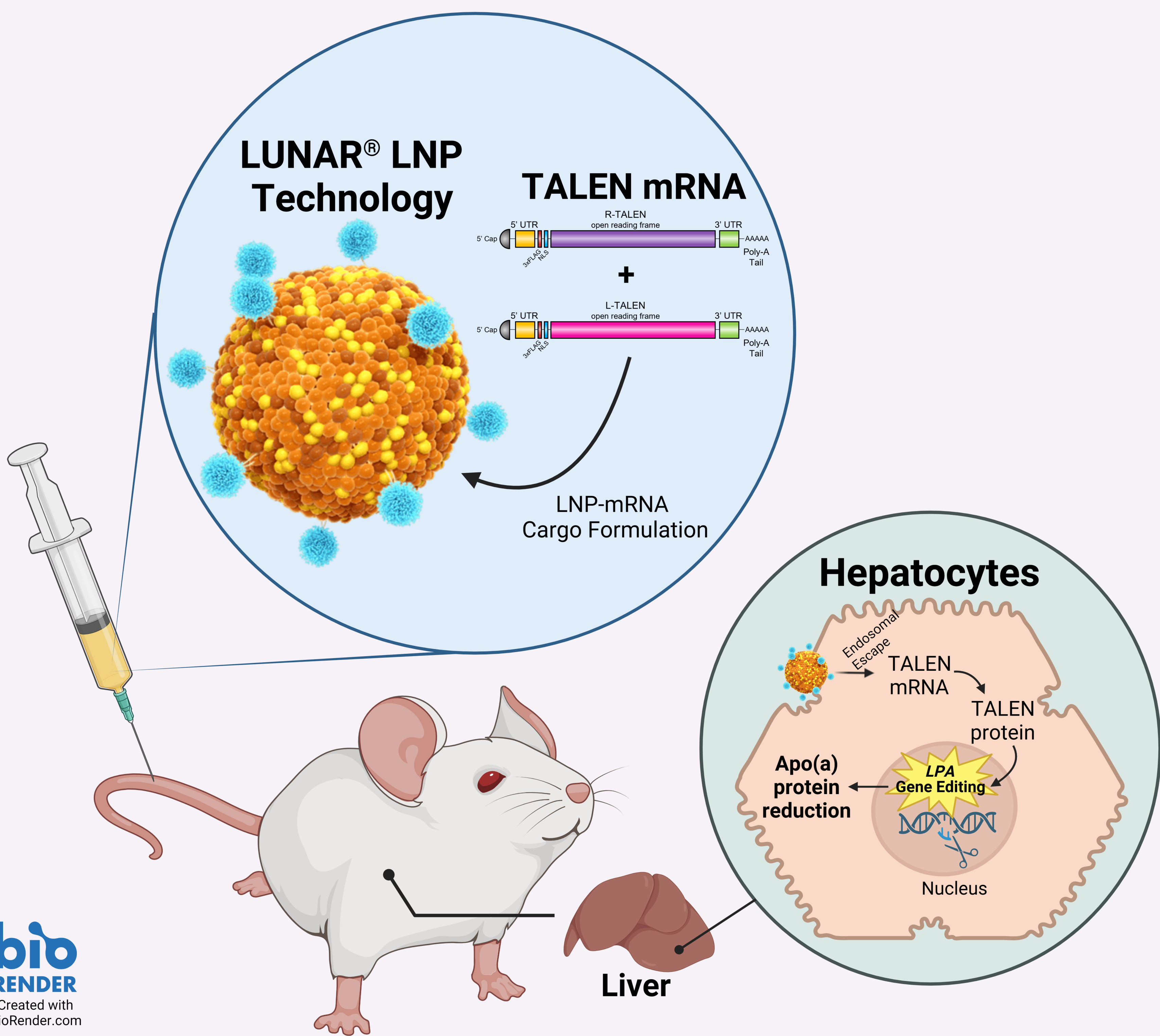




TALENs delivered as mRNA cargo in LNPs cause *LPA* gene editing and Lp(a) reduction *in vivo*.



