

FIG 1

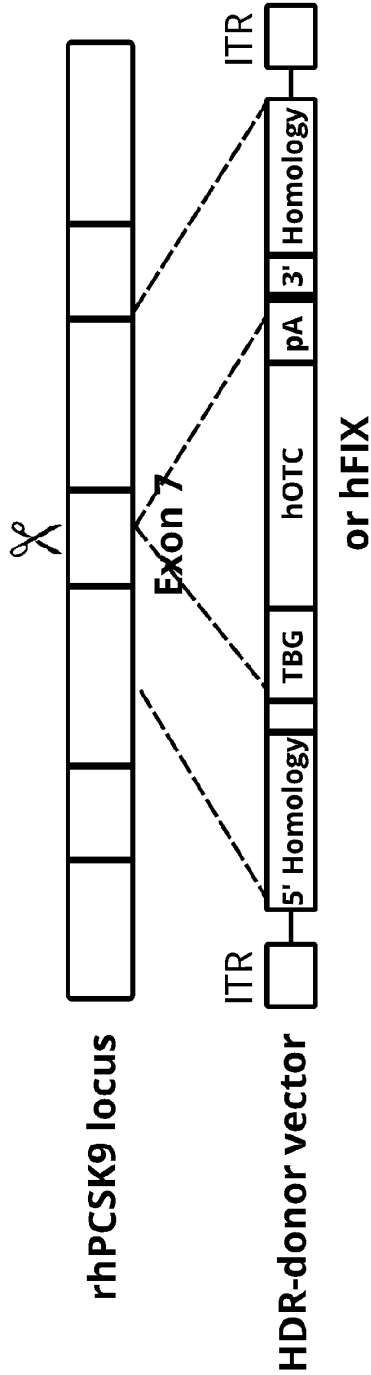


FIG 2

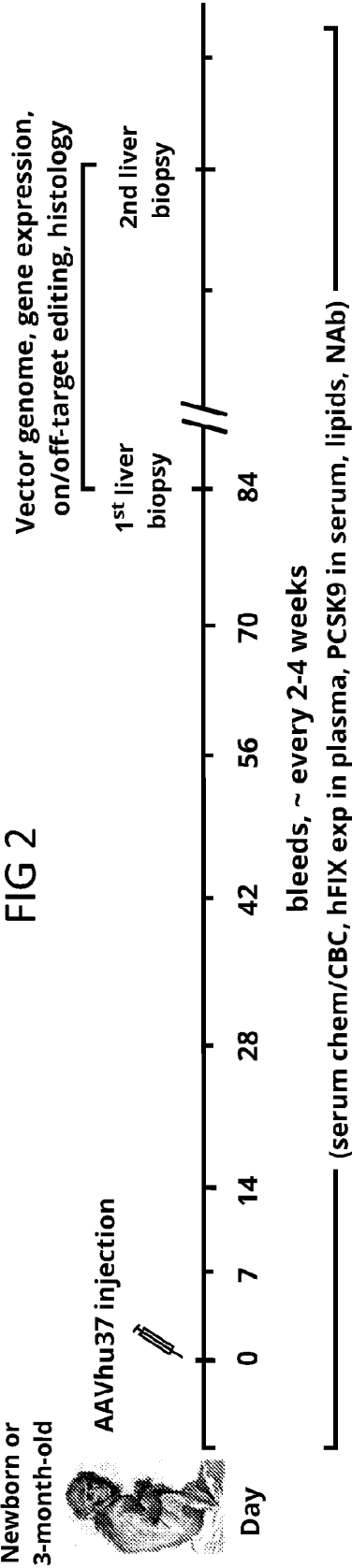


FIG 3A

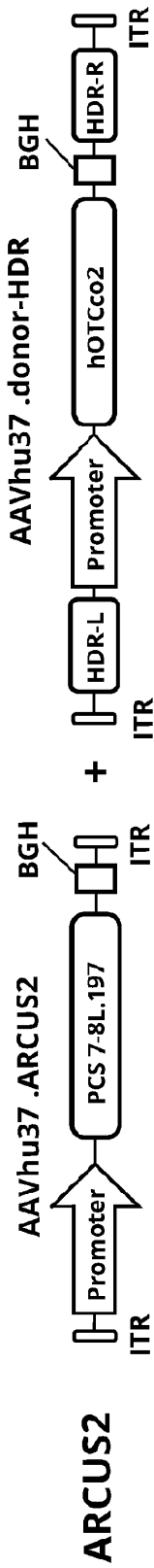


FIG 3B

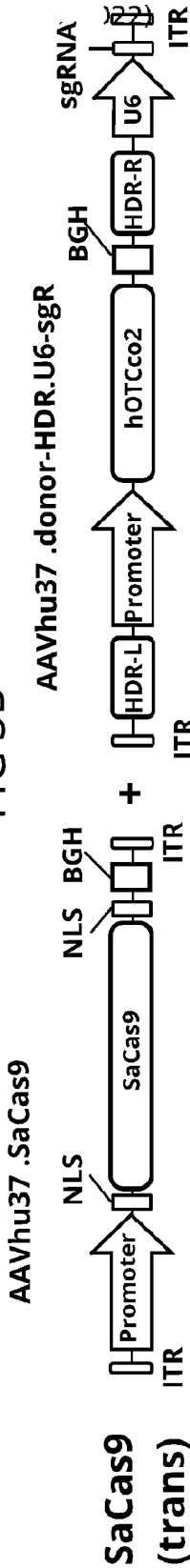


FIG 3C

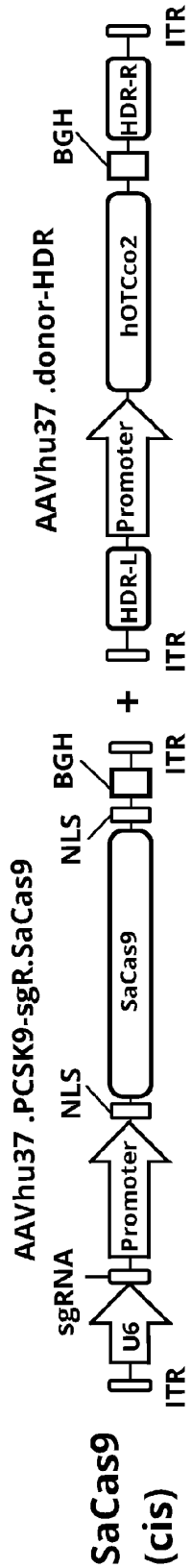
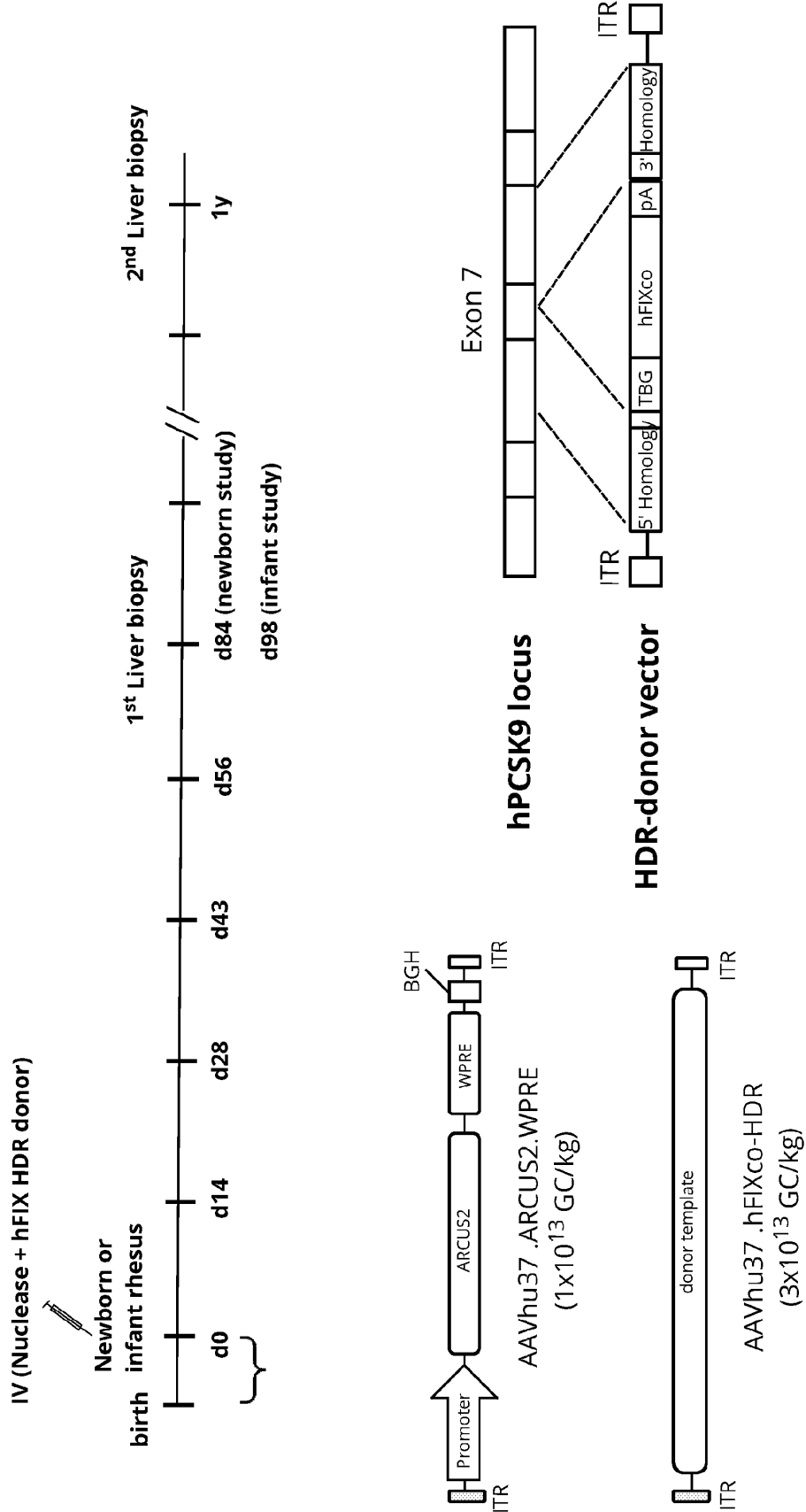


FIG 4A



4/43
SUBSTITUTE SHEET (RULE 26)

