Contact Lenses for Color Vision Deficiency

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Color blindness or color vision deficiency (CVD) affects around 4.5% of the population in Europe. There have been several attempts to assist color-blind individuals using color filter glasses. Here, contact lenses are developed to assist individuals suffering from color blindness. Two dyes (Atto 488 and 565) that provide the desired absorption wavelength ranges are selected to be immobilized in soft contact lenses. The chosen dyes have absorption bands in wavelength ranges of 480–500 and 550–580 nm. Both dyes are individually immobilized in contact lenses, and over 95% of the light in the undesired ranges are blocked. The dyes do not diffuse out from lenses in artificial tears and contact lens storage solution. Performances of the developed contact lenses are compared to commercial color-blind glasses. The contact lenses are tested in color vision deficient patients using Ishihara test. Participants indicate enhancement in the visibility of the colors and their contrast in a color rich environment. The proposed contact lenses show enhanced results as compared to commercial color-blind glasses in indoors and achieved similar outcomes outdoors.

1. Introduction

Human eyes see color via cone cells which are located in a 0.3 mm² spot of the retina near the back of the eye called the fovea centralis (Figure 1a).[1] There are three types of cone cells: S-cones, M-cones, and L-cones which denote to the short, medium, and long wavelengths cones, respectively.[2] They are also commonly referred to as blue, green and red photoreceptor cells (Figure 1b). There are six to seven million cone cells in a human eye of which, 64% are red sensitive, 33% are green sensitive and 3% are blue sensitive.[3]

Color vision deficiency (CVD) is caused when one or more of the cone types are faulty or absent due to mutation. This causes the brain to receive incomplete or incorrect information that prevents distinguishing between different colors (Figure 1b). The type of CVD depends on the type of faulty or missing cone cell. As for protanomaly, the sensitivity of red cone cells is shifted to a shorter wavelength and this type does affect 1.08% of males and 0.03% of females. Deuteranomaly occurs when the sensitivity of green cone cells is shifted to a longer wavelength and it is the most common form of CVD affecting 4.63% of males and 0.36% of females. In tritanomaly, the blue cone is displaced and this is the most uncommon type affecting only 0.0002% of males (Figure 1).[3] If a cone is missing the patient is diagnosed as dichromacy, which is classified into three types: i) protanopia, where the red cone is missing, affecting 1.01% of men and 0.02% of women, ii) deuteranopia, where the green cones are missing, affecting 1.27% of men and 0.01% of women, iii) tritanopia, where the blue cones are missing, and it is the most uncommon form of dichromacy, affecting only 0.0001% of males. The most severe kind of CVD is the monochromacy which arises when no cones or only blue cones are present and it is extremely rare affecting 0.00003% of males.[4] In monochromacy conditions, no colors can be perceived. Protanomaly, deuteranomaly, protanopia and deuteranopia are all classified under the common term “red-green color blindness.”[5]

“Normal” color vision is trichromatic, with color being created using all three different types of cones with the activation level in all three cones allowing the brain to determine the color (Figure 1b).[6] When light of a specific wavelength enters the eye, it excites the cones cells to a known activation level, and the combined signal from the different types of cone cells is analyzed by the brain and the color is observed (Figure 1c).[5] For example, when light of a wavelength of 520 nm is observed by normal individuals, the cones are activated at different levels: 0%, 90%, and 55% for blue, green, and red respectively. However, for protanomaly, the activation of the red cone cells is changed to be 75%, and for deuteranomaly, the activation of green cone cells is 60% (Figure 1c (ii–iv)). This causes the red and green cones to be activated to similar levels in protanomaly and deuteranomaly conditions causing confusion, which results in the wrong color being perceived.[7]

The prevalence of color blindness may be affected by ethnical heritage: most common in Caucasians and least...
common in African-Americans. Diagnosis of color blindness is challenging in children with inherited CVD as they have been taught the color of objects from an early age and have no concept of true color. Despite the fact that many of these individuals have adapted to live with this condition, CVD affects them in many ways. In many countries, people who are color blind are not allowed to drive as some may not distinguish between the different colors of traffic lights and road signs. Suffering from color blindness also prohibits individuals from performing some professions such as pilot or firefighter due to safety concerns over their visual disadvantage. To date, there is no cure for any type of CVD, but there have been several attempts to improve color vision. One of the attempted methods has been to surgically improve the color data sent to the brain using adeno-associated virus (AAV) gene therapy. In 2007, a customized form of the virus was injected into the retina of mice for curing achromatopsia. An improvement in behavioral and electrophysiological functions were observed in the majority of the mice tested. In 2009, the improvement of protanopia was investigated in adult monkeys. This provided positive results as the enhancement of a third type of cone cell dramatically improved the red-green color discrimination in the treated monkey.

