

specification of mesenchymal progenitor cells, primarily of neural crest origin.¹⁷⁻²² *Pitx2*, expressed in the POM, is required for specification of NCC into the aforementioned structures (shown in Figure 1) through the three waves of cell movement.⁴

Pitx2 is also a downstream effector that is activated in response to tissue-to-tissue signaling from the lens in the embryonic stage.²³⁻²⁵ Lens ablation experiments, wherein the lens is removed in an animal model, have shown that lens formation plays a critical role in the development of the cornea and anterior segment.^{23,26-28} This is because the lens acts as a transforming growth factor beta (TGF- β) signaling centre that controls the development of NCC-derived ocular structures, demonstrated by the failure of the NCC to form the corneal endothelium and stroma in the absence of the lens.^{23,29} This finding illustrates the complexity involved in the formation of anterior segment tissues via inductive signaling between the lens and POM.

FOXC1 is another class of transcription factors closely related to ASD, though *FOXC1* mutations have relatively milder prognoses for glaucoma development when compared to the combination of *PITX2* and *FOXC1* defects.⁷ Tight control of the two genes is necessary for normal development, as 40% of patients with ARS have shown mutations of either *FOXC1* or *PITX2*.⁷ Notably, recent findings have shown co-localization of *PITX2A* and *FOXC1* within a common nuclear subcompartment, with *PITX2A* shown to negatively regulate *FOXC1* activity.⁷ Expression of the two proteins in the POM and the physical complex they form with one another has also been shown.⁷ In mice, *PITX2A* and *FOXC1* transcription factors are co-expressed in cells of the presumptive anterior segment that later becomes corneal endothelium or stroma. This finding successfully demonstrates the presence of both transcription factors during anterior segment development and a possible bidirectional relationship between them.⁷

Activating Protein-2 Beta (AP-2 β)

A more recent finding pertaining to the AP-2 β transcription factor and its role in neural crest cell specification is gaining attention and providing further insight into genes associated with the onset of ASD. The gene *Tfap2b* has been shown to encode the transcription factor AP-2 β , which is largely implicated in the development of the corneal layers and the formation of the iridocorneal angle.¹⁷ AP-2 β , like *PITX2* and *FOXC1*, is also high-

ly associated with ASD, particularly corneal defects.¹⁷ It has been found that AP-2 β is required for the establishment of angiogenic privilege (corneal avascularity) in the developing cornea, formation of the anterior angle, as well as the specification of the three corneal layers: corneal epithelium, stroma, and endothelium.¹⁷ The loss of this transcription factor led to the development of synechia (adhesion between iris and cornea) and anterior subcapsular cataracts (loss of lens transparency).¹⁷

AP-2 β is largely implicated in the development of primary closed angle glaucoma. Closed angle in the anterior eye contributes to increased IOP as it disrupts the circulation of aqueous humor within the eye. Consequently, this results in loss of retinal ganglion cells and a damaged optic nerve. AP-2 β NCC knockout (KO) mutants have also exhibited a variety of corneal phenotypes, which affect all three corneal layers, leading to complete absence of the endothelial layer.¹⁷

Overall, the AP-2 β NCC KO model used in the study demonstrates that this transcription factor follows a similar regulatory network for anterior segment development as *Pitx2* and *Foxc1*.¹⁷ Mutant mice with conditional deletion of *Pitx2* in the POM or its derivatives exhibit a lack of angiogenic privilege and develop neovascularization (formation of new blood vessels) of the cornea.¹⁸ Also, the mice present with similar anterior segment as the AP-2 β NCC KO phenotypes since they show failure in the formation of the corneal endothelium, disorganization of the corneal stroma, and defects of the corneal epithelium.¹⁷ Furthermore, Chen et al. demonstrated that AP-2 β levels are significantly reduced in the absence of *Pitx2* in the POM.¹⁸

TREATMENT

With consistent patterns of corneal defects present in ASD, regenerative medicine can be further explored in order to mitigate problems associated with corneal abnormalities. Regenerative medicine involving the use of a patient's own stem cells to repair dysfunctional tissues is a growing area of research. Recent findings indicate that dental stem cells (DSCs) may be a potential alternative treatment for corneal opacities and endothelial disorders.³⁰ Corneal transplantation, the current standard of care, is highly invasive and limited by the number of available donor tissues. Embryonic stem cell (ESC) therapy has also been used in the eye.^{30,31} One study showed that patients exhibited improved vi-