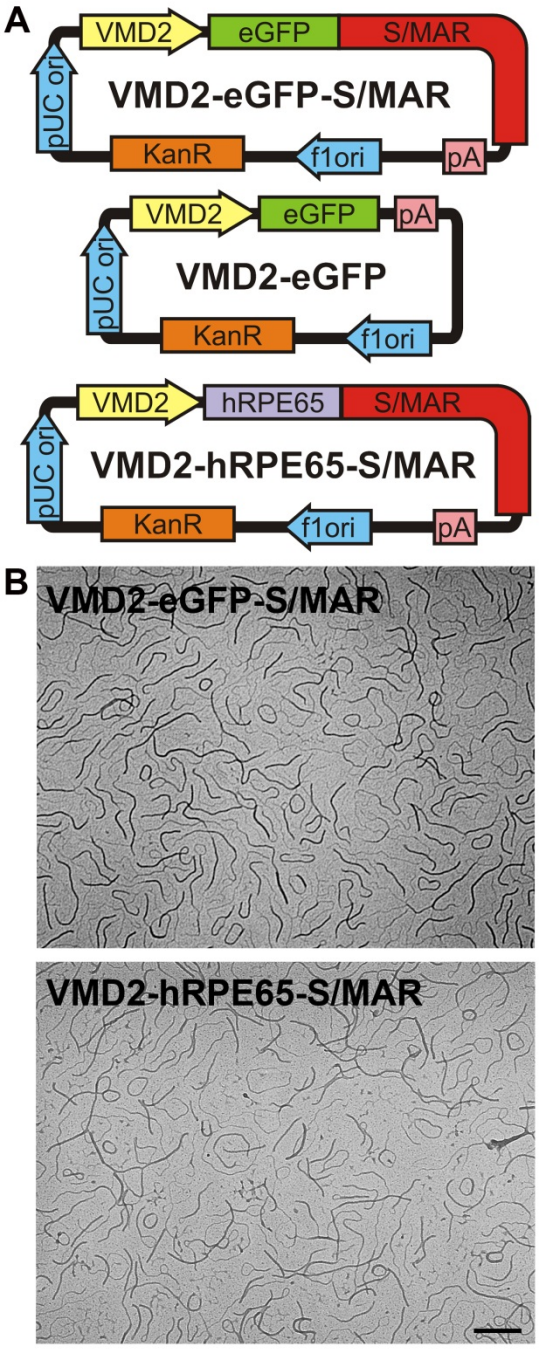
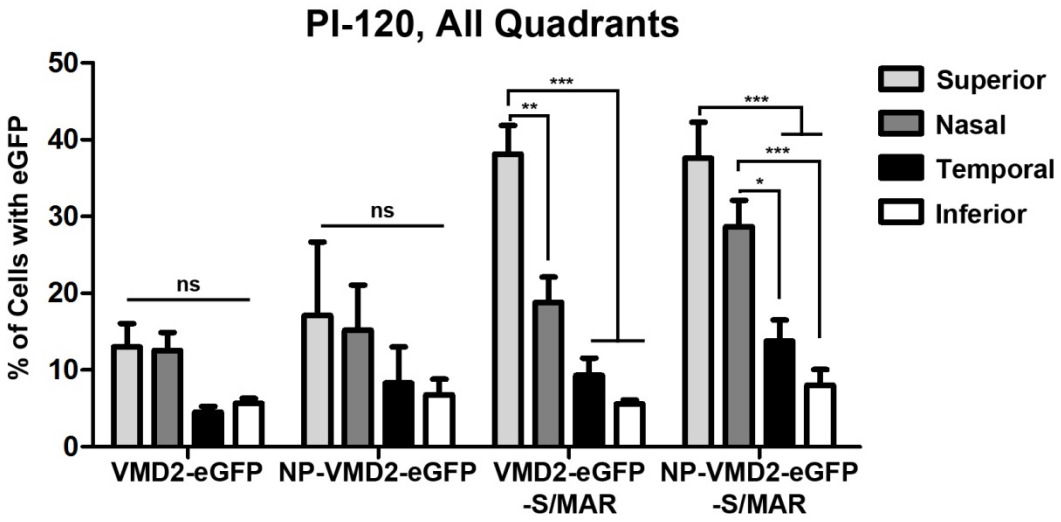
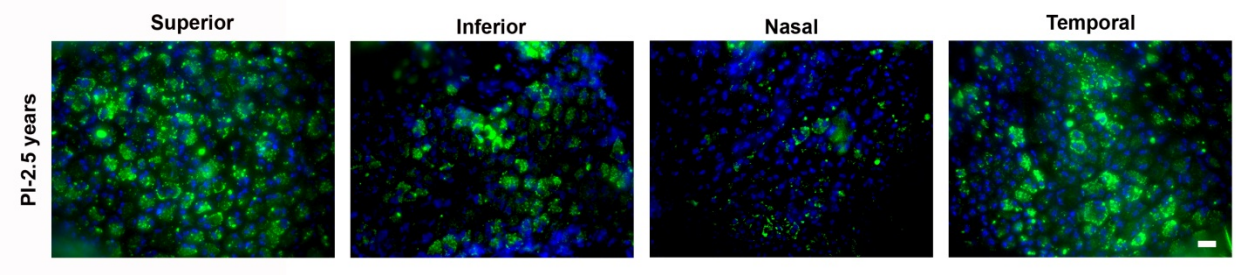
SUPPLEMENTARY INFORMATION