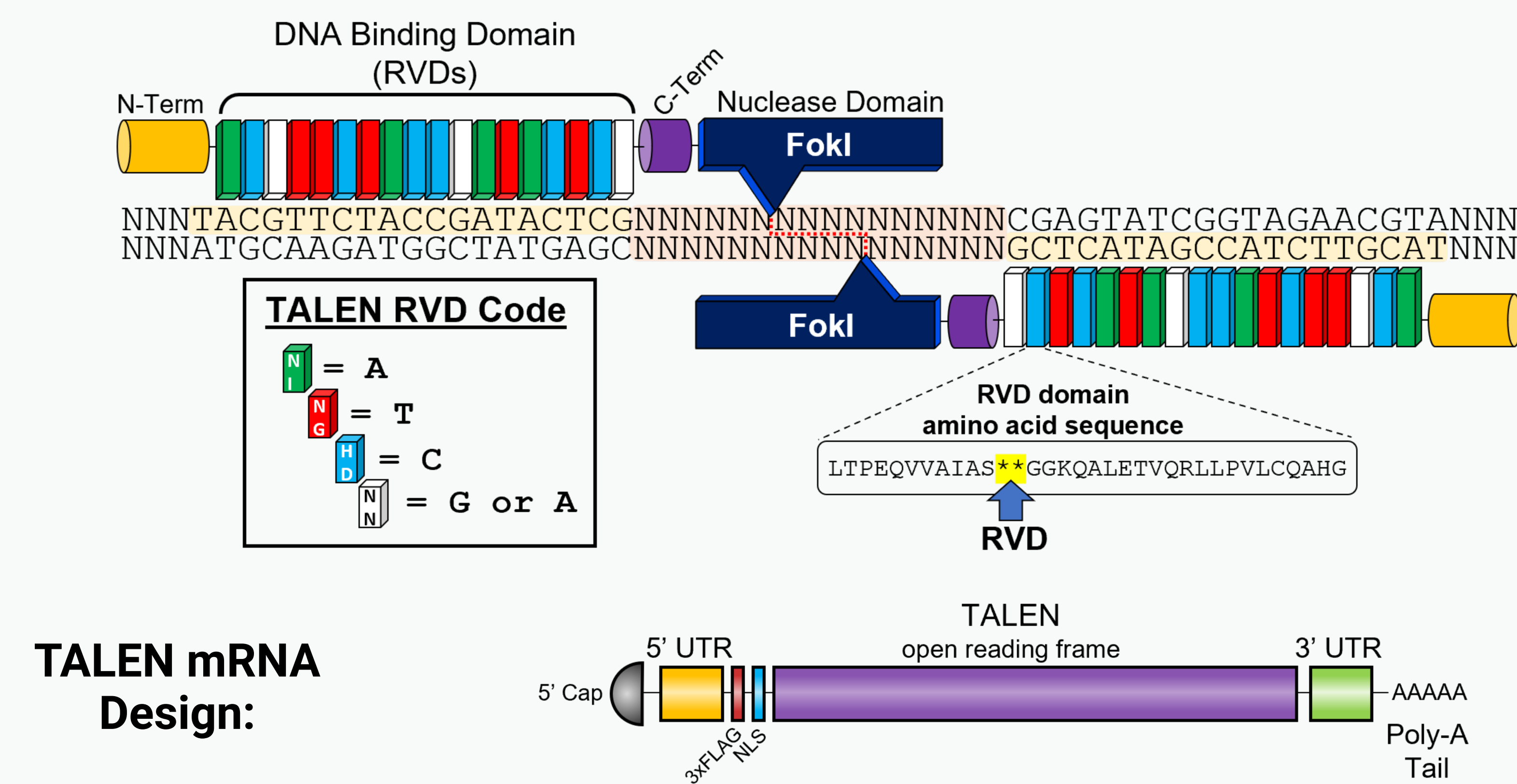
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TALEN-Mediated Gene Editing of *LPA* Causes Gene Disruption and Plasma Lipoprotein(a) Reduction in Transgenic Mice.