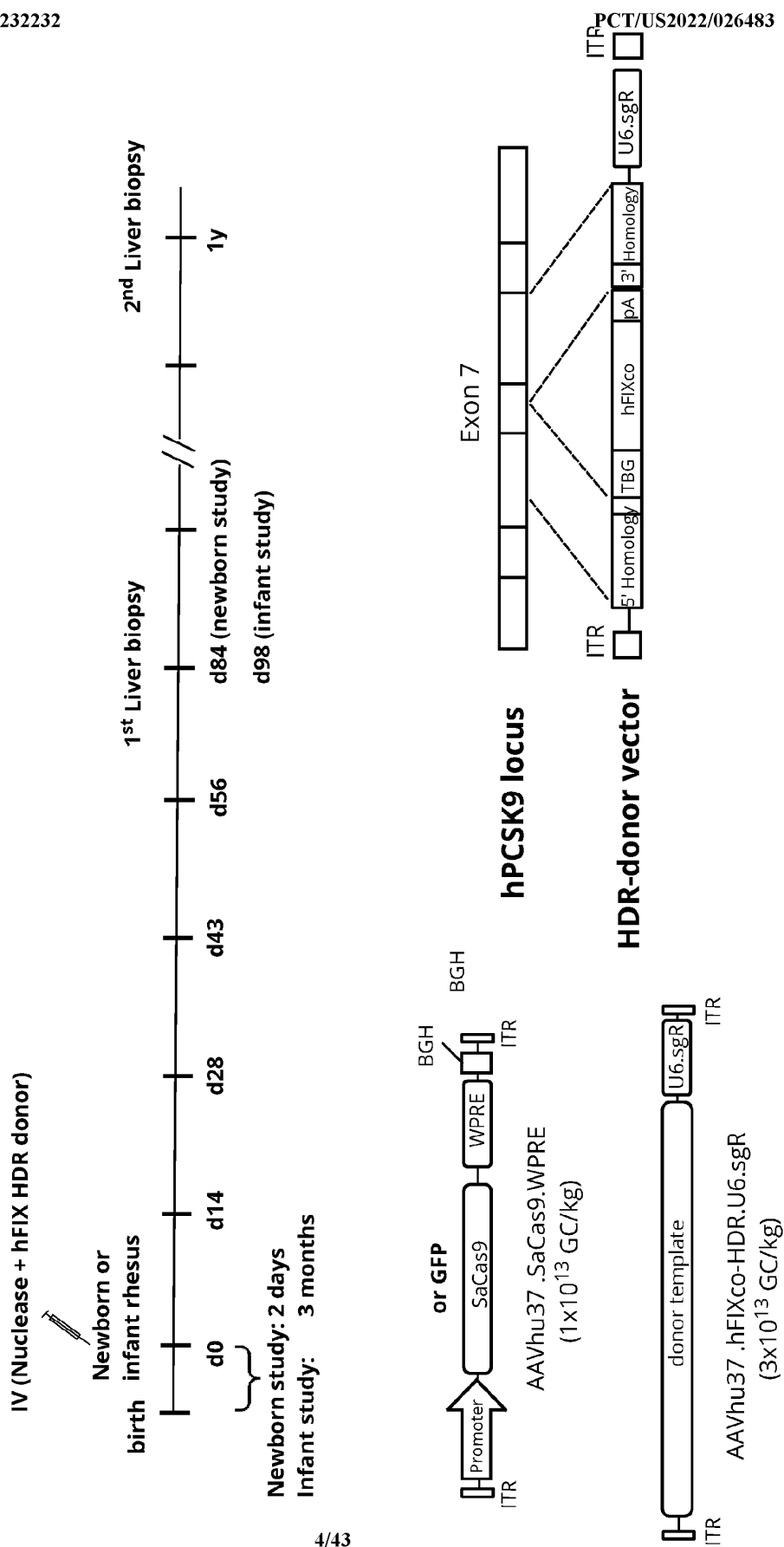


FIG 4C

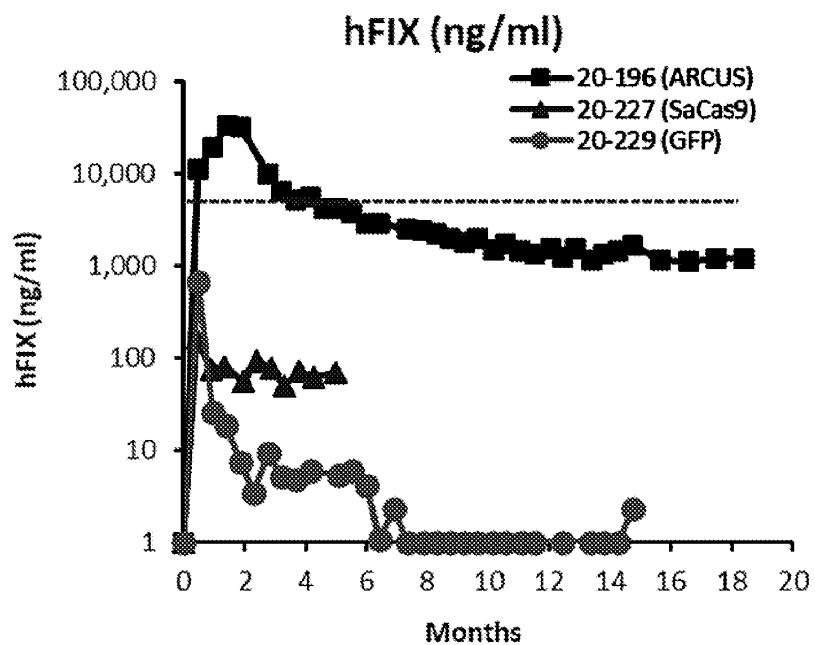


FIG 4D

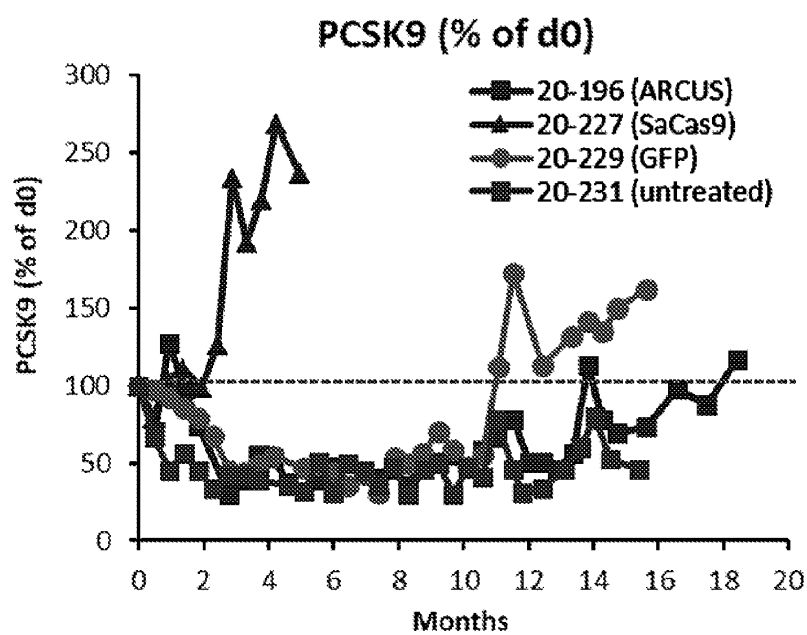


FIG 4E

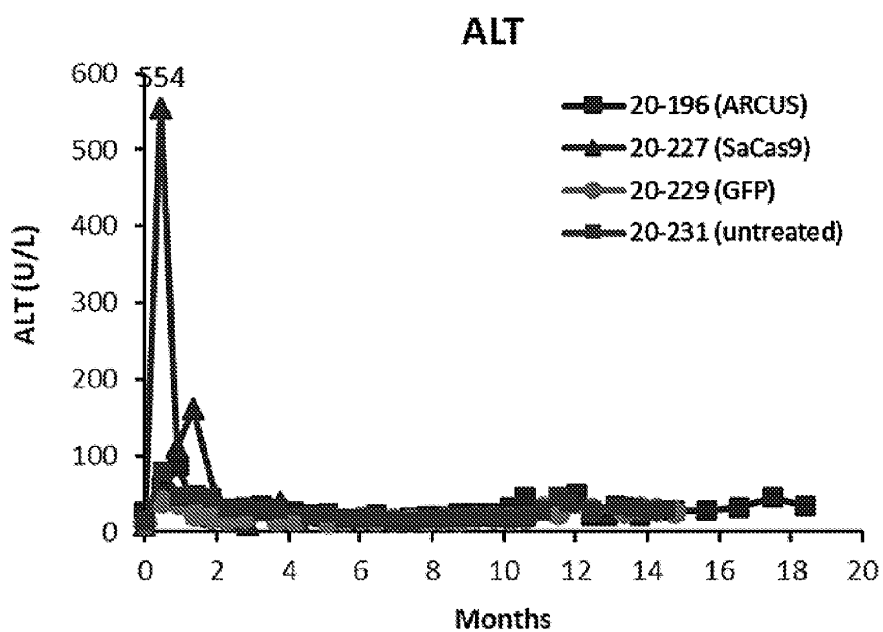


FIG 4F

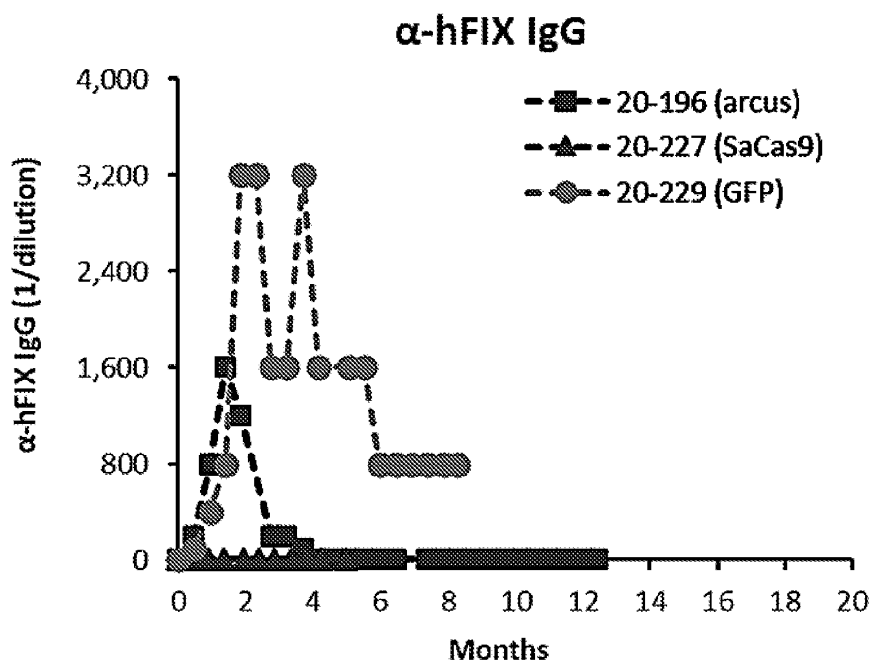


FIG 4G

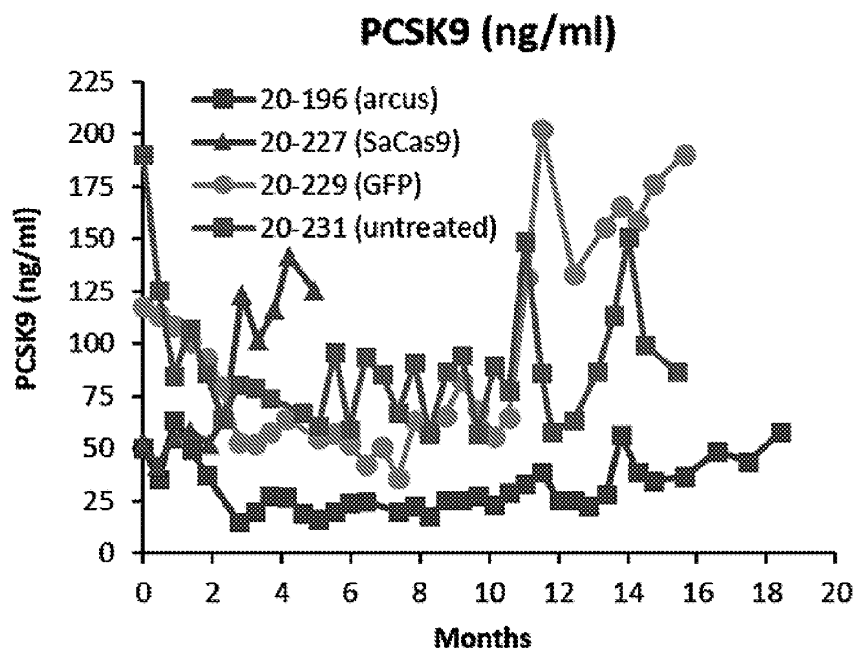


FIG 4H

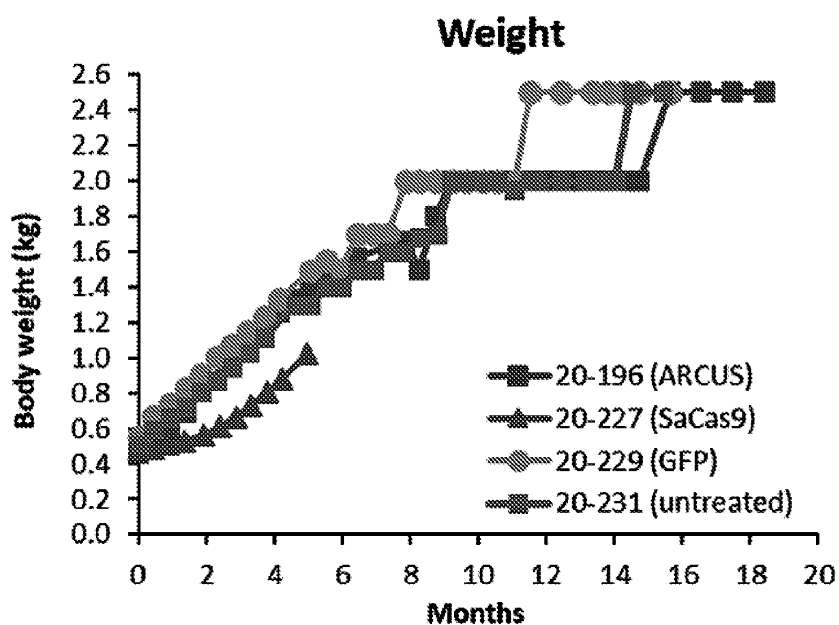


FIG 5A

