


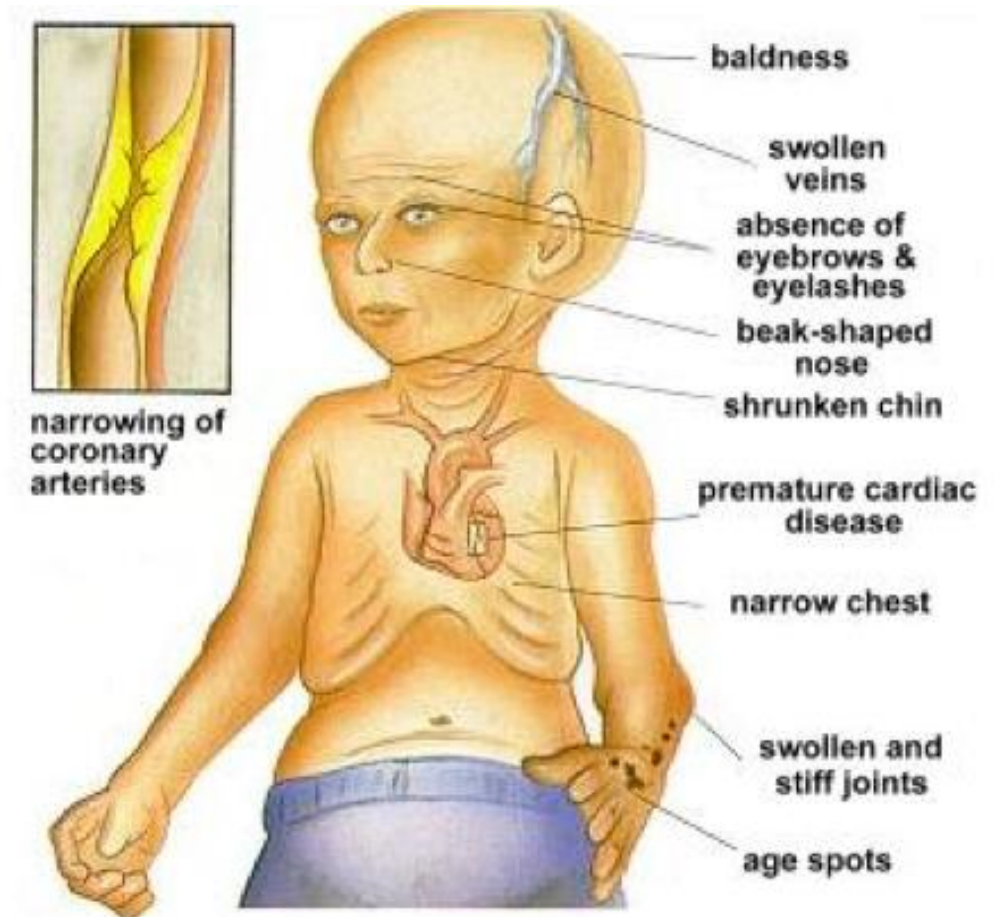


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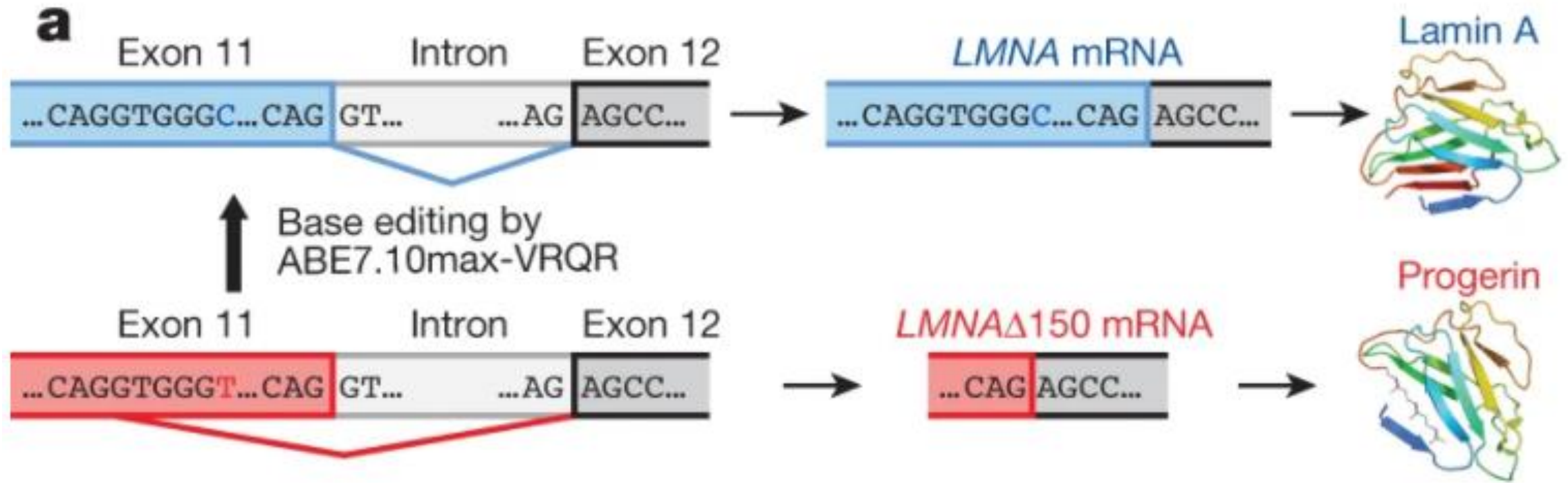
In vivo base editing rescues Hutchinson–Gilford progeria syndrome in mice

Luke W. Koblan, Michael R. Erdos, Christopher Wilson, Wayne A. Cabral, Jonathan M. Levy, Zheng-Mei Xiong, Urraca L. Tavares, Lindsay M. Davison, Yantenew G. Gete, Xiaojing Mao, Gregory A. Newby, Sean P. Doherty, Narisu Narisu, Quanhu Sheng, Chad Krilow, Charles Y. Lin, Leslie B. Gordon, Kan Cao, Francis S. Collins , Jonathan D. Brown  & David R. Liu 

What is Progeria?



What causes Progeria?



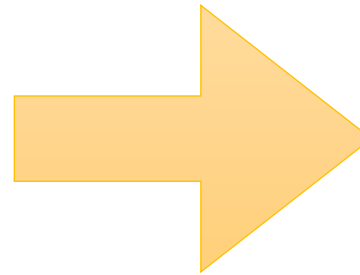
C-G to A-T mutation in the LMNA protein producing progerin

What does progerin do?