The most prominent wearables utilized by color-blind patients are tinted glasses/lenses, which are based on colored filters. The idea of using colored filters came from Seeback in 1837. By using a red filter and a green filter, Seeback noticed patients could distinguish between the relative brightness of different shades of red and green. The first pair of glasses using this idea was then built by Maxwell in 1857. These glasses used one lens dyed red and the other lens dyed green. Using the glasses, subjects were able to distinguish between many colors which they had not been able to previously. Based on these results, Maxwell hypothesized that after prolonged exposure to the glasses, subjects maybe be able to differentiate between more shades of red and green.

In 2015, Enchroma released a set of glasses to aid color-blind patients (Figure 2a). These glasses received many positive responses and worked to compensate for the deficiency of the medium wavelength cone cells. This was possible by blocking out ranges of light that caused similar levels of activity between the red and green, and the green and blue cone receptor cells. Enchroma glasses were found to filter out the green-blue crossover range of 480–500 nm and the red-green crossover range of 550–580 nm. Efficiency of the Enchroma glasses has been evaluated by testing its performance on 48 CVD individuals. The color perception for the examined subjects was enhanced with 5% and 9% when they performed Ishihara and FM Hue 100 tests, respectively. Therefore, Enchroma glasses failed to significantly enhance the color perception or allowing the subjects to pass the color vision tests. Another study was carried out on 10 CVD volunteers for evaluating the performance of Enchroma glasses. Colordx software which is the digital version of Ishihara test, and FM Hue 100 test were used to investigate the efficacy of the Enchroma glasses. The results showed that only two patients who suffers severe deutrans and protans, scored higher in Ishihara test. However, the rest of the subjects did not show better scores either in Ishihara or FM Hue 100 tests. Performance of other brands of CVD glasses such as VINO has been evaluated as well. For instance, a study was carried out on 52 CVD individuals using Ishihara and FM Hue 100 tests. The examined subjects recorded better score in Ishihara test than that in FM Hue 100. In a comparison evolution for the VINO against Enchroma, VINO glasses showed better results, especially for deutan.

Tinted contact lenses may compensate for the deficiency caused by color blindness. The appeal of using the dye to block out the undesirable wavelengths, instead of quantum dots or nanoparticles is the lower cost and simplicity which make them ideal for mass production. ChromaGen have released red tinted lenses which can be used either on the nondominant eye or, in some cases, both eyes, and help to distinguish red and green. These received excellent responses with 97% of tested subjects reporting significantly improved color vision. The current commercial price of two lenses, which last for up to six months, is €425.

In this work, we have developed in-house contact lenses for color blindness. The performance of the lenses was tested on CVD patients and compared to four glasses models available in market.
2. Result and Discussion

Previous studies recommended blocking out wavelengths of ranges, 480–500 and 550–580 nm to enhance the color vision of the color blindness patients (Figure 2a). Therefore, the used dyes should have absorption peaks in these ranges to filter out the undesired wavelengths. The dyes have to adhere to strict health and safety regulations as they are in contact with eyes. From the dyes that suited these requirements, Atto 488 and Atto 565 dyes were chosen. Atto dyes are a series of fluorescent dyes which are commonly used for labeling proteins, nucleic acids and other biomolecules. According to the literature, Atto 565 is nontoxic for corneal cells. The absorption peaks of the Atto 488 dye lies at wavelength of 488 nm, whilst for Atto 565 dye lies at 565 nm (Figure 2b,c). The Atto 488 dye was used to block wavelengths of the incident light on the eye which activate the blue and green cone cells at similar levels. Similarly, Atto 565 dye was used to block light which activates the green and red cone cells. The Atto dyes also have a high thermal stability, photostability, and slightly hydrophilic.