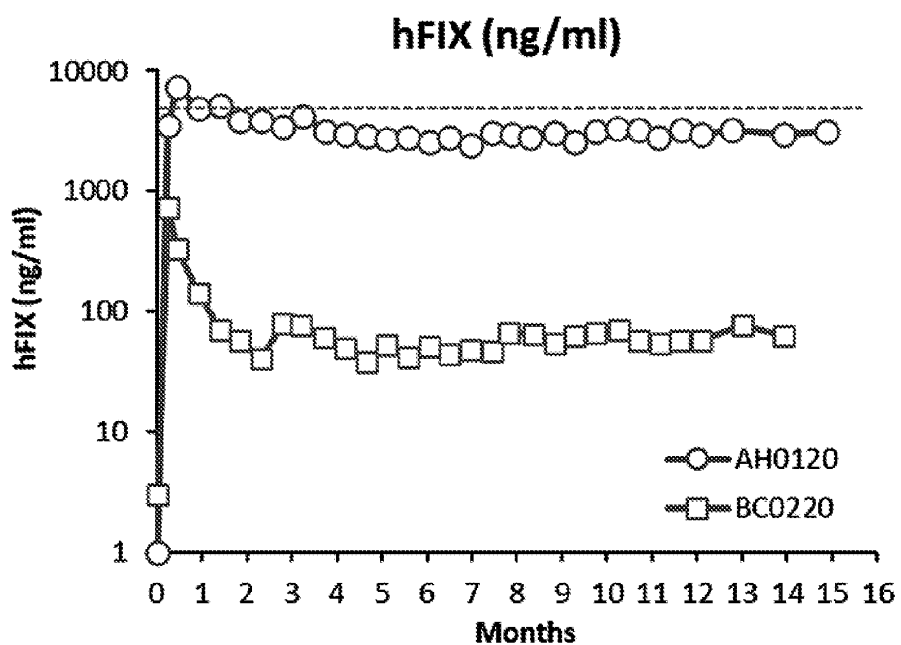


FIG 5B

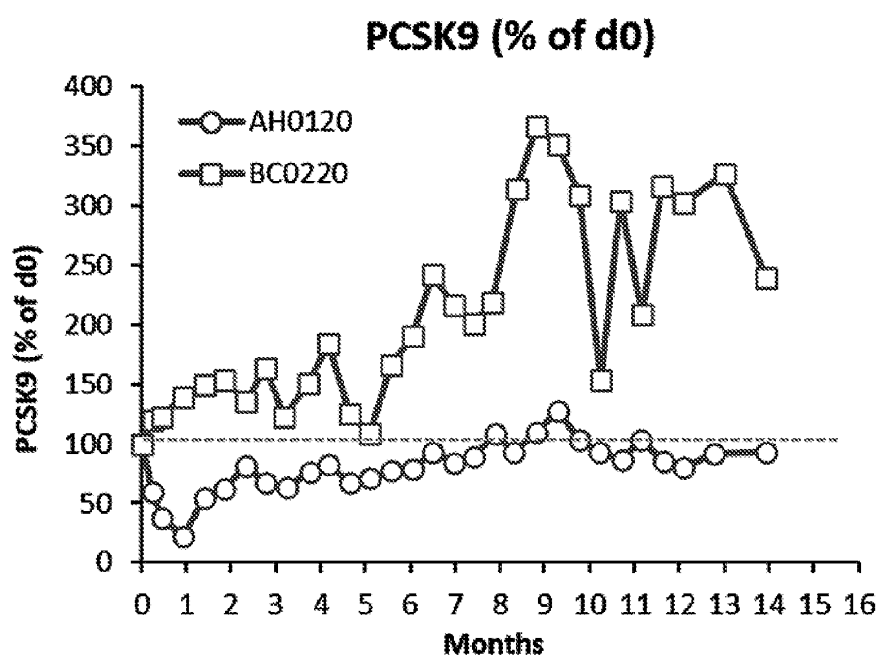


FIG 5C

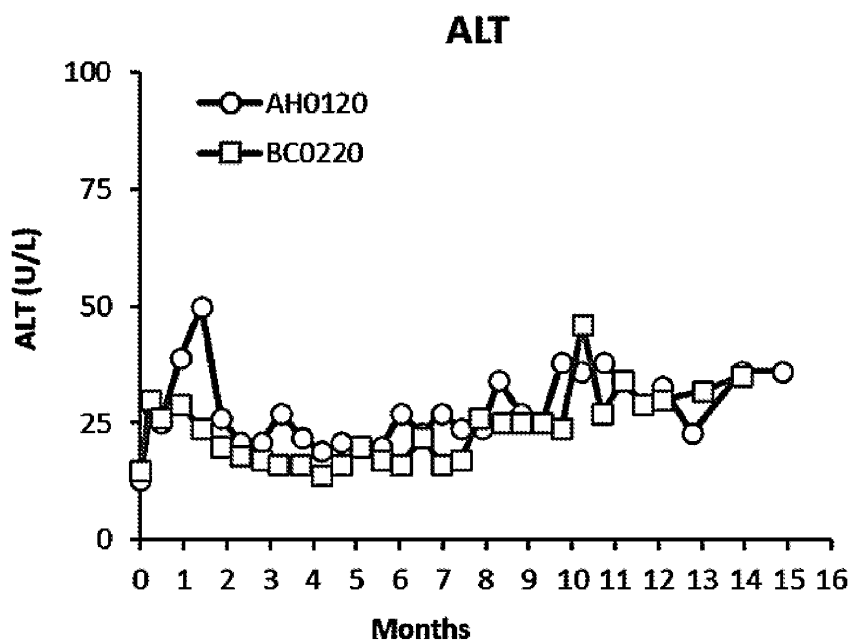


FIG 5D

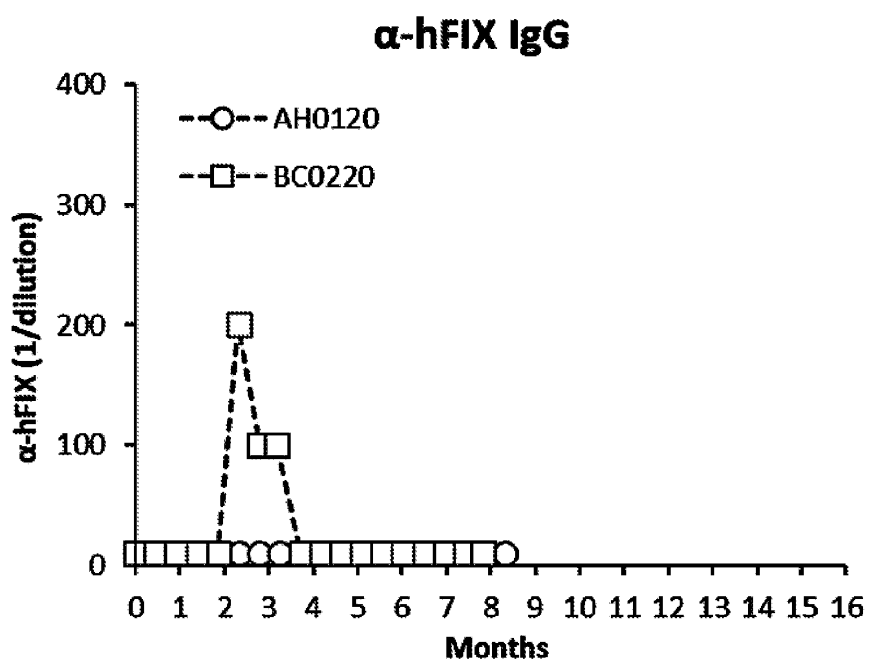


FIG 5E

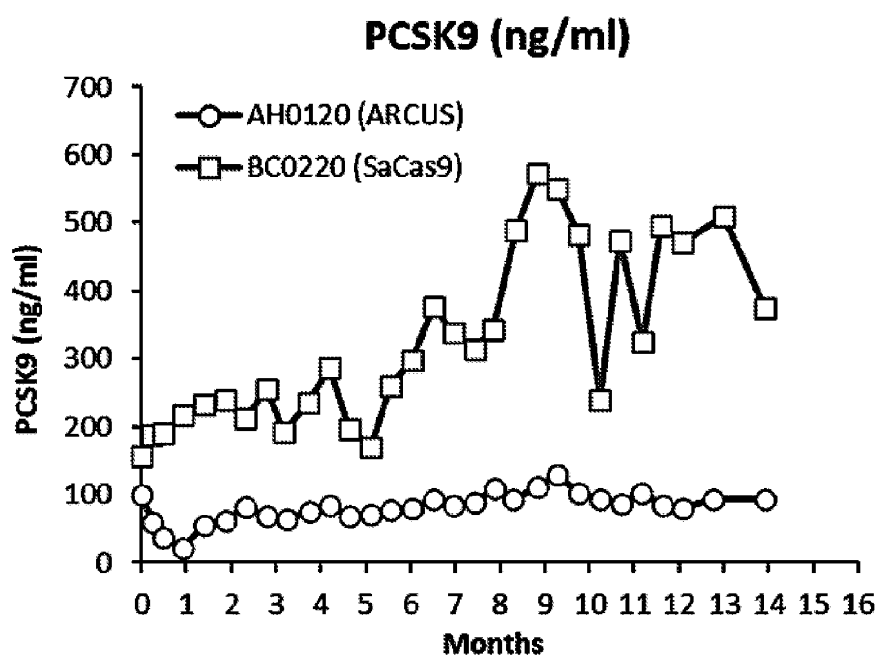


FIG 5F

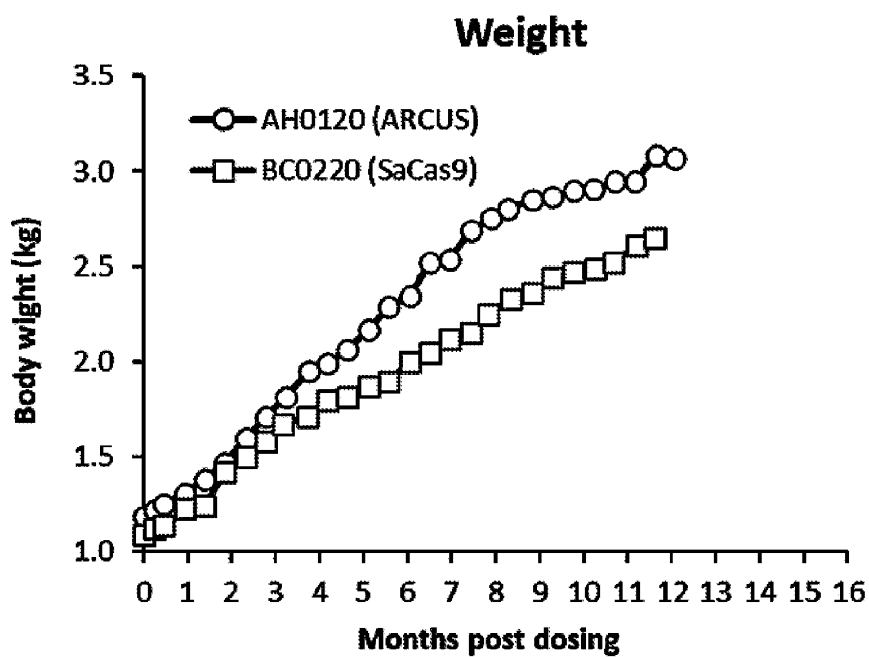


FIG 5G

Animal ID	Nuclease	Age at dosing (day)	Biopsy or Necropsy Time points (day)	Peak hFIX (ng/ml) (time point)	Recent hFIX (ng/ml) (time point)	Anti-hFIX IgG	hFIX transduction %	WPRE transduction %	Indel %	# of loci by ITR-seq
20-196	ARCUS	2	84 366	32,446 (d43)	1,169 (d560)	Transient (d14 -d98)	12.3 11.8	0.20 0.11	10.3 12.1	12, 29 3, 28
AH0120	ARCUS	89	98 364	5,185 (d42)	3,161 (d448)	< detection limit	20.4 20.5	0.33 0.05	14.4 22.2	7, 18 29, 19
21-120	ARCUS	191	100	7,327 (d28)	753 (d84)	< detection limit	To be done			
20-227	SaCas9	2	151	160 (d13)	68 (d151)	< detection limit	0.8	0.02	0.11	4
BC0220	SaCas9	89	96 364	733 (d7)	62 (d421)	Transient (d70 -d96)	1.6 0.07	0.02 0.00	0.14 0.10	4, 0 1
20-229	EGFP	2	84	672 (d14)	1 (d448)	Persistent (d28 - present)	0.1	0.00	0.10	0
20-231	Untreated	3*	84	NA	NA	NA	0.01	0.00	0.04	0