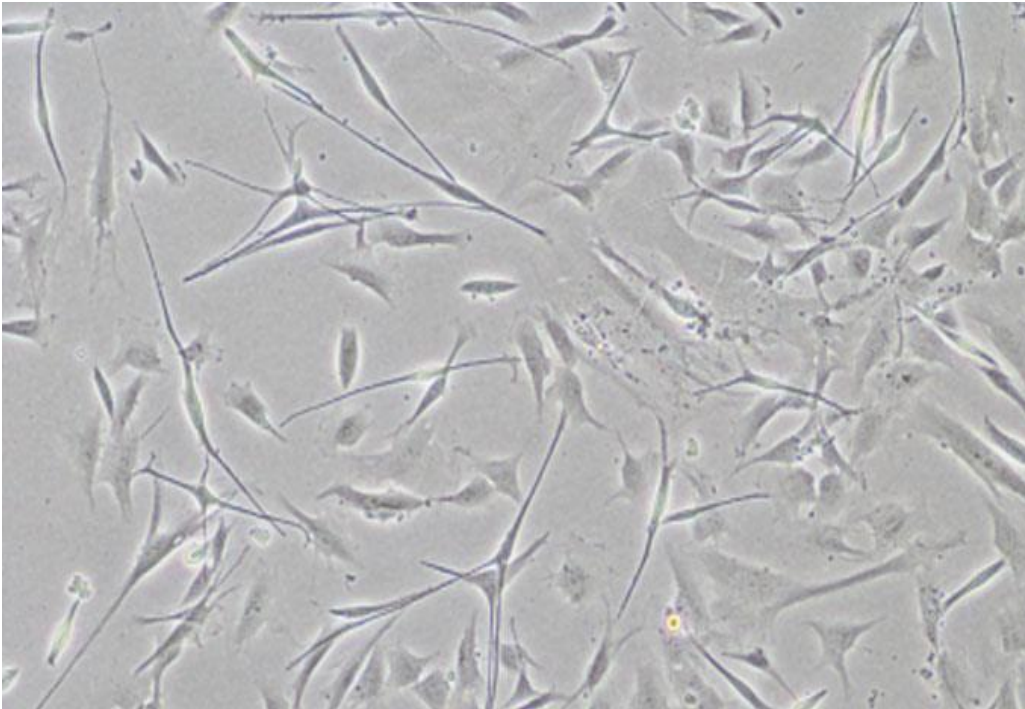
Nuclear Envelope
Defects

Goal: To directly reverse the mutation that causes HGPS

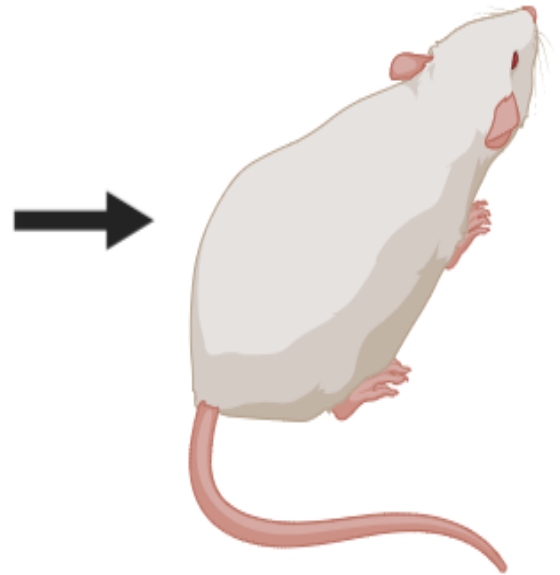


Can it be reversed using modern genetic methods??

What model organism did they choose to model HGPS?