A crosslinking process was developed to link the chosen Atto dyes and the in-house made soft contact lenses (HEMA), to fabricate tinted contact lenses for color-blind individuals. The two Atto dyes were cross-linked separately to individual contact lenses, and their stability over time was tested in artificial tears and contact lens’ storage solution (Figure 3a–d). The visual appearance/color and transmission spectra of the contact lenses generally remained unchanged throughout the entire duration of the experiments which means that the dyes were successfully chemically bounded to the contact lens matrix and did not leak in either artificial tears or the storage solution (Figure 3a–d). These results are extremely significant as the tinted lenses need to be stable during the storage period and when placed on the eye. Although, there are small discrepancies in the transmission spectra among the tested hours, which seems to be random errors as there is no pattern of the changes in transmission spectra over time. For the Atto 488 tinted lens, it was found that the absorption peak lies in the desired region (490 nm) (Figure 3a,b). On the other hand, the absorption peak for the Atto 565 tinted lens was at 565 nm indicating that the crosslinking did not affect the dye’s chemical structure (Figure 3c,d). The tinted lenses absorbed a maximum of 30% of the incident light within the desired ranges. However, the absorbance of the lens can be controlled by changing the dye concentration.

Figure 2. Wavelength-selective dyes for color blindness. a) Glasses used for color-blind deficiency filtering out the incident light, and a schematic of the desired transmission spectra versus the sensitivity of eye cone cells. Absorption and fluorescence spectra of the Atto b) 488 and c) 565 dyes.

Adv. Mater. Technol. 2021, 6, 2000797
Figure 3. Transmission spectra of the Atto 488 tinted contact lens over time while the lens was immersed in contact lens's a) storage solution and b) artificial tears. Transmission spectra of the Atto 565 tinted contact lens over time when the lens was submersed in contact lens' c) storage solution and d) eye tears. e) Transmission spectra of the double layer contact lens, and photos for cross-sections of the in-house made contact lenses tinted by Atto 488 and 565 nm—scale bar = 100 µm.
A double layer contact lens was fabricated utilizing both Atto dyes. The dyes were cross-linked in the double layer lens separately (Figure 3e). The double layer lens showed two distinctive transmission dips in its spectra at wavelengths of 495 and 565 nm. At these wavelengths, up to 90% of the incident light was absorbed—this high absorption is due the high concentration of the used Atto dyes. The absorbance could be optimized by changing the dye concentrations that allows for customizability the tinted lenses to suit the user's deficiency. Images of cross-sections of each lens were taken to check the dye distribution showing that the dyes were spread evenly through the lens cross-section with uniform distribution (Figure 3e inset).

For patient test objectives, highly tinted contact lens materials of Atto 488 & 565 were synthesized and attached to glass slides, so patients do not need to wear the lenses but instead they were looking through (Figure 4a,b). The blocked percentages were in the range of 85–95% for the individually tinted lenses (Figure 4a,b). The double layer lens blocked 90% of the undesirable wavelength bands (Figure 4c). The transmission spectra of the double layer made of the contact lens materials (DLC) and Enchroma were found to be relatively similar (Figure 4c). As both introduced absorption bands in the blue-green and green-red regions; however, the blue-green absorption band for the DLC was slightly shifted to longer wavelengths to be the peak position at 505 nm as compared to 492 nm for Enchroma. The absorption bands of Enchroma were wider covering the wavelength ranges 480–500 nm and 560–580 nm, but the absorption peaks of the DLC extended in the ranges of 505–515 and 560–570 nm. Furthermore, Enchroma glasses blocked completely the undesirable spectra (100% absorption) compared to 90% block showed by the DLC. Advantageously, the DLC presented higher transmission spectra for all transmission bands improving the lens’s transparency and consequently the vision clarity. On the other side, Pilestone glasses of models TP-025 and TP-012 showed only one absorption peak each in the green-red region and presented low transparency in the blue region: 37% for the TP-025 at 477 nm, and 18% for the TP-012 at 472 nm (Figure 4d). Most importantly, the undesired spectra bands were not completely blocked as 10% and 20% of the incident light was transmitted for TP-12 and TP-25 models, respectively. On the contrary, HB-585-LB glasses completely absorbed the blue light range yielding the widest and deepest absorption band compared to all the other samples (Figure 4d). The glasses blocked most of the incident colors by absorbing 100% of the incident light along the extinction band which extends from 390 to 570 nm represent more than half of the visible light band (380-740 nm).[20] The tested commercial

Figure 4. a,b) Transmission spectra of highly tinted in-house made contact lens materials which were made in the form of layers attached on glass slides, scale bar:1.5 cm. c) Transmission spectra of the in-house made double layer lens versus Enchroma glasses’ spectra. d) Transmission spectra for three models of commercial glasses used for color blindness. e) Photographs for the commercial glasses used in the patient test.
glasses are shown in Figure 4e. Each glasses/lens showed distinguished optical properties.