FIG 5H

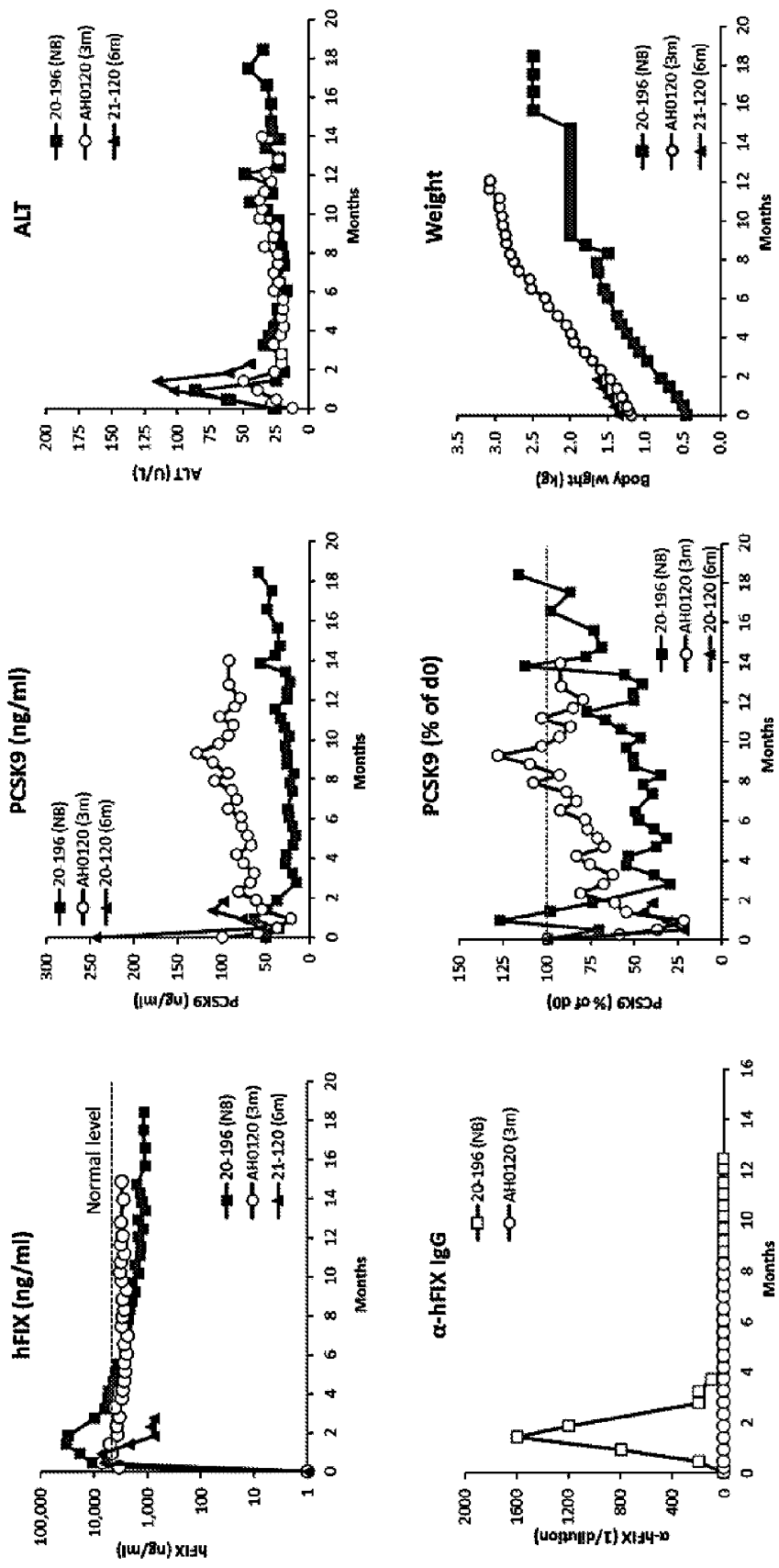


FIG 6A

GC in liver

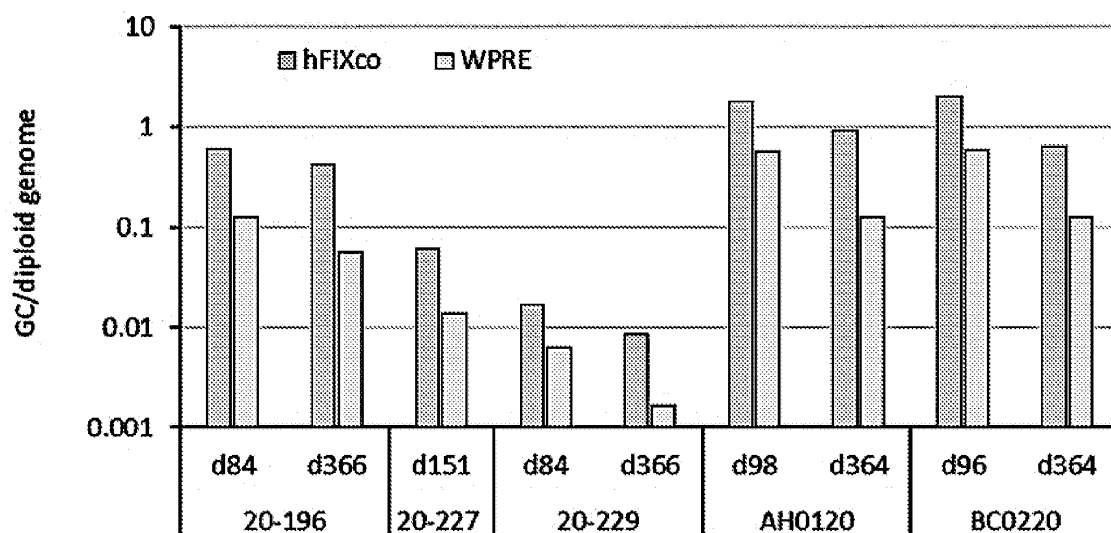


FIG 6B

Transgen RNA in liver

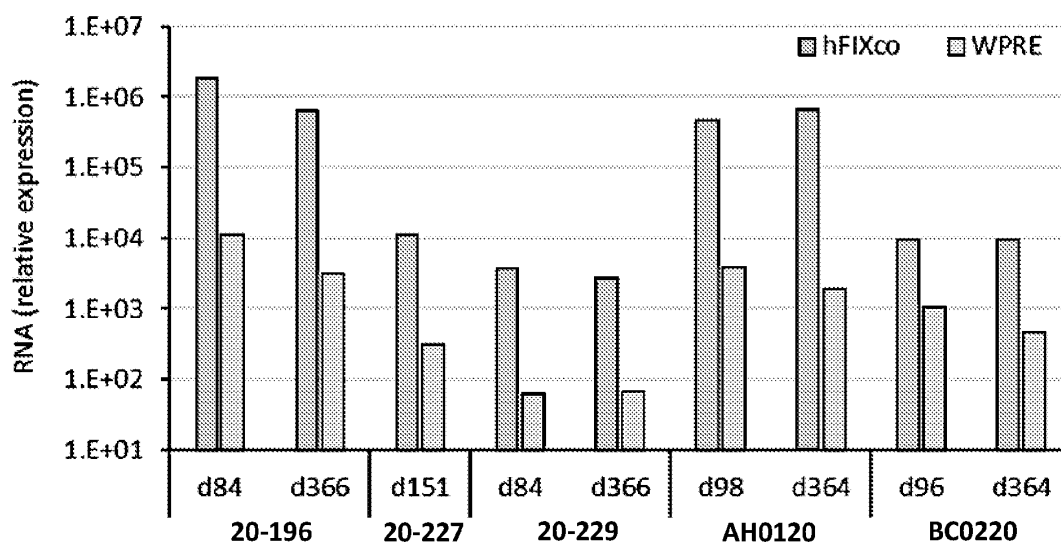


FIG 6C

Stable Transduction in Liver

Dual ISH (green=hFIXco, red=ARCUS or GFP)