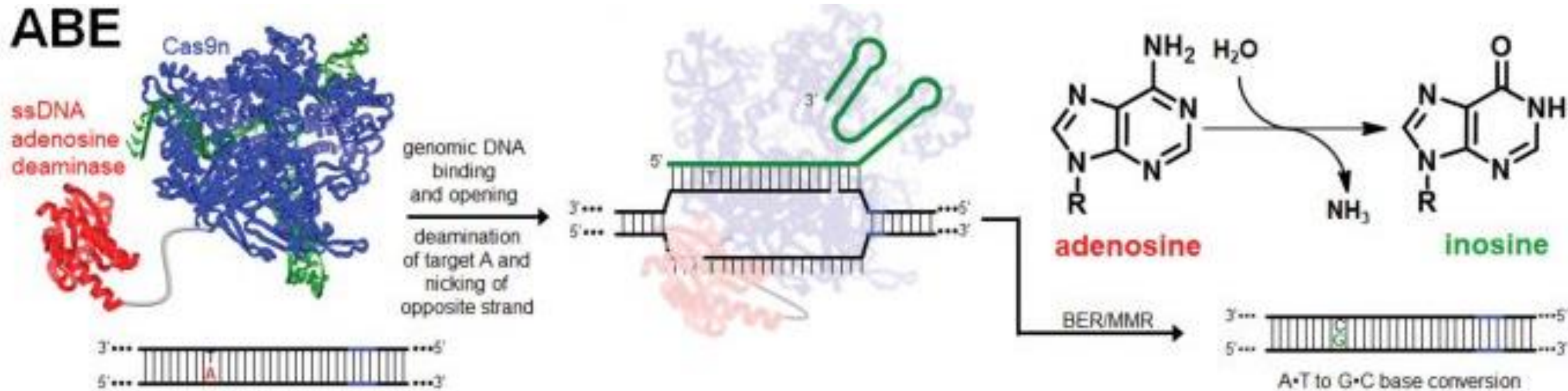


**Fibroblast from children
with Progeria**



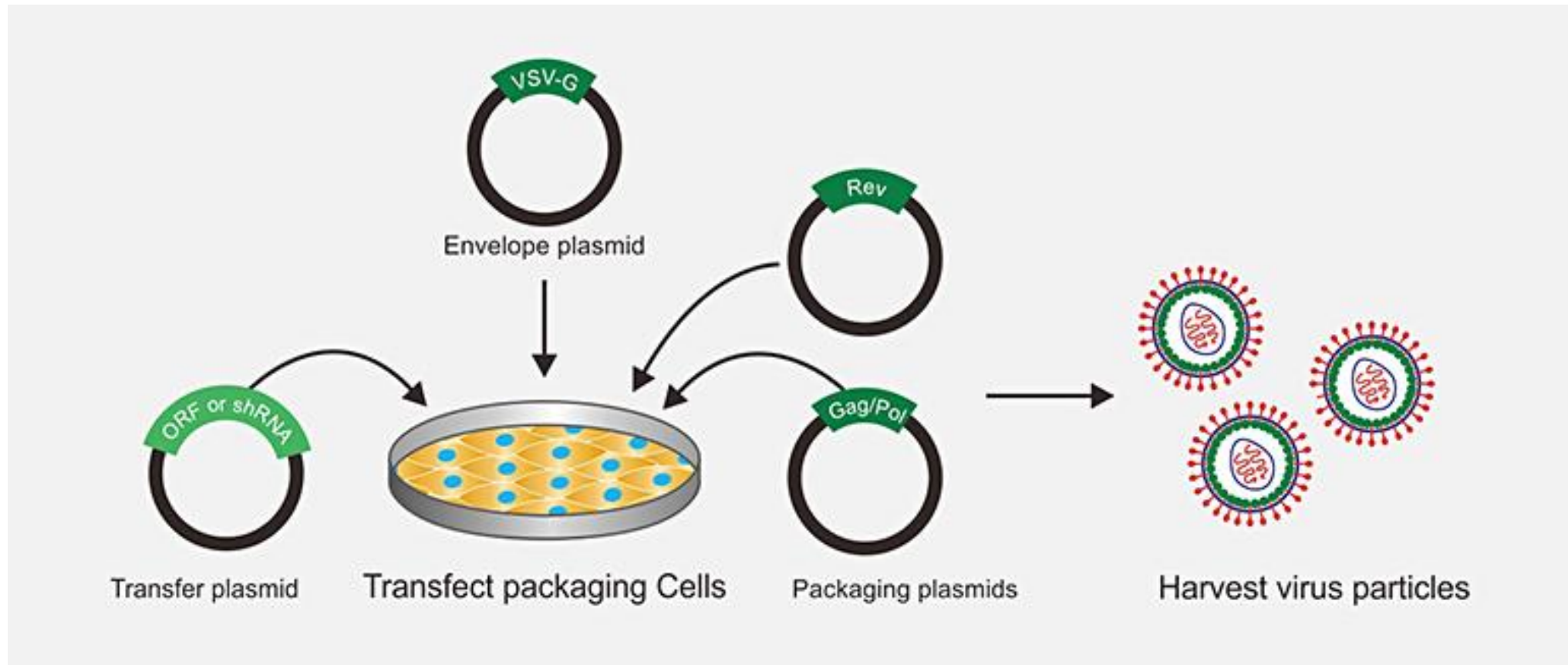
**Mice homozygous for the
transgene**

What are ABEs?



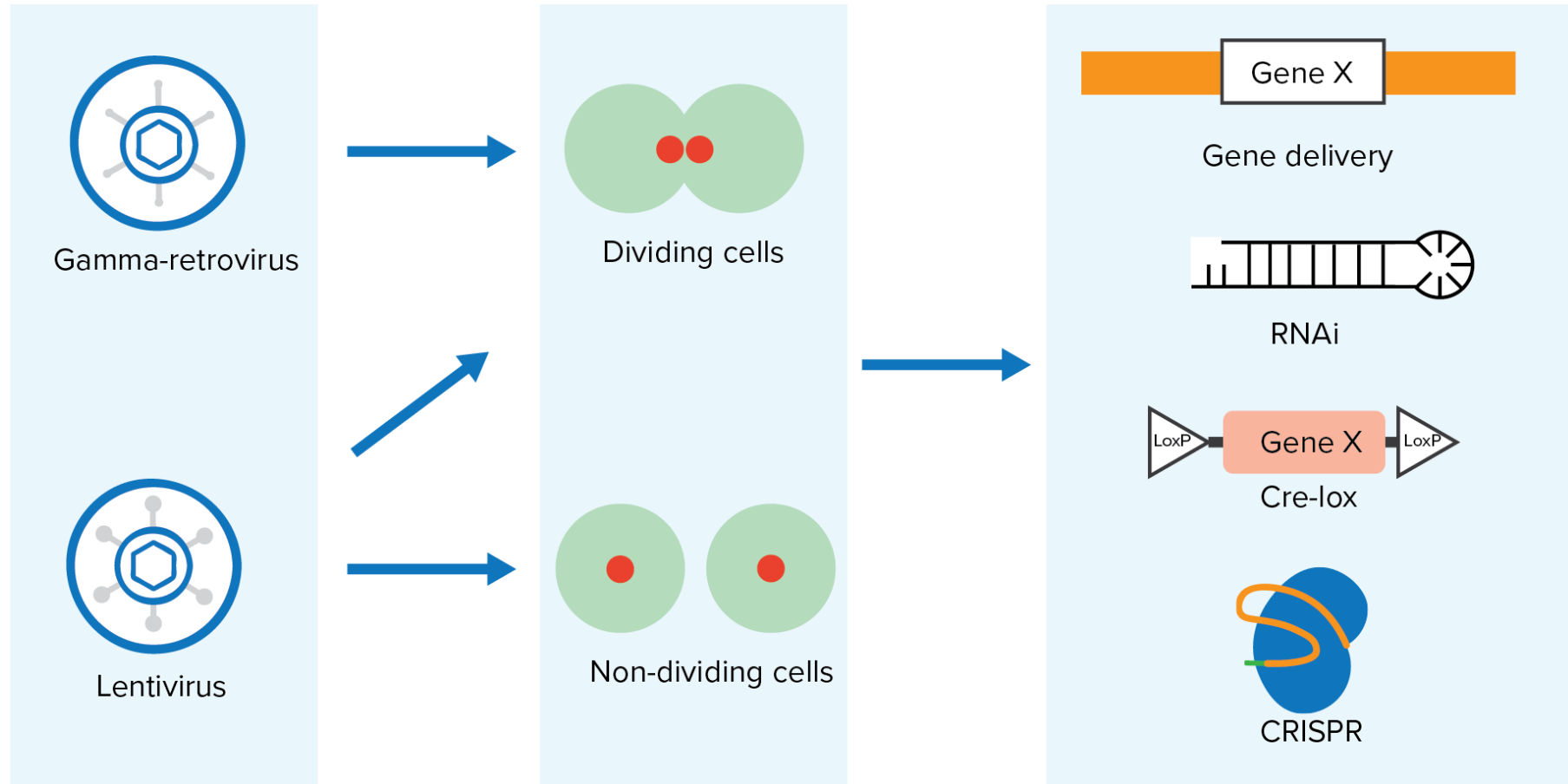
Adenine base editors convert A-T base pairs to C-G base pairs

How are ABEs administered to HGPS fibroblasts?