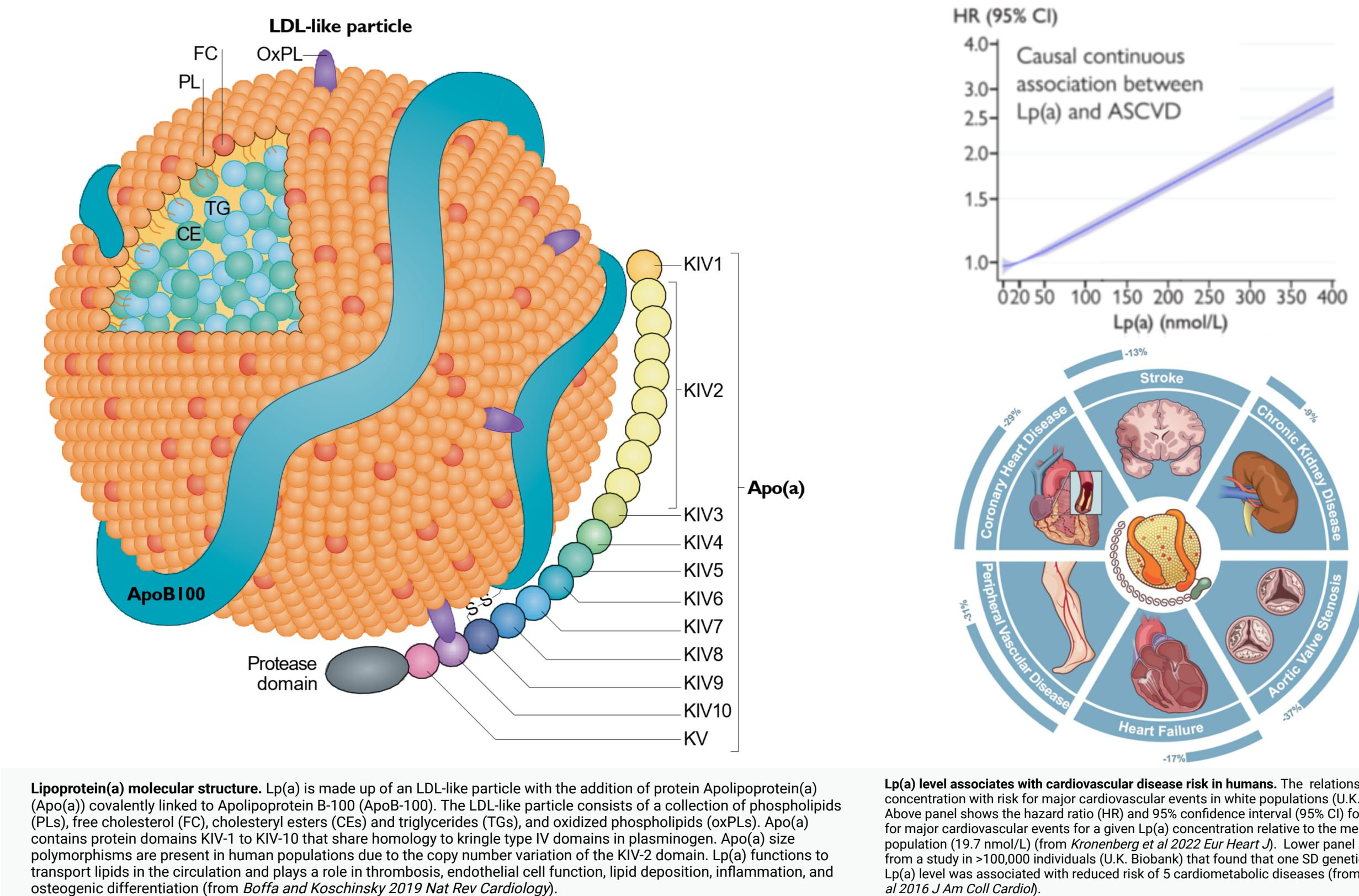
Daniel A. Garcia, Abigail Pierre, Linda Quirino, Grishma Acharya, Aishwarya Vasudevan, Yihua Pei, Michael Endow, Kristen Kuakini, Michael Breshahan, Maria Chumpitaz, Adrian Dukanovic, Suezanne Parker, Pad Chivukula, Stefan A. Boehme, Ramon Diaz-Trelles

Arcturus Therapeutics, Inc., 10628 Science Center Drive, Suite 250, San Diego, CA 92121, USA

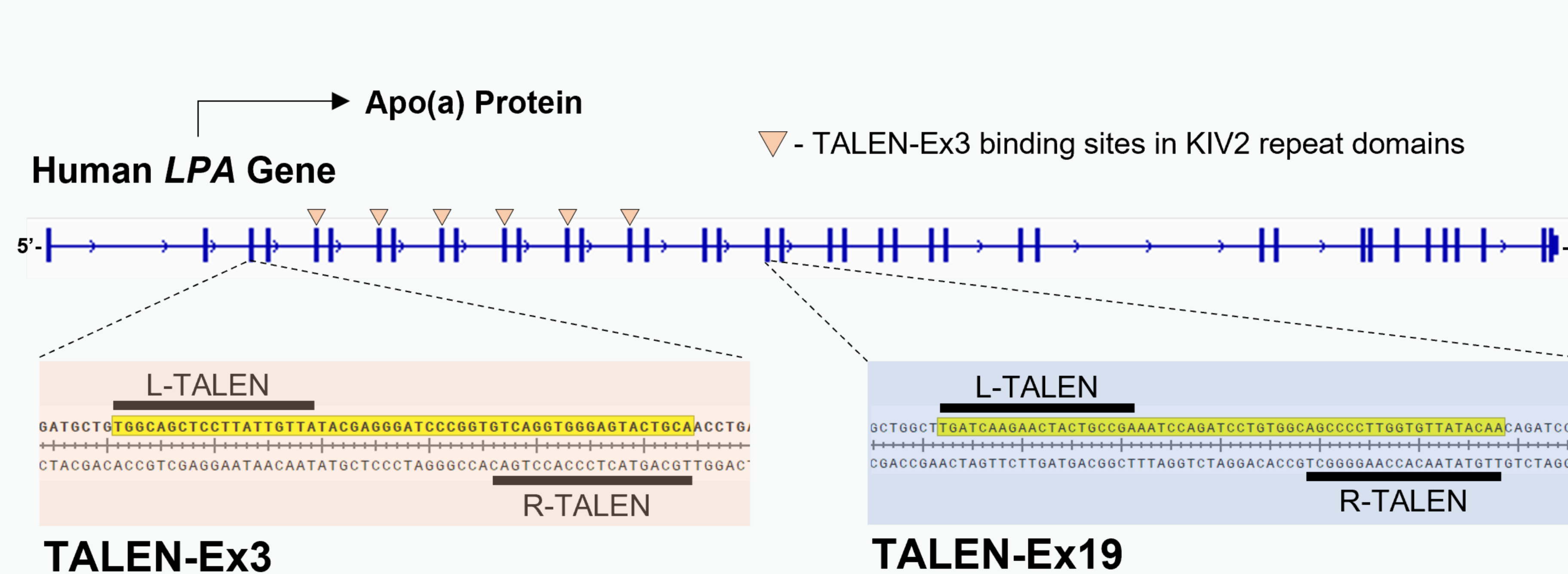
TALENs: programmable gene editing proteins