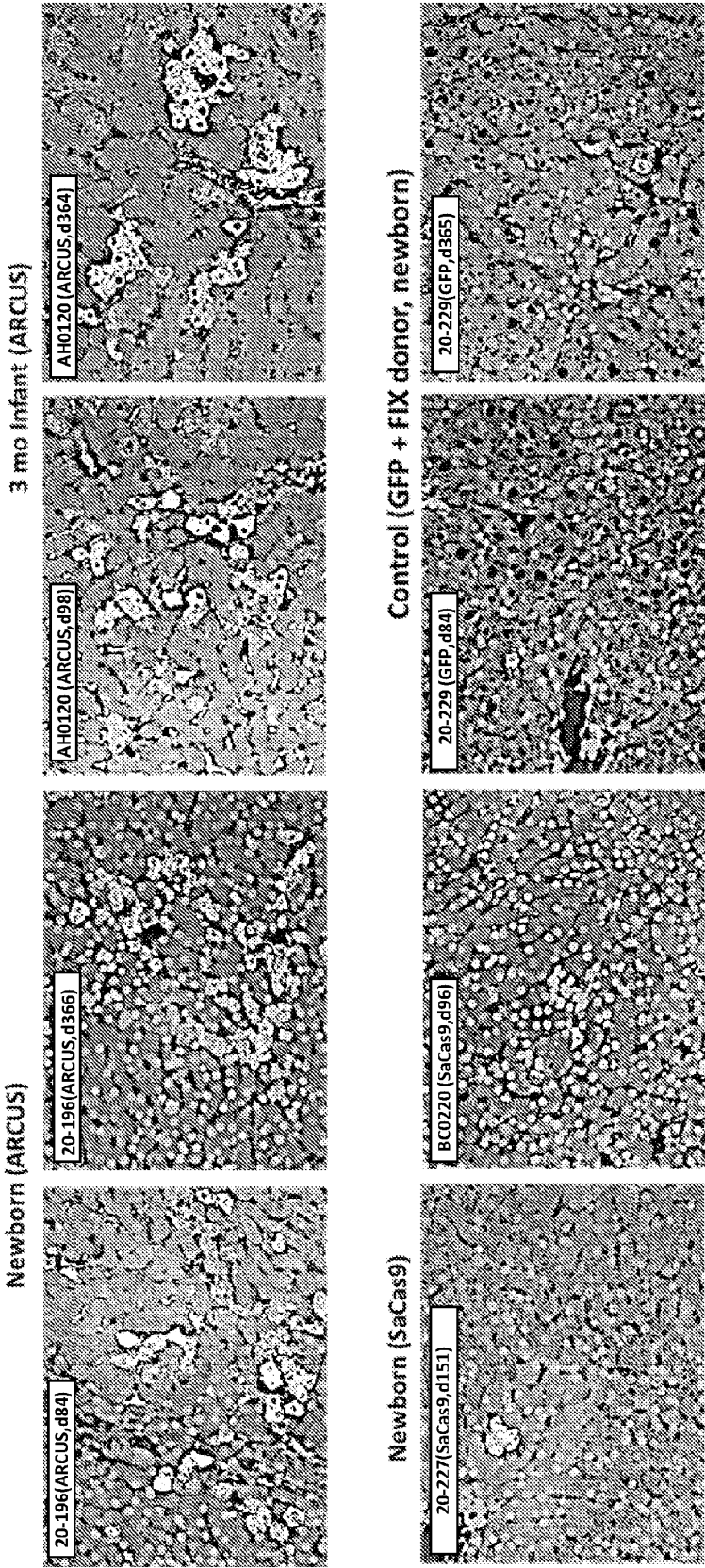


FIG 6D

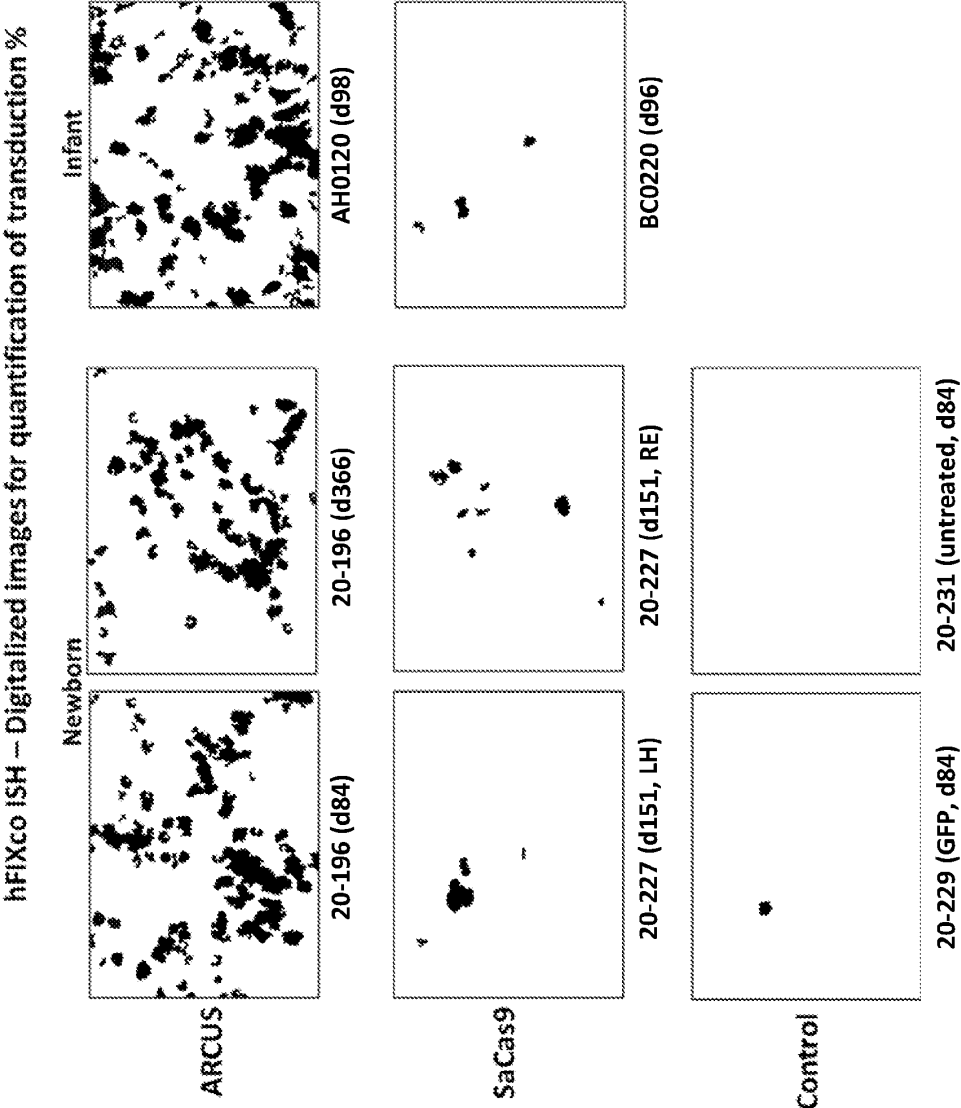