The performance of the developed lenses and the commercial glasses was tested on 21 color-blind individuals of age 18 to 32 years who have been diagnosed with deuteranopia and deuteranomaly.

There are various types of online tests which are currently being used to detect or accurately assess CVD type and severity. The most commonly used test by the optometrists and companies is the Ishihara 38 Plates CVD test. The test consists of number of dotted plates and randomly written numbers in different colors on each of these plates. Plates are held 75 cm away from the patients, and patients are asked to tell the numbers written on the plates one after another within three seconds (Figure 5a). Lighting conditions of the test environment is vital and might affect the results of the test and during the test it was kept at normal room lightening level at 1000 Lux. Since Ishihara test is accurate, easily accessible, and not time consuming, it is highly popular and was used for this research due to the limited time of the patients.

Each of the volunteered subjects performed Ishihara test of 21 plates without lenses to determine their CVD type. In Ishihara test, there are several key plates; for instance, plate number 1, which reads 12, should be recognized by everyone, including patients with all types of CVD. Plates 2, 4, 6, 7, 8 and 9, which read figures 8, 29, 5, 3, 15 and 74, respectively, are designed to diagnose people with red-green CVD. Most CVD sufferers might only be able to distinguish the last four plates which read, 26, 42, 35 and 96, respectively. These plates are designed to diagnose whether a patient suffer from red or green cone shift, as well as the severity.

Subjects performed the same test again by looking through our in-house made contact lens materials attached on glass slides, and commercial glasses (Enchroma, Pilestone TP-025, Pilestone TP-012, HB-585-BL). Upon finishing indoor tests, subjects were taken outdoors to a color rich environment to try all samples. They were asked to identify how colors look different and if they recognize new color shades. Patients were also asked which glasses/lenses they viewed to be the most pleasant and which improves contrast the greatest. CVD subjects were able to distinguish more plates after using the tinted contact lens materials and commercial glasses. However, deuteranopia patients perceived less plates when using the Atto 488 contact lens material (Figure 5c). The number of plates perceived by participants were found to be different for each contact lens material/glasses.

Deuteranomaly and deuteranopia subjects responded differently to the samples used. As for deuteranomaly patients, the most effective glasses were the HB-585-BL, which showed a 53% increase in plates perceived, followed by Pilestone TP-012 with a 33% increase (Figure 5d). Pilestone TP-025, DLC, and Atto 565 sample showed similar performance presenting
an increase of 21 ± 1% while Enchroma glasses and Atto 488 sample were the least effective (Figure 5d). Results from deuteranomaly patients showed a similar trend with the effectiveness of samples but generally with half the percentage increase. This is aside from the in-house made DLC which showed the best performance; an increase larger than that seen by deuteranomaly patients with a 24.8% increase, opposed to 22.6%. Pilestone TP-012 glasses effectiveness was also a third of that seen by deuteranomaly patients. The error bars presented in Figure 5d show the standard deviation in the percentage increase compared to no glasses for each tested sample. For all samples but Enchroma, for deuteranomaly patients, the standard deviation was at least half of the increased percentage, showing that the effectiveness of each sample varies greatly from patient to patient, even within the same classification of CVD. This highlights the difference seen between the same type of CVD and how different each patient appears to be. This also reflects the significant need of optimizing the lenses for each patient. Despite Enchroma glasses being the market leader, it showed to be the least effective at increasing each participants’ ability to read Ishihara plates as compared to each of the alternatives available for green-red CVD sufferers.