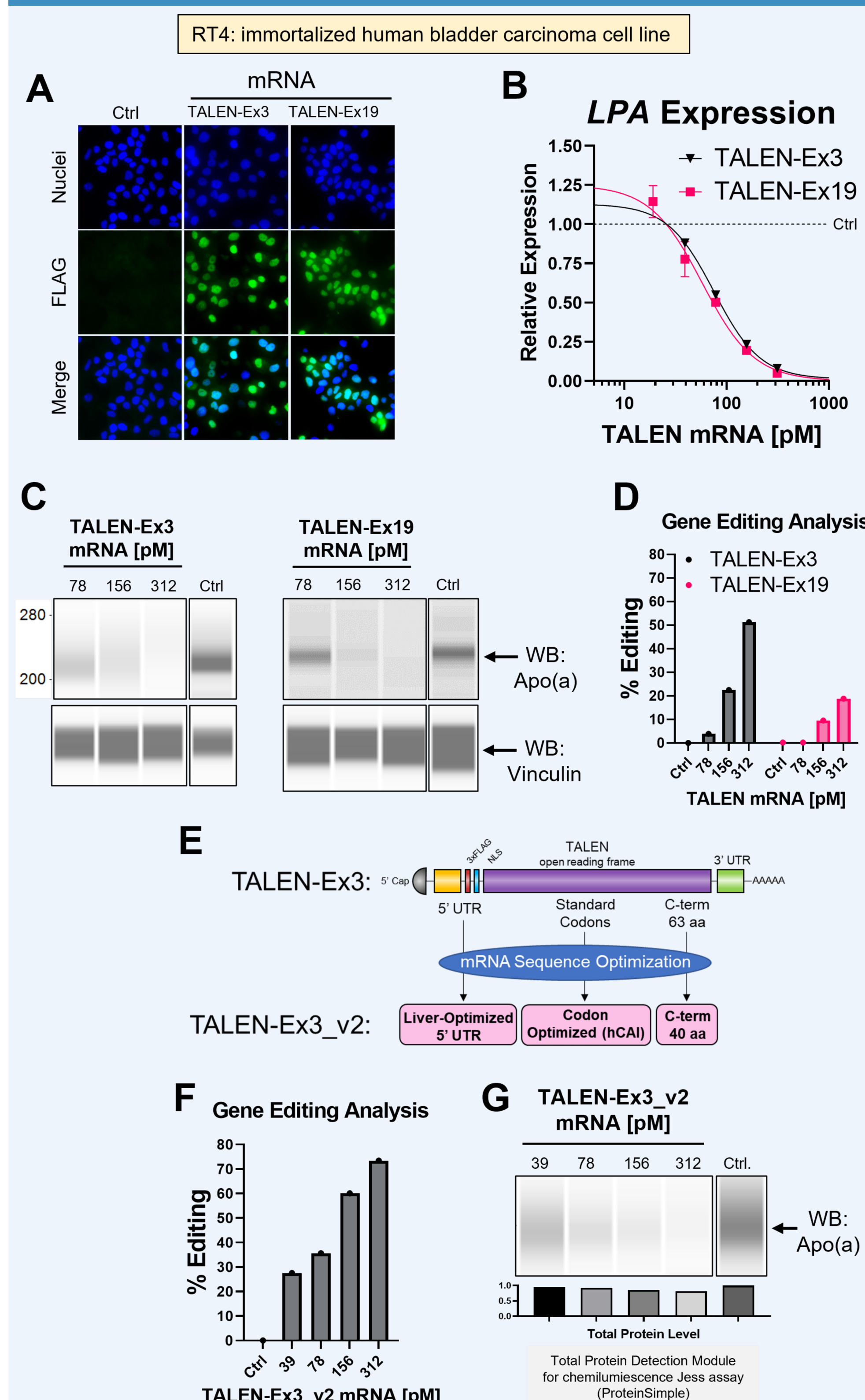
Lipoprotein(a) and cardiovascular disease