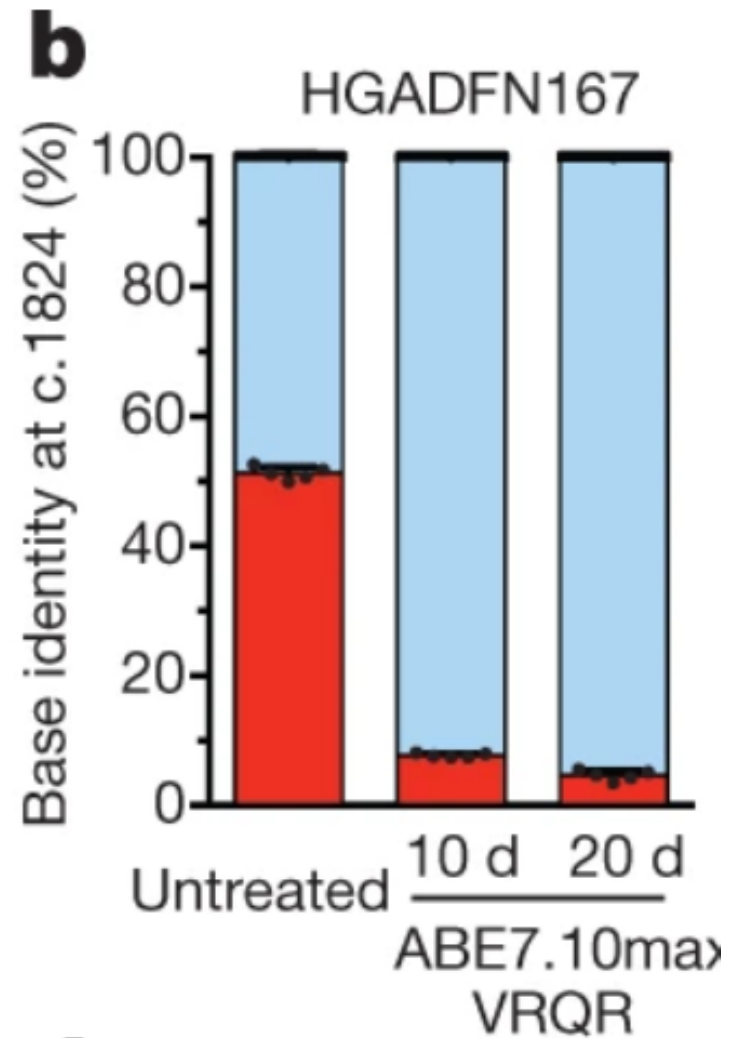
A lentivirus is used to deliver ABEmax-VRQR and sgRNA.

Why choose lentivirus over other viral vectors?

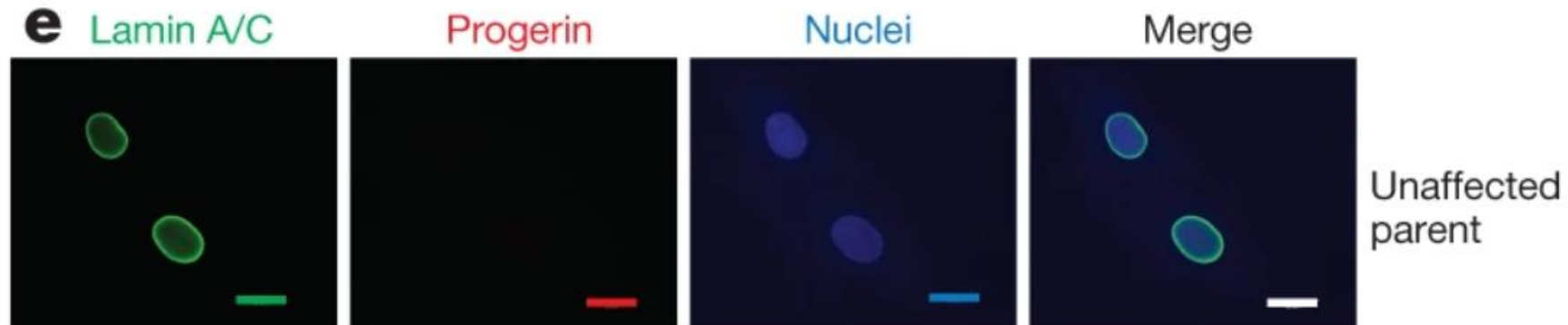


Fibroblasts divide infrequently in resting tissues.

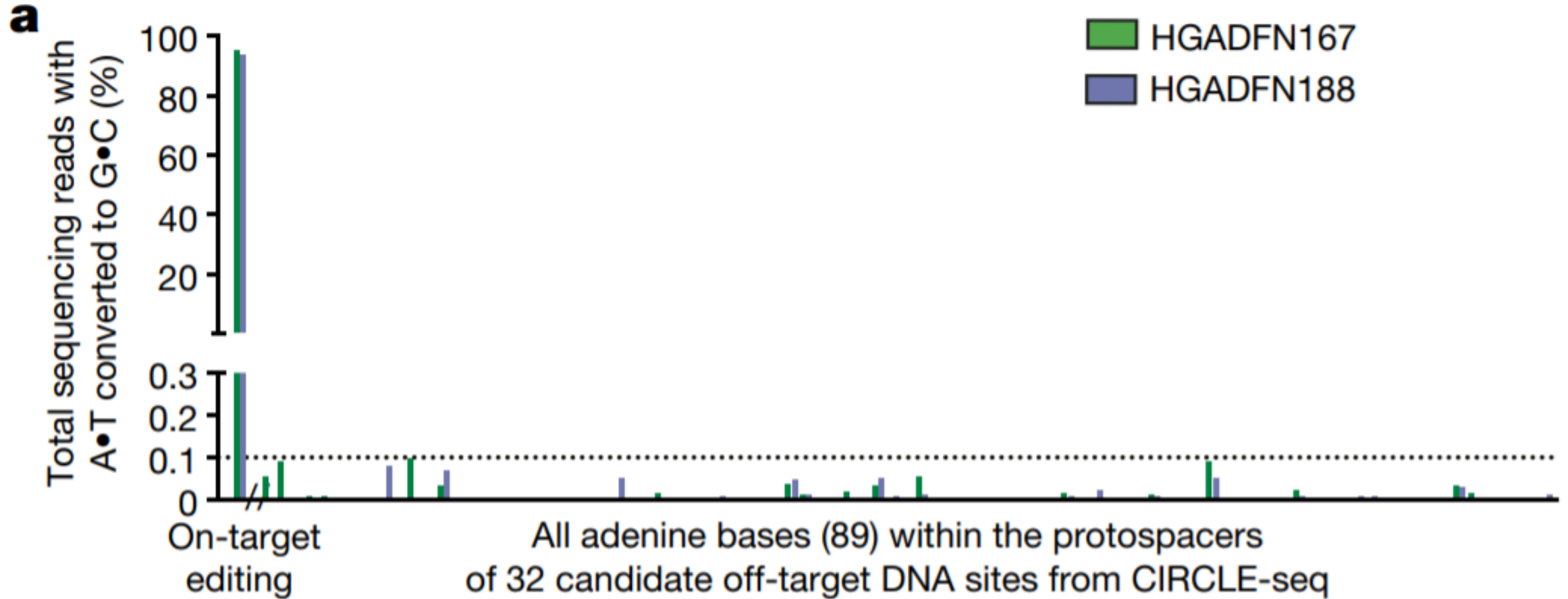
Fig 1b. Is ABE effective in fibroblasts?



