Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-6737

Reviewer Comments

Comment 1: A well-written comprehensive review of the topic. Consider adding a figure of fundus changes associated with DR in human eyes.
Reply 1: A figure comprised of Fundus color photo, Fluorescein angiogram and OCT of a patient with Diabetic retinopathy and associated changes was added.

Comment 2: Line 54: This seems to be a very high rate of resistance to antiVEGF therapy. Reference cited are review articles. Please confirm and clarify what you mean by resistance. Do you mean vision loss persists despite this therapy or that NV and DME don't regress?
Reply 2: We agree and further clarification was included. Choi M, et. al (2019) reported the characteristics seen in patient's refractory to anti-VEGF, steroids, or both. Pacella et. al (2016) reported an 18-month follow up of DME resistant to anti-VEGF where steroid implant demonstrated utility.

Comment 3: Line 83: please clarify that "the entire DR pathogensis" refers to disease spectrum seen in human eyes.
Reply 3: Corrected

Comment 4: Line 88 to 90: please include that this is a model of type 1 DM since the pancreas is damaged by pharmacologic agents.
Reply 4: We Clarified that destruction of pancreas models T1DM

Comment 5: Line 97: consider starting new paragraph here.
Reply 5: Agree with suggestion and corrected

Comment 6: Line 99: how does chemical ocular burn induce diabetic retinopathy?
Reply 6: The literature is rather vague on this topic and the technique was not established as a well characterized model of DR. This part was taken out.

Comment 7: Line 126: ref 79 showed lack of ganglion cell loss in their model. So, this is not consistently seen and may vary depending on the genetic background of the mice.
Reply 7: We agree and thank you for pointing this out. Clarification on the variability of ganglion cell loss was included in revision.

Comment 8: Line 176: there appears to be a missing word since incomplete sentence.
Reply 8: Corrected and rephrased.

Comment 9: Line 189: replace “diabetic” with “diabetes”
Reply 9: Corrected

Comment 10: Line 209: is NV seen in this model? Is thinning of ONL or INL seen?
Reply 10: A sentence describing the characteristics of db/db mouse was included along with supported citations

Comment 11: Line 299: This model is used more commonly as a model of retinopathy of prematurity although can be used as a model of NV associated with any retinal vasculopathy, including DR. Also include the NV is transient and regresses spontaneously in this model.
Reply 11: Thank you for the comment. Emphasis on this model being used for ROP was included. We also added more details regarding NV phenotype.

Comment 12: Line 331: change “Swine” to “Swines”
Reply 12: Corrected

Comment 13: Line 332: change to “…vasculature; these are appealing…”
Reply 13: Corrected

Comment 14: Line 336: where are the RPE cells injected? Intravitreal?
Reply 14: Intravitreal injection is correct and clarified

Comment 15: Line 349: change to “Typical agent used is STZ…”
Reply 15: Corrected

Comment 16: Line 355: type error; change “mak” to “make”
Reply 16: Corrected

Comment 17: Line 388: does zebrafish have a macula to develop macular edema? Do you mean retinal edema?
Reply 17: Thank you for bringing this up. Correction was made and term “retinal edema” was used in the manuscript.

Comment 18: Suggest adding a short concluding paragraph
Reply 18: Great suggestion. A concluding paragraph was added at the end.

Comment 19: Please reformat listed references in format specified for the journal.
Reply 19: Corrected