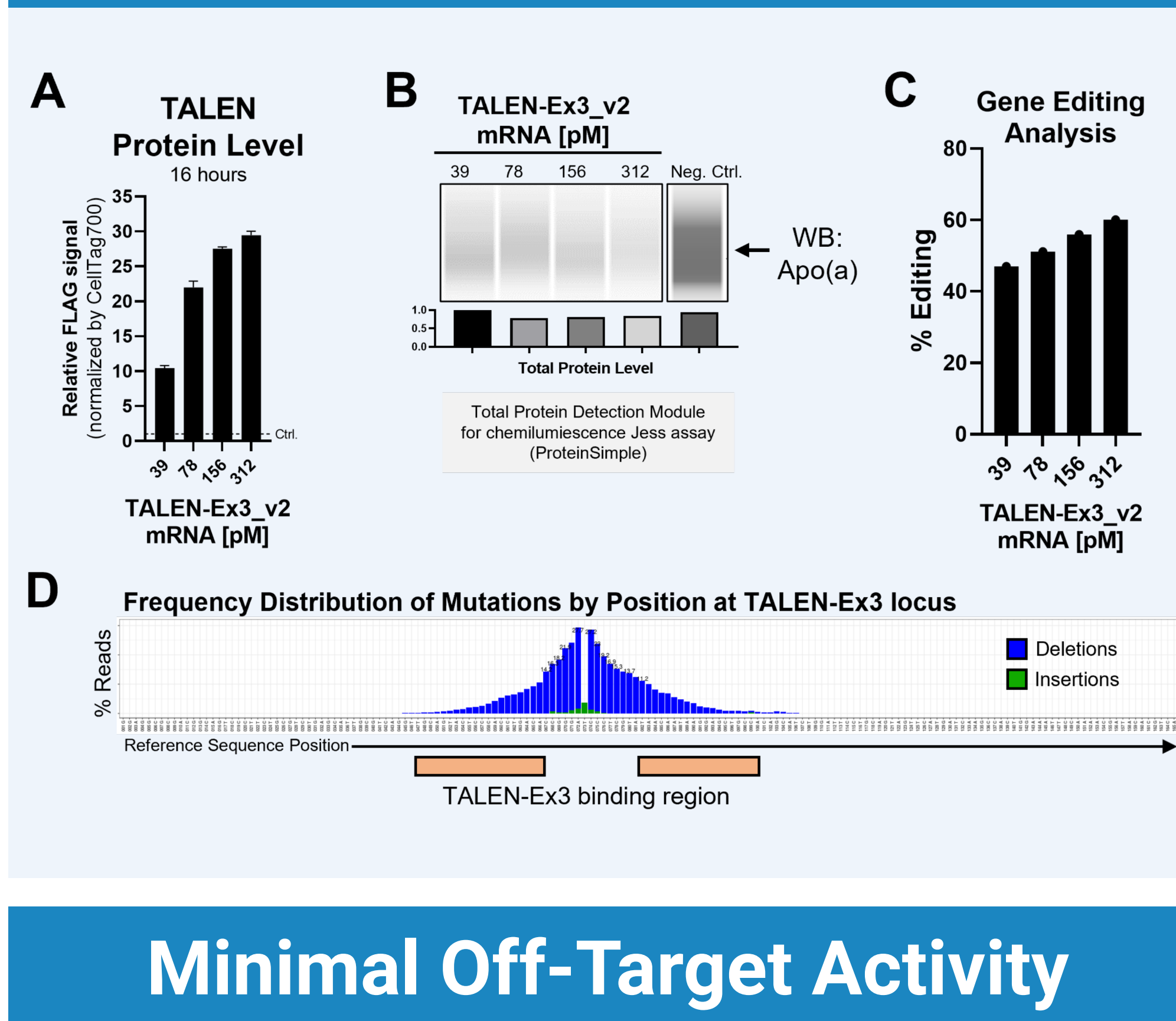
Designed TALENs targeting *LPA*



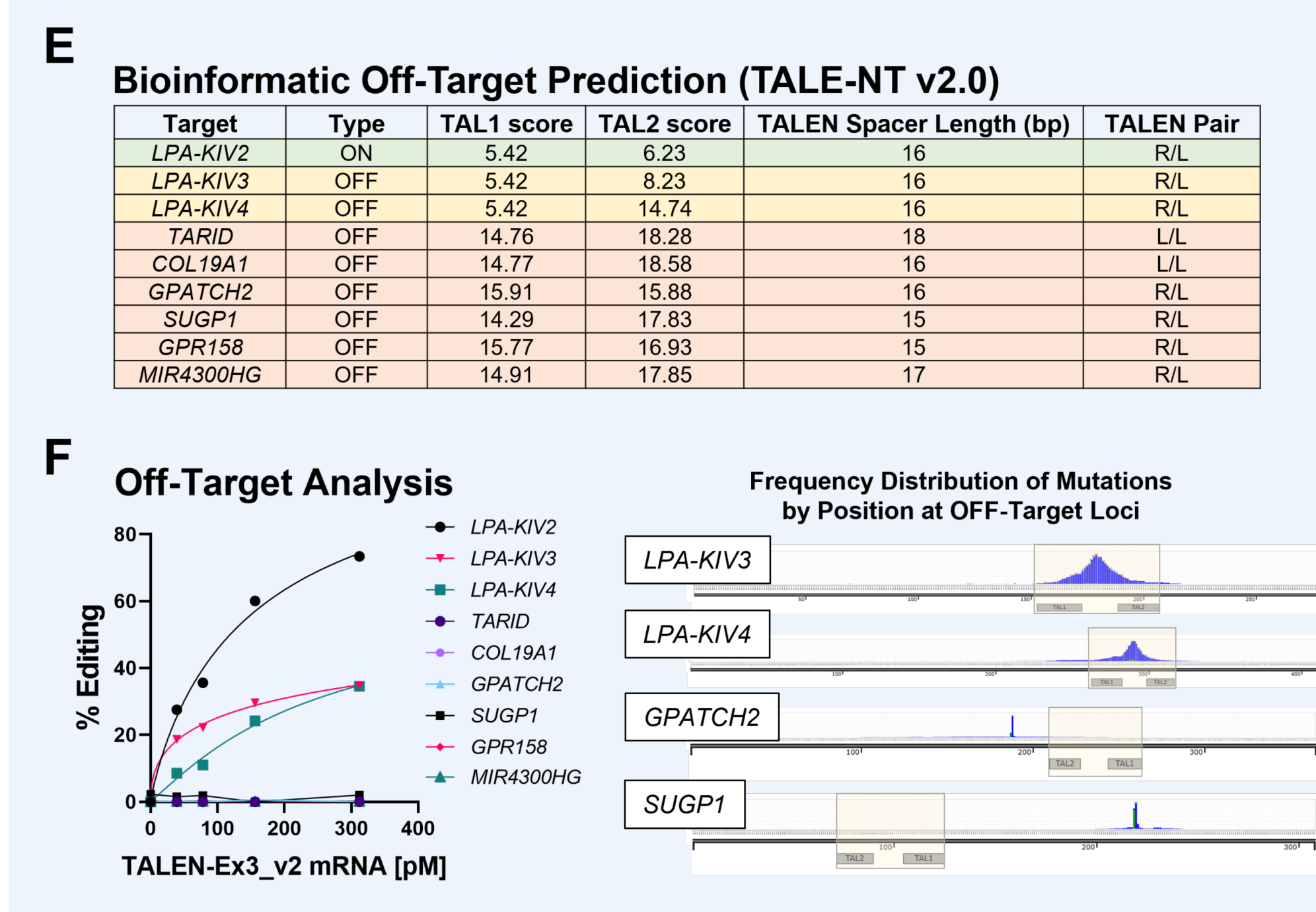
In vitro screening of TALEN mRNAs



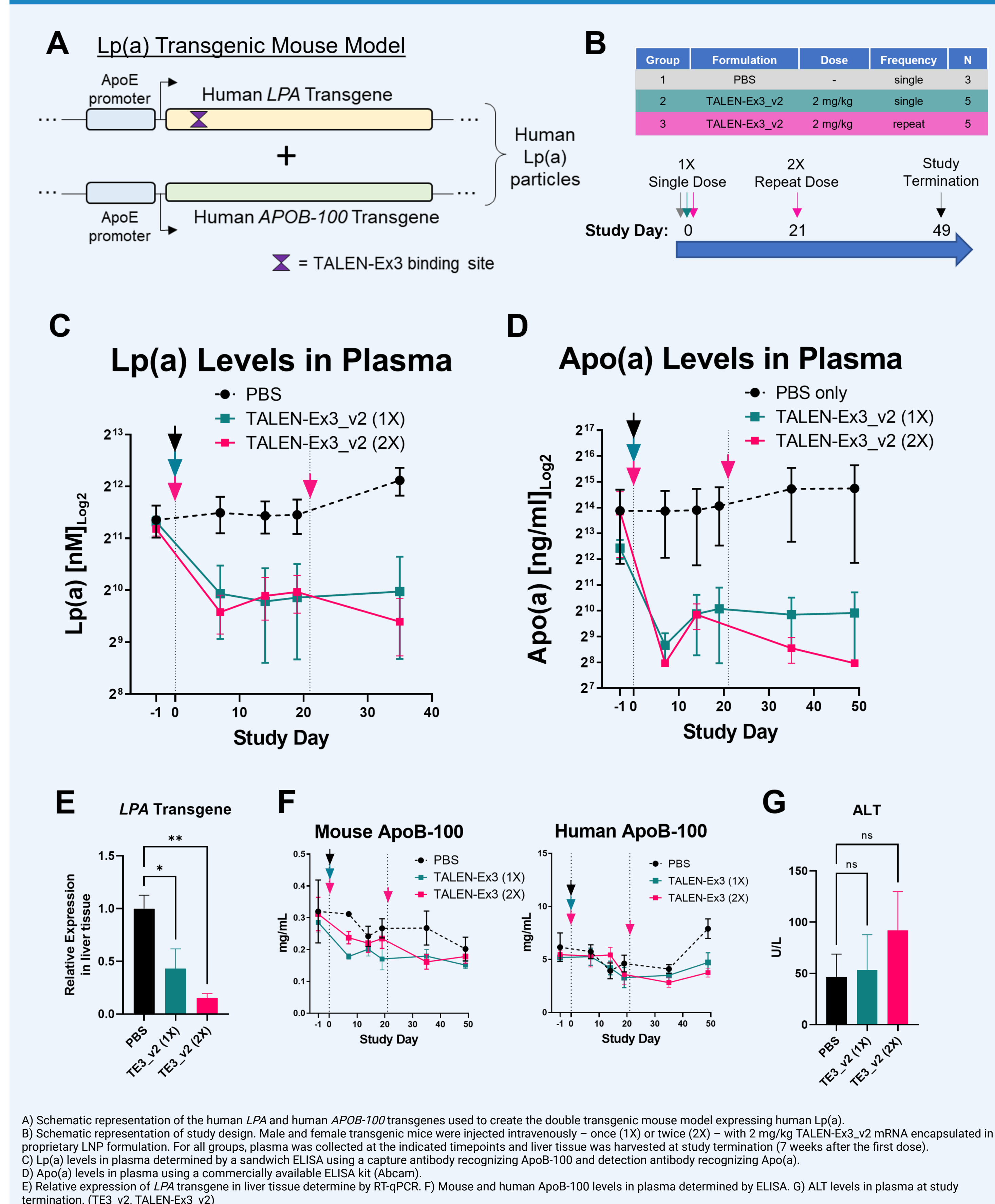
Efficacy in Primary Human Hepatocytes



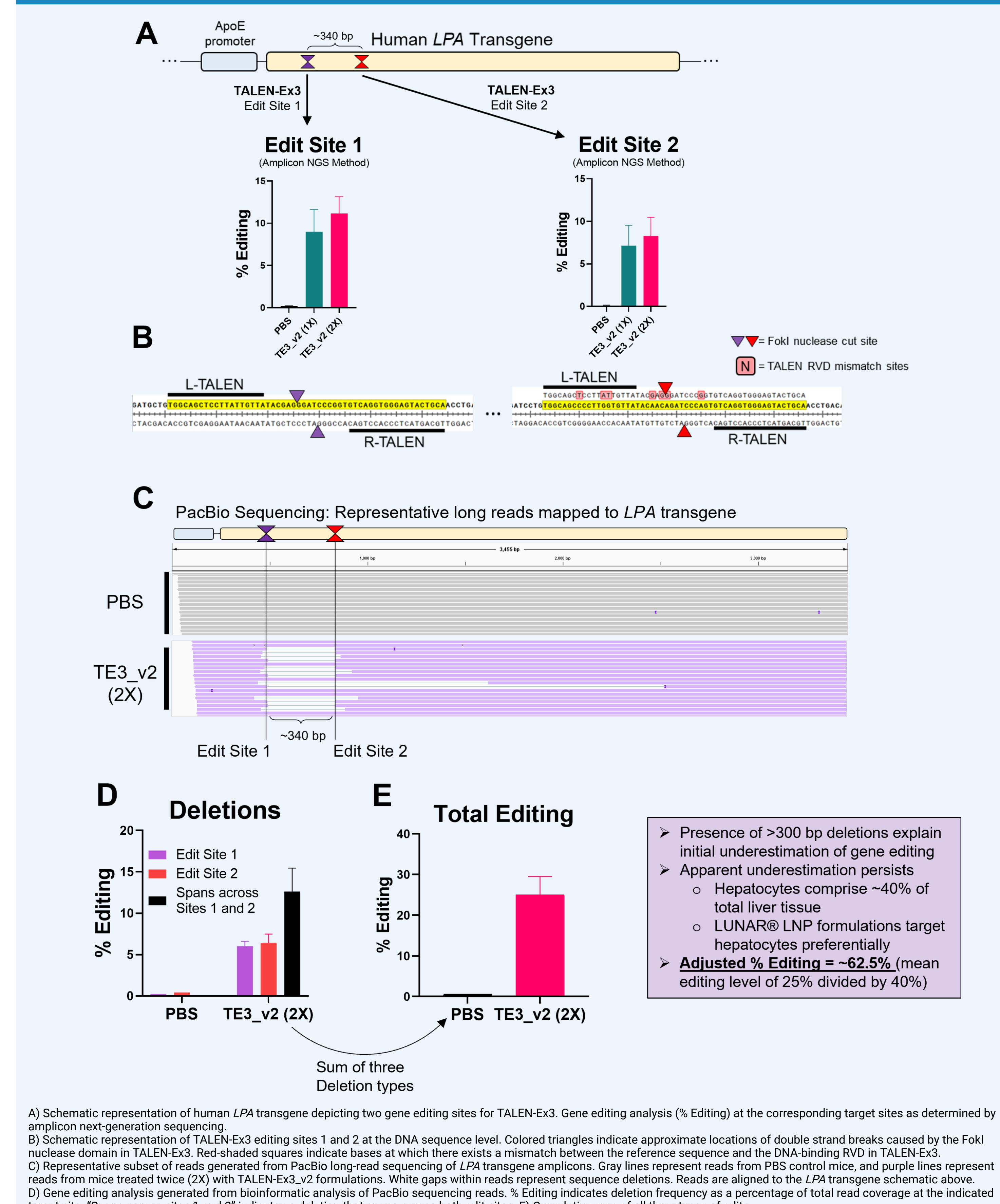
Minimal Off-Target Activity



TALENs reduce Lp(a) in transgenic mouse model



TALENs induce gene editing in transgenic mouse model



SUMMARY

- Achieved proof-of-concept for TALEN-mediated Apo(a) reduction *in vitro* using TALEN mRNAs
- Demonstrated *in vivo* efficacy by LNP delivery of TALEN mRNA that led to Lp(a) reduction in a transgenic mouse model