What happens to nuclear morphology 20days after ABE-expressing lentivirus infection ?



Does unwanted editing occur?



How is ABE delivered to mice?

a

ABE-AAV9 injection

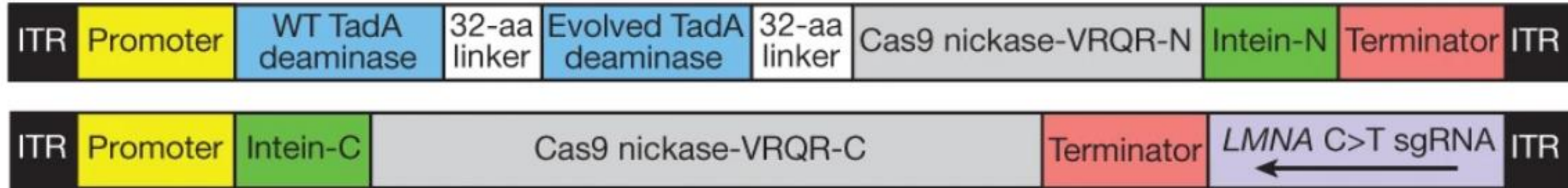
P3 retro-orbital

P14 retro-orbital

P14 intraperitoneal

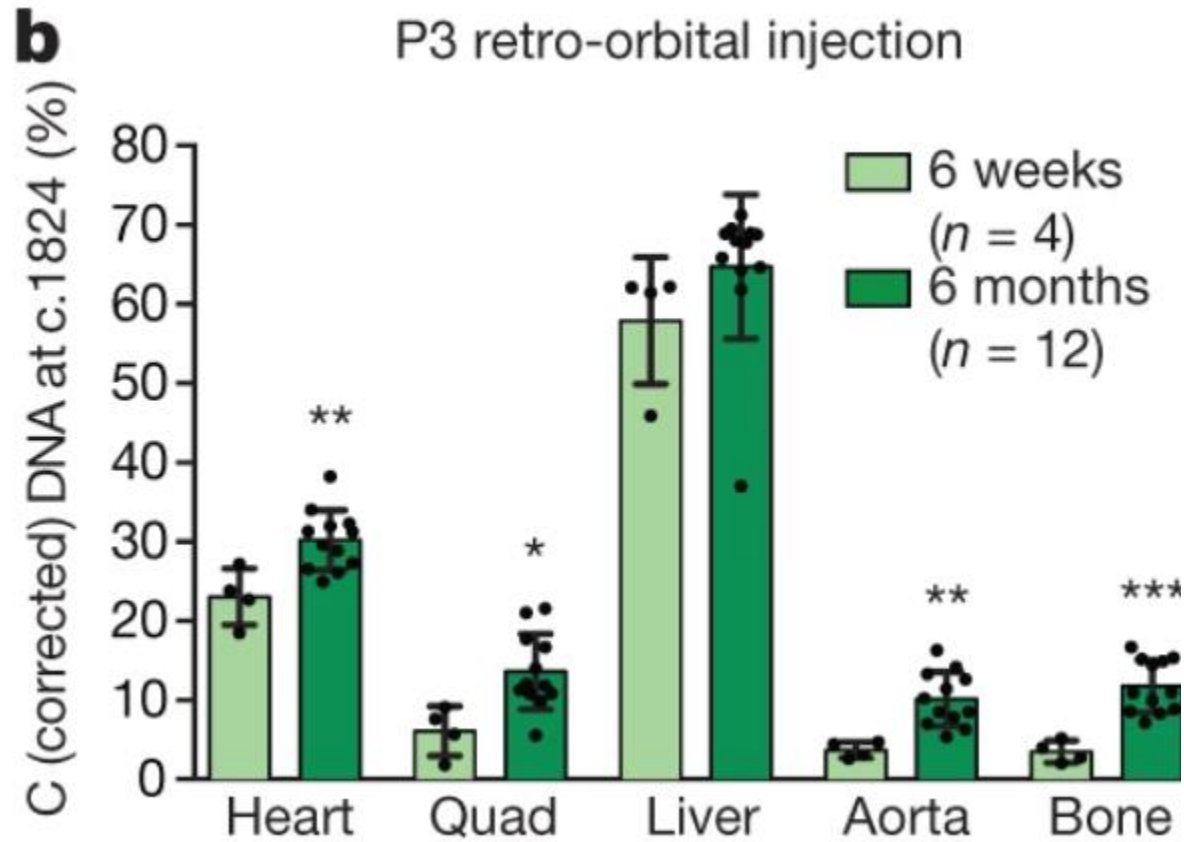


Homozygous
LMNA c.1824 C>T
(progeria) mice



Adeno-associated viruses used for in-vivo delivery of ABE_{max}-VRQR and sgRNA

Which method is best for DNA correction?



Highest overall editing levels in **P-14 injected mice.**

How does this impact **LMNA** protein levels?