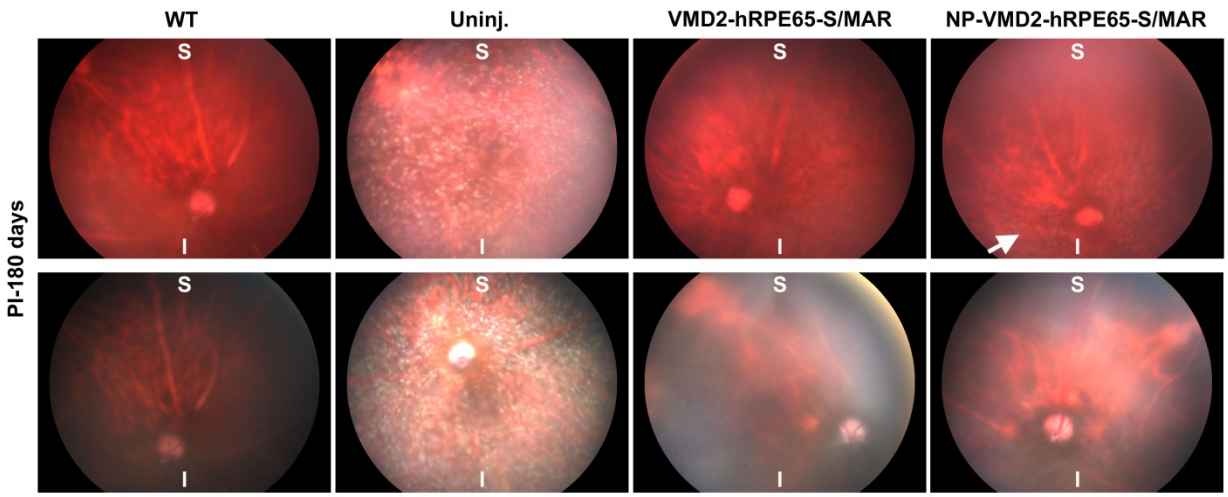
Supplementary Figure 1. Vector maps and NP formulation. A. Vectors maps of VMD2-eGFP, VMD2-eGFP-S/MAR and VMD2-hRPE65-S/MAR. **B.** Nanoparticle EM for the S/MAR containing plasmids. The minor diameter of the particles is ~ 8-11 nm. Scale bar, 200 nm.