- TALEN-mediated gene editing was dose responsive
- TALEN mRNA-LNP formulations were well-tolerated *in vivo*
- No detectable off-target activity *in vitro*

REFERENCES

1. Boffa MB, Koschinsky ML. Oxidized phospholipids as a unifying theory for lipoprotein(a) and cardiovascular disease. Nat Rev Cardiol. 2019;16(5):305-18.
2. Cermak T, Doyle EL, Christian M, Wang L, Zhang Y, Schmidt C, et al. Efficient design and assembly of custom TALEN and other TAL effector-based constructs for DNA targeting. Nucleic Acids Res. 2011;39(12):e82.
3. de Alwis R, Gan ES, Chen S, Leong YS, Tan HC, Zhang SL, et al. A single dose of self-transcribing and replicating RNA-based SARS-CoV-2 vaccine produces protective adaptive immunity in mice. Mol Ther. 2021;29(6):1970-83.
4. Doyle EL, Broder NJ, Standage DS, Voytas DF, Brendel VS, Vandyk JK, et al. TAL Effector-Nucleotide Targeter (TALEN-NT) 2.0: tools for TAL effector design and target prediction. Nucleic Acids Res. 2012;40(Web Server issue):W117-22.
5. Emdin CA, Khera AV, Natarajan P, Klarin D, Won HH, Peloso GM, et al. Phenotypic Characterization of Genetically Lowered Human Lipoprotein(a) Levels. J Am Coll Cardiol. 2016;68(25):2761-72.
6. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J. 2022;43(39):3925-46.
7. Miller JC, Tan S, Qiao G, Barlow KA, Wang J, Xia DF, et al. A TALE nuclease architecture for efficient genome editing. Nat Biotechnol. 2011;29(2):143-8.
8. Schneider M, Witzum JL, Young SG, Ludwig EH, Miller ER, Tsimikas S, et al. High-level lipoprotein [a] expression in transgenic mice: evidence for oxidized phospholipids in lipoprotein [a] but not in low density lipoproteins. J Lipid Res. 2005;46(4):769-78.



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