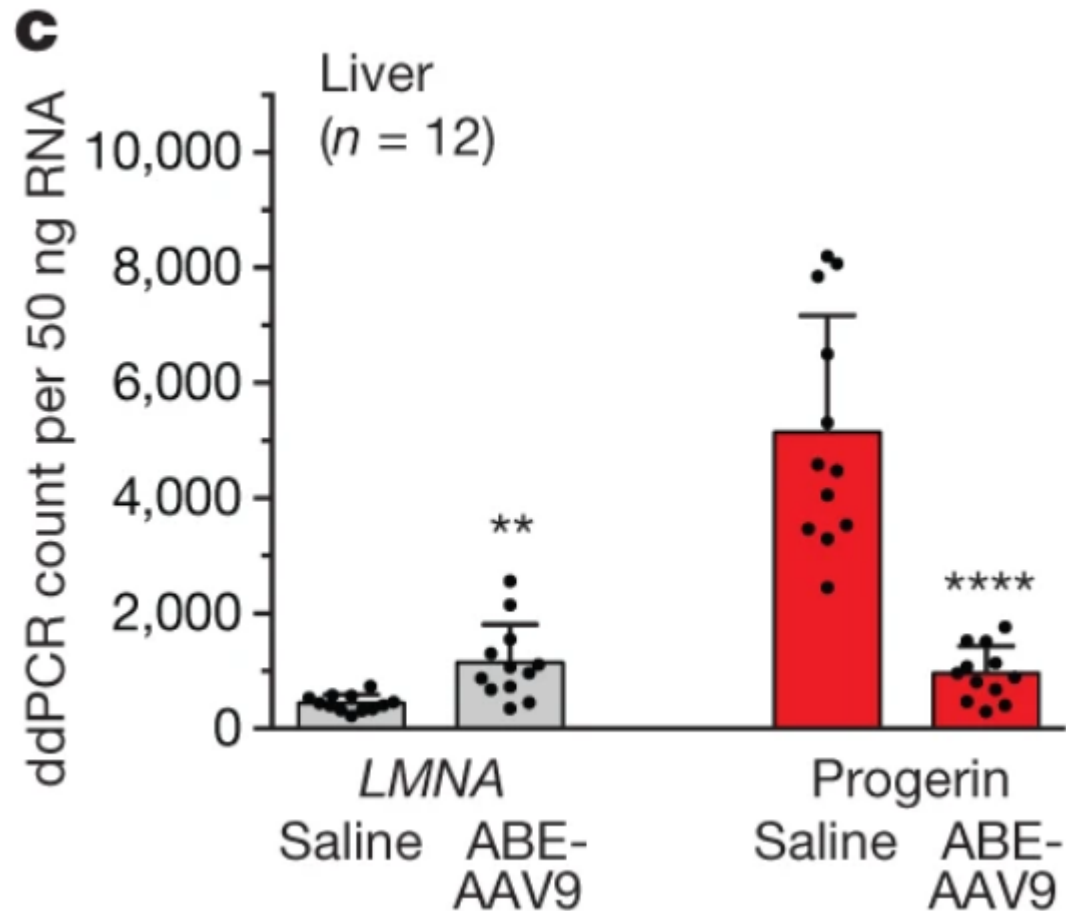
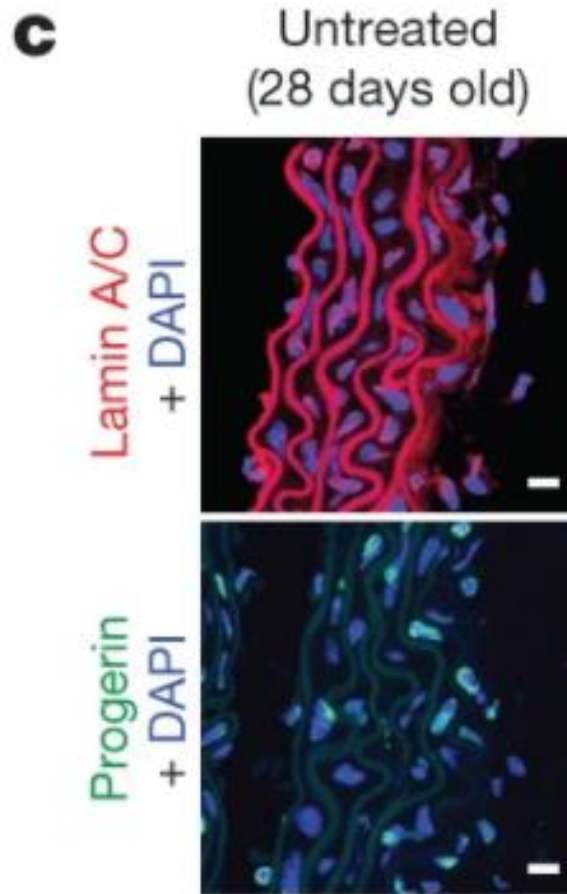


Fig 4: What happens to the heart after ABE-AAV9 injection?

