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Letter to the Editors: Concerning “Long-term safety and efficacy of AAV gene therapy in the canine model of glycogen storage disease type Ia” by Lee *et al.*

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Dear Editors,

Recently Lee *et al.* reported seven dogs with glycogen storage disease (GSD) type Ia treated with adeno-associated virus (AAV) vector-mediated gene therapy that apparently prevented long-term hepatic or renal complications (Lee *et al.* 2018). However, there are problems with this conclusion. Notably, Lee *et al.* describe how dogs underwent 24-hr care receiving glucose feeds every 30–60 min. Furthermore, Lee *et al.* describe two GSD Ia dogs on this same rigorous dietary therapy that lived >5 years of age with mostly normal laboratory values, implying that gene therapy had few additional benefits over nutritional therapy.

Our group recently published a very similar gene therapy study, but the GSD Ia dogs were maintained on a more typical diet of only three feedings per day (Brooks *et al.* 2018). However, 4/5 AAV vector-treated dogs developed hepatocellular adenomas and carcinoma and 3/5 developed chronic kidney disease. The key difference between the two studies was the degree of nutritional support and not the gene therapy. Both studies demonstrated low hepatic glucose 6-phosphatase (G6Pase) activity in dogs at the endpoint, as well as marked hepatic glycogen accumulation. Figure 1 in Lee *et al.* also demonstrates a decrease in blood glucose over time in GSD Ia dogs, without specifying if the dogs were fed or fasted. Brooks *et al.* fasted dogs to demonstrate prevention of hypoglycemia. Both studies reported very small amounts of vector DNA at the end of life in most of the GSD Ia dogs. Two dogs in Lee *et al.* had very low vector DNA present in liver at the end of the study (0.01 to 0.02 copies/

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Contributions of Authors:

Elizabeth Brooks wrote the letter.

Priya Kishnani edited the letter and provided expert opinion.

Dwight Koeberl edited the letter and provided expert opinion.

Conflict of Interest:

Elizabeth D. Brooks, Priya Kishnani, and Dwight D. Koeberl have no conflicts of interest to report.

cell) and correspondingly low G6Pase activity from 2.2 to 3.8% of activity in the liver of normal carriers. One dog in Lee *et al*/had elevated vector DNA (Figure 2; dog GE) in association with low G6Pase activity (Figure 3). In contrast, Brooks *et al*/reported higher vector DNA (0.04–0.16 copies/cell; Supplementary Figure 2) and G6Pase activity (28% of carrier activity; Figure 1) in the liver. Thus the effect of gene therapy was similar in both studies.

Lee *et al*/reported no renal complications, other than proteinuria in one dog and mild, intermittent increases in BUN and/or creatinine in two different dogs (Lee et al 2018). Importantly, recombinant AAV8 vectors highly like the one used by Lee *et al*/had no effect on kidney involvement in *G6pc^{-/-}* mice with GSD Ia (see references therein), and therefore gene therapy would not be protective of the kidneys in dogs. The kidney sparing in Lee *et al*/can be attributed to intensive dietary therapy (Lee et al 2018). Brooks *et al*/reported tubule-interstitial lesions and glomerular changes in the older GSD Ia dog cohort treated with AAV vectors (Brooks et al 2018).

In conclusion, both papers demonstrate that gene therapy has greatly prolonged life in GSD Ia dogs and led to low levels of G6Pase activity persistence. However, evidence is lacking that gene therapy in the absence of a strict dietary regimen can prevent hepatocellular tumors and renal disease.

References

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Synopsis:

Gene therapy in the absence of rigorous dietary therapy does not prevent long-term complications of glycogen storage disease Ia.

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