, Kinoshita S. Morphological changes of human corneal endothelial cells after rho-associated kinase inhibitor eye drop (Ripasudil) administration: A prospective open-label clinical study. PLoS One 2015;10:e0136802.
12. Okumura N, Koizumi N, Ueno M, Sakamoto Y, Takahashi H, Hirata K, *et al.* Enhancement of corneal endothelium wound healing by rho-associated kinase (ROCK) inhibitor eye drops. Br J Ophthalmol 2011;95:1006-9.
13. Koizumi N, Okumura N, Ueno M, Nakagawa H, Hamuro J, Kinoshita S, *et al.* Rho-associated kinase inhibitor eye drop treatment as a possible medical treatment for Fuchs corneal dystrophy. Cornea 2013;32:1167-70.
14. Okumura N, Koizumi N, Kay EP, Ueno M, Sakamoto Y, Nakamura S, *et al.* The ROCK inhibitor eye drop accelerates corneal endothelium wound healing. Invest Ophthalmol Vis Sci 2013; 54:2493-502.
15. Koizumi N, Okumura N, Ueno M, Kinoshita S. New therapeutic modality for corneal endothelial disease using rho-associated kinase inhibitor eye drops. Cornea 2014;33 Suppl 11:S25-31.
16. Okumura N, Inoue R, Okazaki Y, Nakano S, Nakagawa H, Kinoshita S, *et al.* Effect of the rho kinase inhibitor Y-27632 on corneal endothelial wound healing. Invest Ophthalmol Vis Sci 2015; 56:6067-74.
17. Borkar DS, Veldman P, Colby KA. Treatment of Fuchs endothelial dystrophy by descemet stripping without endothelial keratoplasty. Cornea 2016;35:1267-73.
18. Moloney G, Chan UT, Hamilton A, Zahidin AM, Grigg JR, Devasahayam RN, *et al.* Descemetorhexis for Fuchs' dystrophy. Can J Ophthalmol 2015;50:68-72.
19. Moloney G, Petsoglou C, Ball M, Kerdraon Y, Höllhumer R, Spiteri N, *et al.* Descemetorhexis without grafting for Fuchs endothelial dystrophy-supplementation with topical ripasudil. Cornea 2017;36:642-8.
20. Paufique L. In: Rycroft BW, editor. Lamellar Keratoplasty in Corneal Grafts. London, England: Butterworth and Co.; 1955. p. 132-3.

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