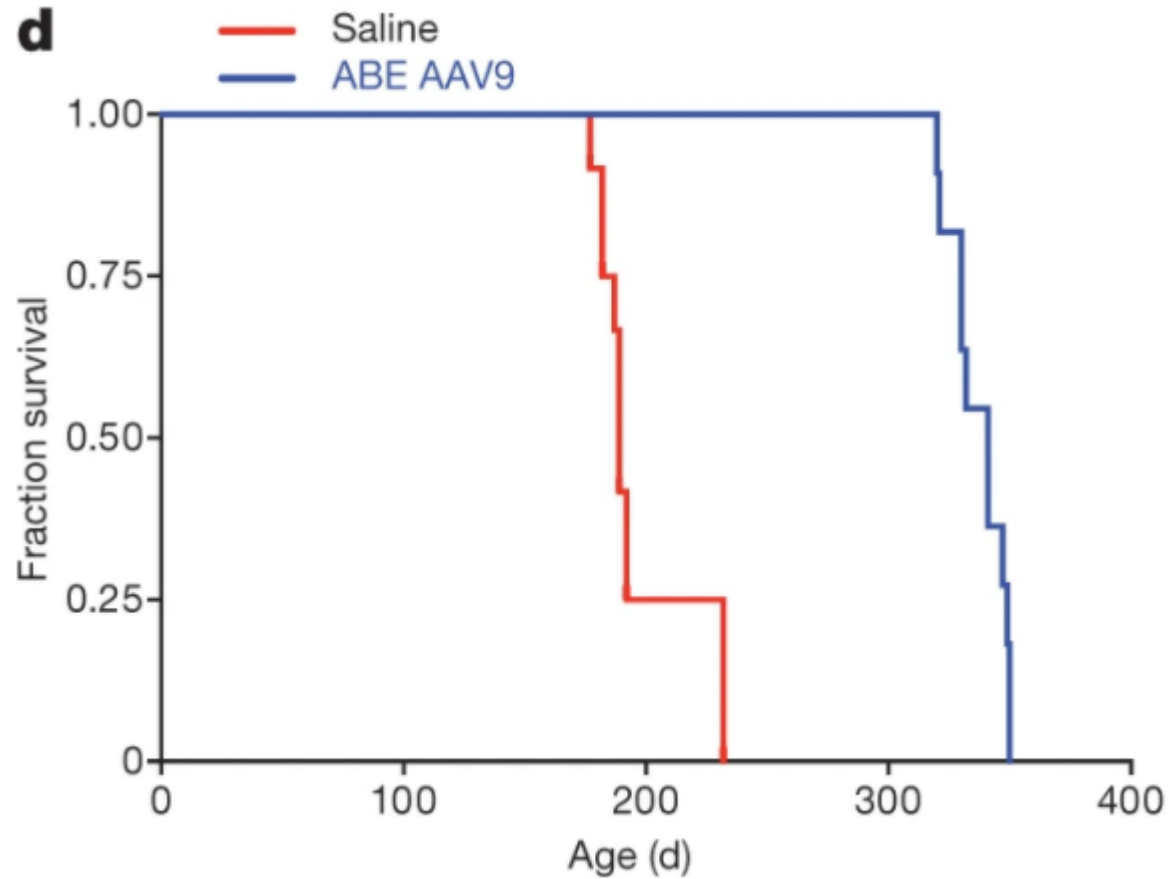


Fig. 4c: What happens to Lamin A/C in aortic VSMCs at 6 months old?

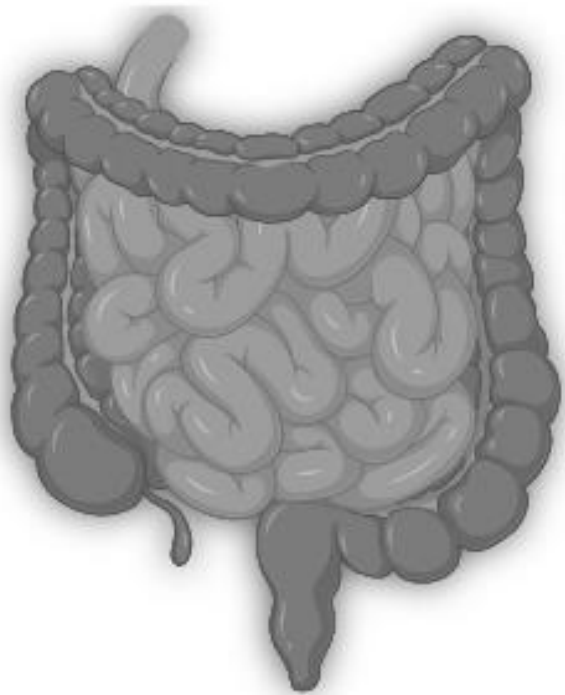


Robust staining
for both.

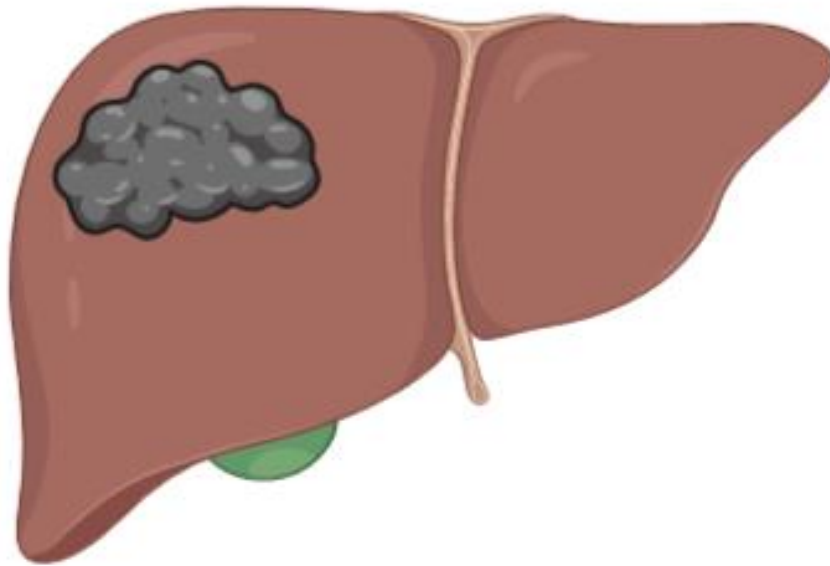
Does ABE AAV9 injection affect lifespan?



What is the cause of death in P14-injected ABE-treated mice?