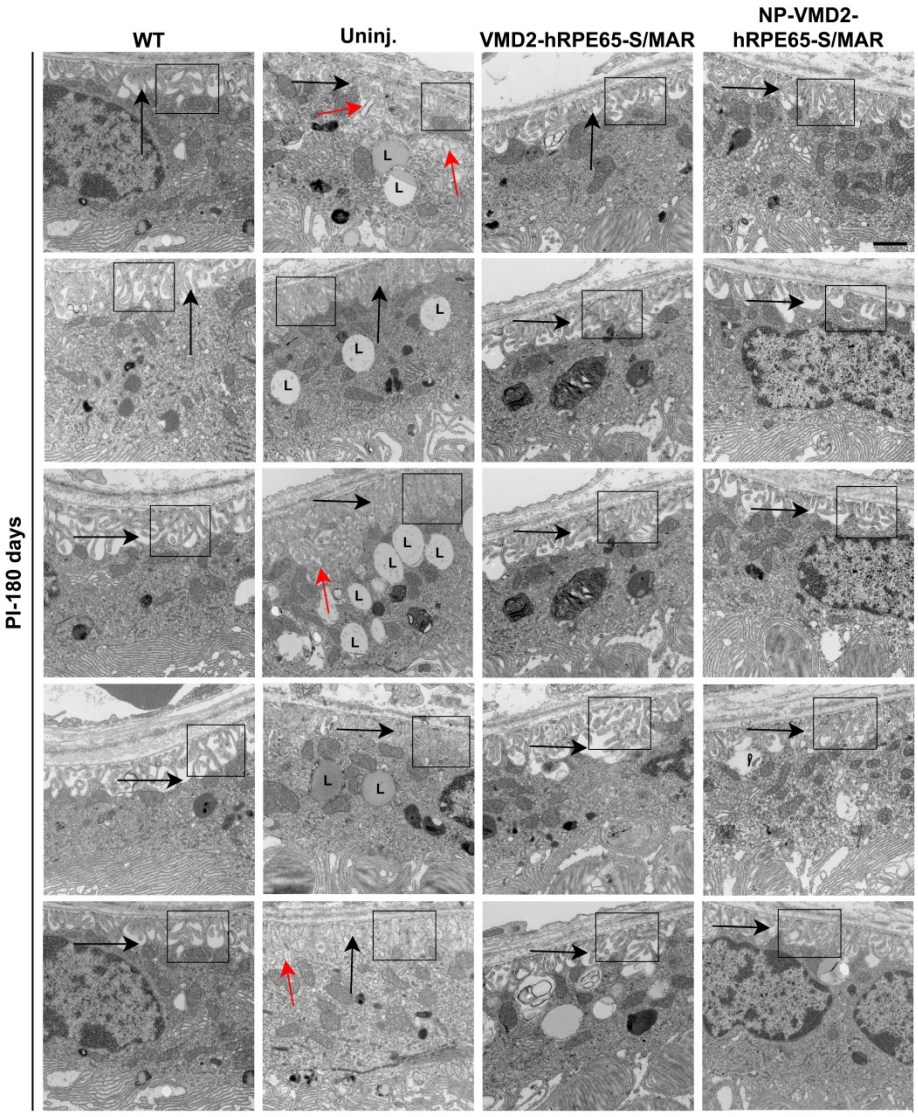
Supplementary Figure 2. PI-120 GFP expressing cells plotted by quadrant. Data from **Figure 1H** are replotted here to demonstrate the distribution of expression from quadrant to quadrant. In all cases, the superior quadrant exhibits the most expression, with NP-VMD2-eGFP-S/MAR showing the best expression in other quadrants. * $P<0.05$ ** $P<0.01$ and *** $P<0.001$ by Two-way ANOVA (treatment/quadrant) with Bonferroni's post-hoc comparison.



Supplementary Figure 3. S/MAR-containing vectors drive gene expression for 2.5 years post-injection. RPE flat mounts from VMD2-eGFP-S/MAR injected animals collected at PI-2.5 years. Shown are representative native GFP fluorescent images from each quadrant. Expression patterns are similar to that seen at PI-2 years (**Fig. 2D**) Scale bar 20 µm.



Supplementary Figure 4. S/MAR-containing vectors carrying hRPE65 mediate improvement in the *rpe65*$^{-/-}$ fundus phenotype. Examples of two more animals (corresponding to **Fig. 4I**) showing that both naked DNA and NP treatment alleviate the white spicule-like formation associated with accumulation of retinyl esters and RPE atrophy. Mice used in these experiments were of the agouti background.



Supplementary Figure 5. S/MAR-containing vectors exhibit correction of the abnormal basal infolding phenotype in the *rpe65*$^{-/-}$. Maintenance of the proper structure of RPE basal infoldings is a measure of RPE health. Reductions in the space between infoldings (boxed regions), thinning (black arrows) and extension into the cell (red arrows) are features of old age or lack of healthy metabolism in the RPE. Here we show in multiple animals (each row is a different field, taken from 3 different animals/group) that both naked DNA and NP treatment show improvement in these phenotypes. Scale bar, 100 nm.

Supplementary Table 1. Real-time PCR primer sequences

Gene	F/R	Sequence
HPRT	F	GCAAACTTTGCTTTCCCTGGTT
	R	CAAGGGCATATCCAACAACA
eGFP	F	CACATGAAGCAGCACGACTT
	R	AGTTCACCTTGATGCCGTTC
RPE65 *	F	GAGATATGTACTTCCTTT
	R	CTTCTGGTAATTGATTTGAG

*The RPE65 primer sequences are common to human and mouse and were used to enable direct comparison of expression levels.