For deuteranomaly participants, the HB-585-LB glasses proved to be the most effective since patients were able to recognize the highest number of plates (Table 1). Out of the total ten plates, HB-585-LB glasses was the most effective sample as well as it had the greatest average percentage increase in plates read. Additionally, HB-585-LB glasses was the only sample that provided a pass on the Ishihara test for one patient who read all twenty-one plates correctly. However, it left 71% of participants unable to read plate number one, which every subject was able to read easily without any external aid. This glasses also proved to be the least effective for reading the last four plates which could have perceived by deuteranomaly patients without wearing the glasses. A number of the plates which the HB-585-LB glasses were most effective for are similar in style to the one shown in Figure 5b. Participants commented that these plates appeared to be red on the outside and grey for the number while wearing the glasses, making an almost clear black and white like image rather than an increase in color perception of the dots—showing a reduction in contrast. Therefore, lenses having a wide blocking band such as HB-585-LB introduces a bias for the Ishihara plate test and did not represent a true increase in ability to see colors.

Table 1. Results received from deuteranomaly participants.

| Sample       | Slides most effective for | Maximum % increase | Minimum % increase | Average % increase | Standard Deviation |
|--------------|----------------------------|--------------------|--------------------|--------------------|--------------------|
| Enchroma     | [1,4,8,9,18,20,21]         | 33.33              | 0.00               | 12.82              | 12.30              |
| Pilestone TP-025 | [1,4,8,9,20,21]          | 41.18              | –25.00             | 22.90              | 21.63              |
| Pilestone TP-012 | [5,8,9,18,20,21]         | 55.56              | –15.79             | 33.42              | 21.8               |
| HB-585-BL    | [3,6,7,10,11,12,13,14,15,16,17,21] | 113.33              | 15.79               | 33.06              | 33.11              |
| Atto 565 lens | [1,7,8,9,19,20,21]        | 47.62              | –15.00             | 20.04              | 20.32              |
| Double layer lens | [8,9,18,19,20,21]     | 38.89              | –5.00              | 22.60              | 14.60              |
| Atto 488 lens | [1,8,20,21]              | 40                 | –35                | 14.56              | 24.97              |

Table 2. Results received from deuteranopia participants.

| Sample                | Plates most effective for | % Maximum increase | % Minimum increase | % Average increase | Standard deviation |
|-----------------------|----------------------------|--------------------|--------------------|--------------------|--------------------|
| Enchroma              | [1,2,4,18,21]             | 7.69               | 4.00               | 5.65               | 1.88               |
| Pilestone TP-025      | [1,4,5,9,20,21]           | 28                 | –15.38             | 7.71               | 21.83              |
| Pilestone TP-012      | [1,2,8,18,19,20,21]       | 15.38              | 5.26               | 10.88              | 5.15               |
| HB-585-LB             | [3,6,7,8,10,11,12,13,14,15,16,17] | 40                 | 0                  | 21.02              | 20.08              |
| Atto 565 lens         | [1,8,9,19,21]             | 15.38              | 5.26               | 10.88              | 5.15               |
| Double layer lens     | [1,6,7,8,9,18,19,20,21]   | 38.46              | 15.79              | 24.75              | 12.05              |
| Atto 488 lens         | [1,18,19,20,21]           | 8                  | –15.79             | –5.16              | 12.09              |
were unable to differentiate between shades of green and red. All of the participants described wearing these glasses as unpleasant. Therefore, it can be assumed that the wide block band of this glasses causes a hindrance to suffer color perception, particularly on shades that are difficult to distinguish. It is thus unreasonable to consider these glasses as a viable solution to color vision deficiency. Observations about Pilestone TP-012 glasses were similar to those of the HB-585-LB glasses, with the appearance of colors through the glasses being red in color and having reduced contrast as well as a lower range of colors visible; however, this effect was less apparent than that seen within the HB-585-LB glasses which showed a wide blocking band for the incident light as seen in their transmission spectra displayed in Figure 4d. The Atto 488 sample was designed for “tri” patients who are sensitive to blue light, since none of the participants had this diagnosis no difference was observed in contrast.

Patients were then asked to provide their CVD wearable preference. Six out of eleven patients preferred Enchroma while three patients chose the DLC. Two patients had the Pilestone TP-025 and the Atto 565 sample as their preferred wearables. Patients, who had no preferences, did not notice considerable differences in vision or color contrast when using the glasses/lens. Comparing the Atto 565 sample and the DLC, 75% of those who performed trials found viewing through the DLC provided better contrast, with a small pink tinge being seen while viewing through both. However, pink tinge was greater while viewing through the Atto 565 sample. Nevertheless, with DLC and Enchroma, patients were able to see colors they had never seen before, most commonly purple. When showed a picture of the berries, patients saw as blue without glasses/lenses (Figure 6). In addition, they were able to clearly distinguish different shades of green and red, and being able to identify clearly red and green they would have seen as the same color with no glasses/lenses. Figure 6 shows the red leaves and green leaves that participants could distinguish while wearing Echroma glasses or looking through the DLC sample. Therefore, the DLC sample not only improved the range of colors visible, but also the contrast between colors showing higher performance than Enchroma indoors and relatively similar performance outdoors.