1 mouse: gastrointestinal
necrosis



5 mice: liver tumors



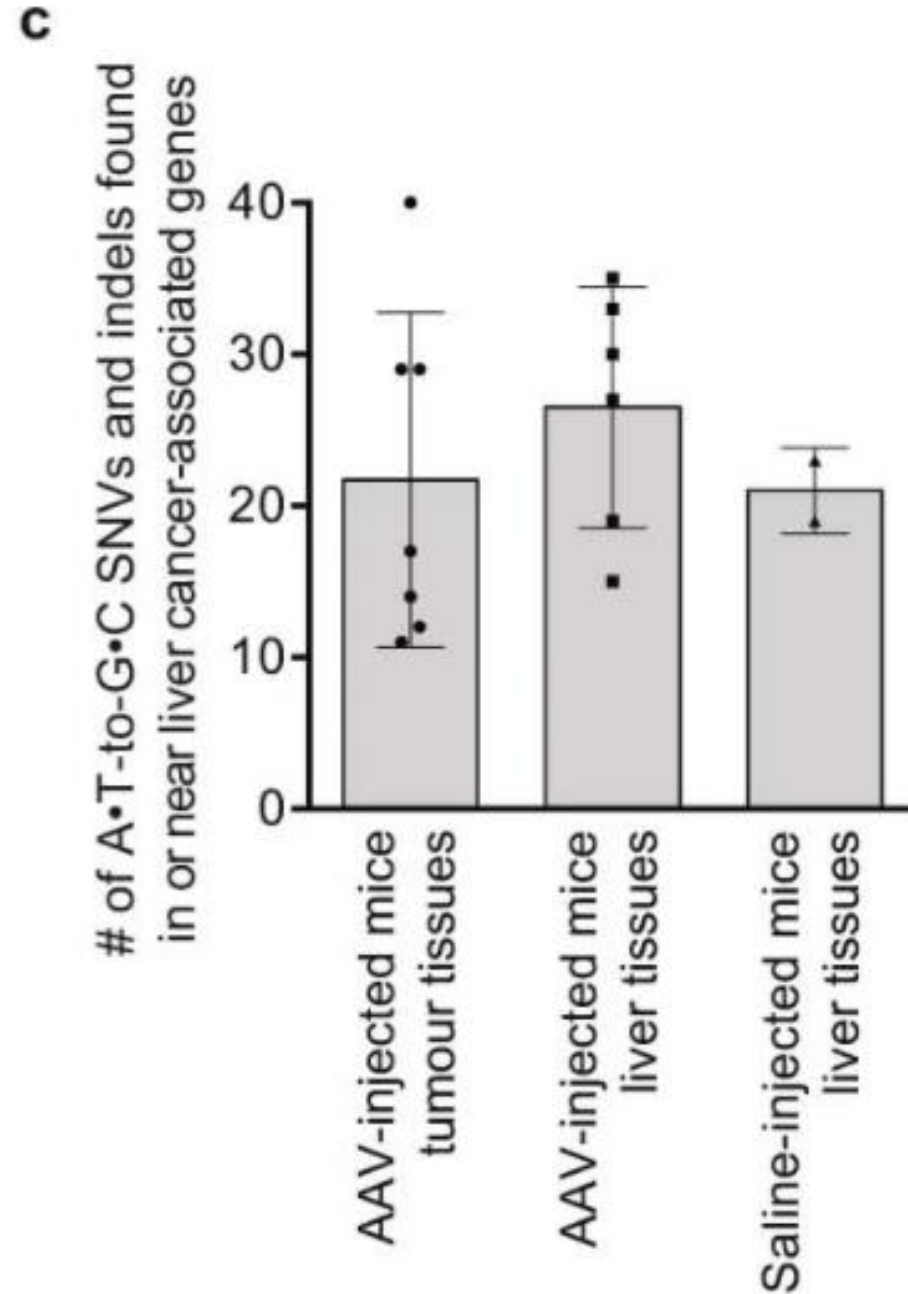
3 mice: normal

Did ABE treatment cause the liver tumors?

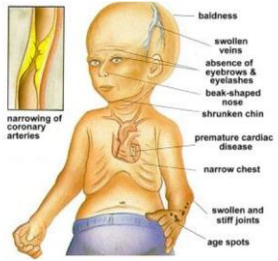
AAV integration may contribute to liver tumor formation.

ABE treatment did not have apparent effect on A-T to C-G point mutations

No apparent role of base editing in tumors.



Base editing provides an opportunity to correct point mutations without requiring DS-DNA breaks



Progeria is caused by a C-G to A-T mutation which causes rapid aging

Where should this research be taken in the future?

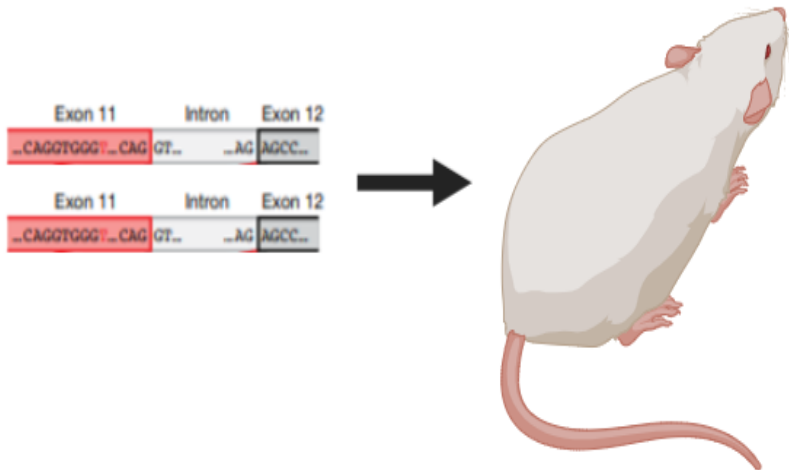
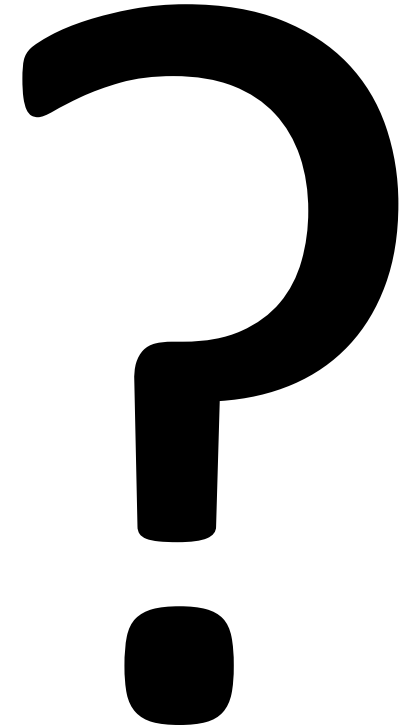
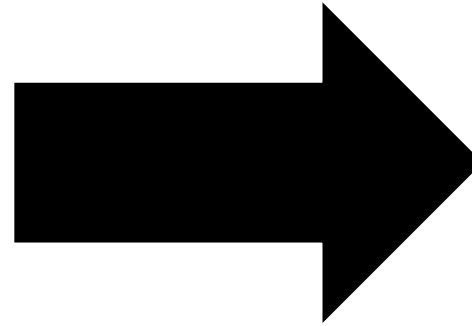
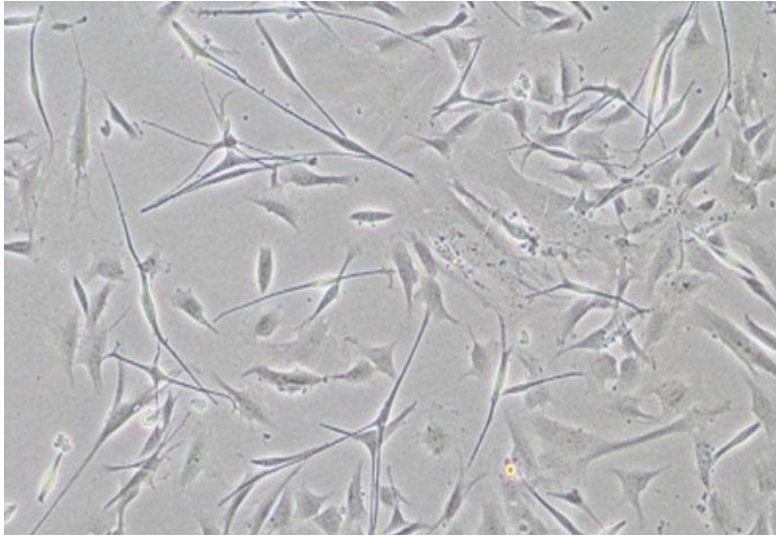


Photo References

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*Several images created in BioRender