The contrasting results noted between Ishihara test and viewing outdoors with samples prove that Ishihara test is not an accurate representation to evaluate the effectiveness of CVD glasses/lenses. Instead, sample testing should be conducted in a color rich environment to determine if more contrast can be perceived. However, any sample cannot be classified as a “cure” without participants passing a form of CVD testing since all of those with trichromatic color vision can pass this testing. Customizing the blocked wavelength range to suit each CVD individual is necessary to achieve the desirable performance.

3. Conclusion

Atto dyes were cross-linked into in-house made contact lenses and showed no leakage whether the lenses were soaked in eye tears or contact lens’ storage solution. Enchroma and the home-made lenses provided an effective improvement for CVD sufferers’ ability to perceive colors and enhance contrast outdoors. However, both did not pass Ishihara test, which indicate that they need to be customized for each CVD patient separately. The performance of the proposed lenses was superior to Enchroma in indoors; however, Enchroma was favorable for a larger number of subjects when they experience it outdoors.

Figure 6. Color rich views used for outdoor test where CVD patients commented on while they were wearing the samples and looked through.
Prior to recommending the proposed contact lenses for patients, the shelf life effect, oxygen permeability, and water content should be investigated. Also, Ishihara test cannot solely be used as a measure to determine the effectiveness of CVD glasses/lenses. This is mainly due to the fact that some of the commercial glasses tested produced effective improvements in plate testing without enhancing the color perception. Therefore, outdoor testing in a color rich environment was utilized as an additional measure to evaluate the efficacy of the in-situ fabricated lenses in comparison to the commercial glasses.

4. Experimental Section

Materials: Ethylene glycol dimethacrylate, 2-hydroxyethyl methacrylate (HEMA), 2,2-dimethoxy-2-phenylacetophenone, Atto 488, Atto 565, and phosphate buffer saline (PBS) were purchased from Sigma-Aldrich and used without further purification. Enchonel, Pilestone TP-012, Pilestone TP-025, and HB-585-LB glasses were purchased online to compare their performance with the in-house made lenses.

Fabrication of Contact Lenses: A process was developed to crosslink the Atto dyes (Atto 488 and 565) and the contact lens monomer to fabricate tinted contact lenses for color blindness. The precursor solution, consisting of HEMA, ethylene glycol dimethacrylate, and a photoinitiator (2,2-dimethoxy-2-phenylacetophenone), was mixed with the Atto dye solution. The mixture was poured in the contact lens mold and cured by UV lamp of wavelength 365 nm for 5 min. For the double layer contact lenses, the Atto 488 tinted lenses were prepared according to the aforementioned protocol; then, the prepolymerized solution of the Atto 565 tinted contact lens was drop casted on the convex face of the lens and cured immediately.

Testing the Dye Leakage: The fabricated lenses were submersed in eye tears and contact lens’s storage solution to investigate the dye leakage over time. The optical transmission spectra of the lenses were recorded using a spectrophotometer (Ocean Optics USB2000) over time.

Supporting Information
Supporting Information is available from the Wiley Online Library or from the author.

Data Availability
The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

Acknowledgements
The authors acknowledge Khalifa University of Science and Technology (KUST) for the Faculty Startup Project (Project code: 8474000211-FSU-2019-04) and KU-KAIST Joint Research Center (Project code: 8474000220-KKJRC-2019-Health1) research funding in support on this research. H.B acknowledges Sandoq Al Watan LLC for the research funding (SWARD Program - AWARD Project code: 843400391-EX2020-044). A.K.Y. thanks the Engineering and Physical Sciences Research Council (EPSRC) for a New Investigator Award (EP/T013567/1).

Conflict of Interest
The authors declare no conflict of interest.

Keywords
Atto dyes, biomaterials, color blindness, contact lenses, vision correction

Received: August 12, 2020
Published online: November 30, 2020

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