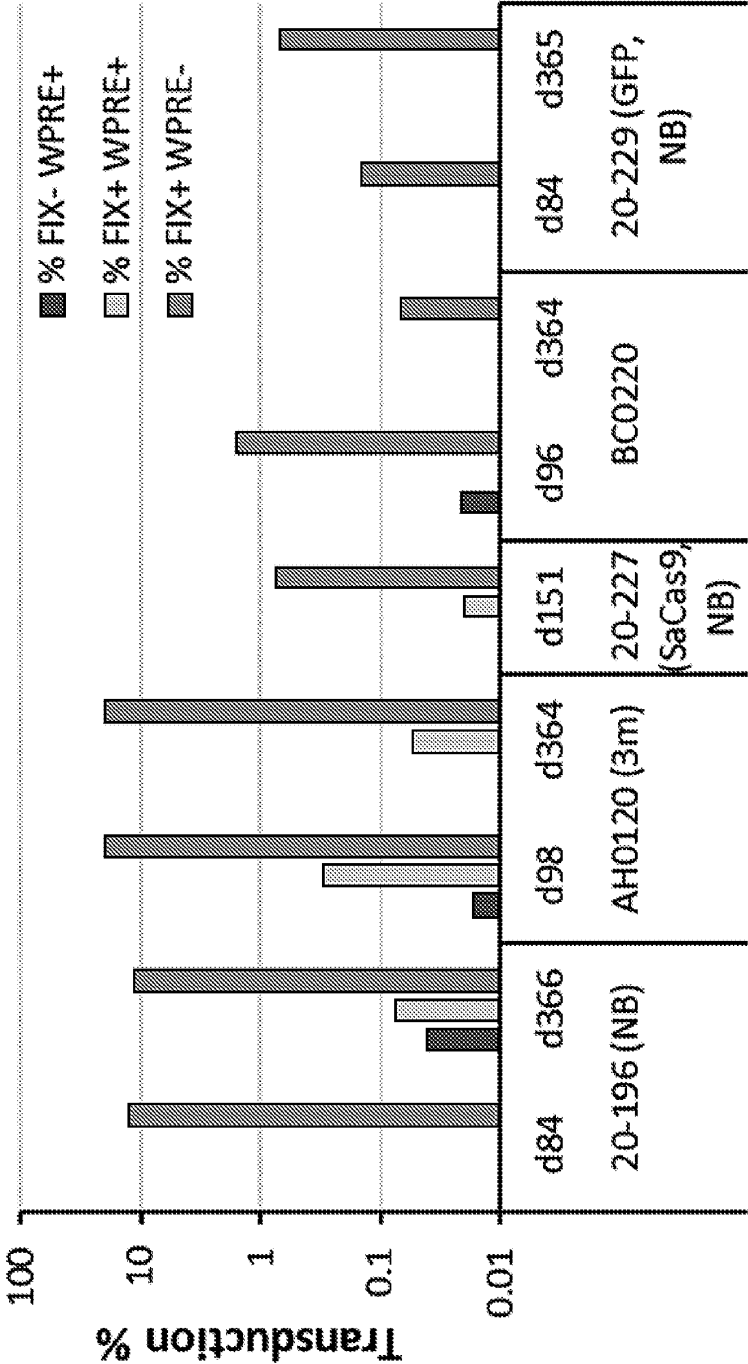
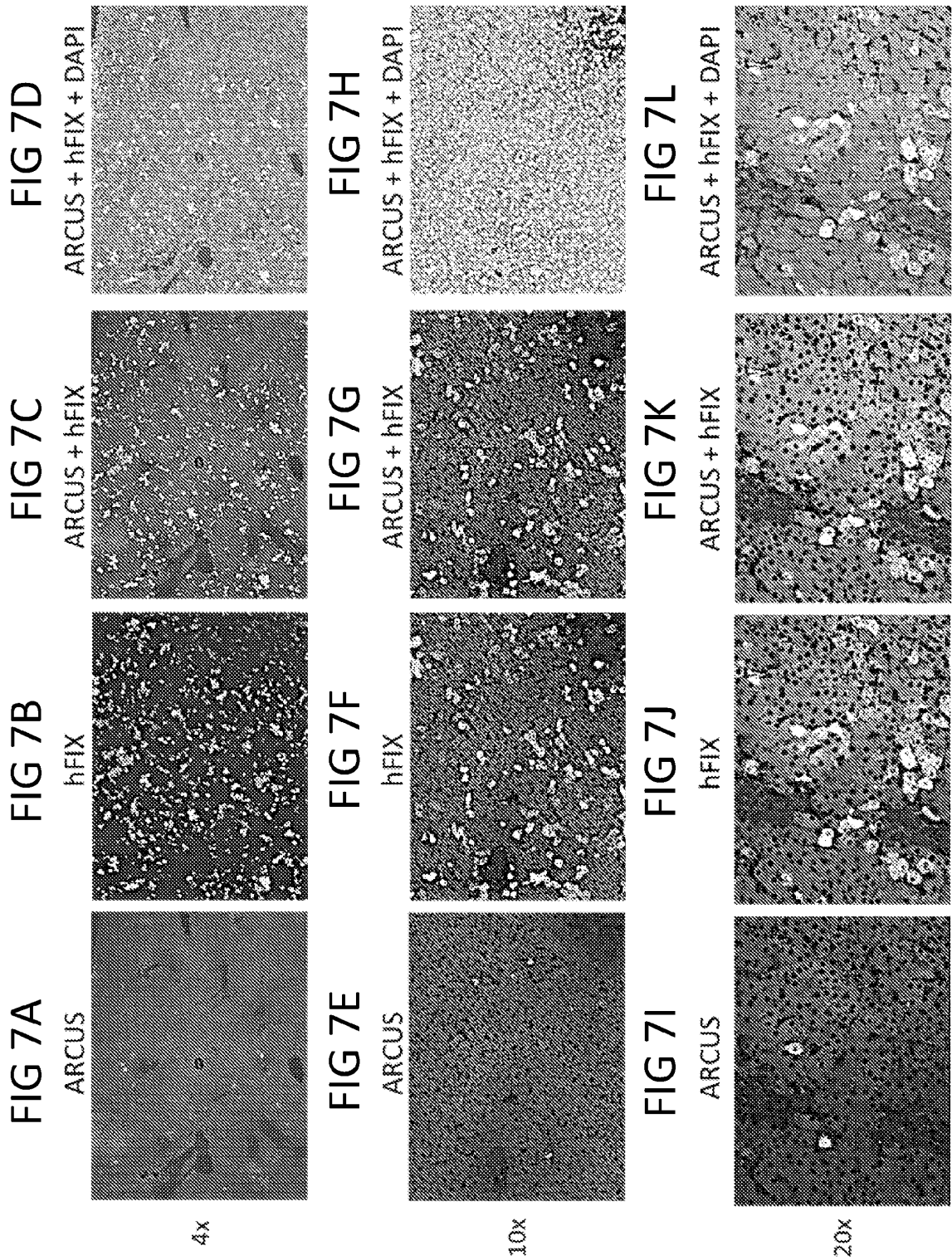


FIG 6E

% of Transduction by dual ISH





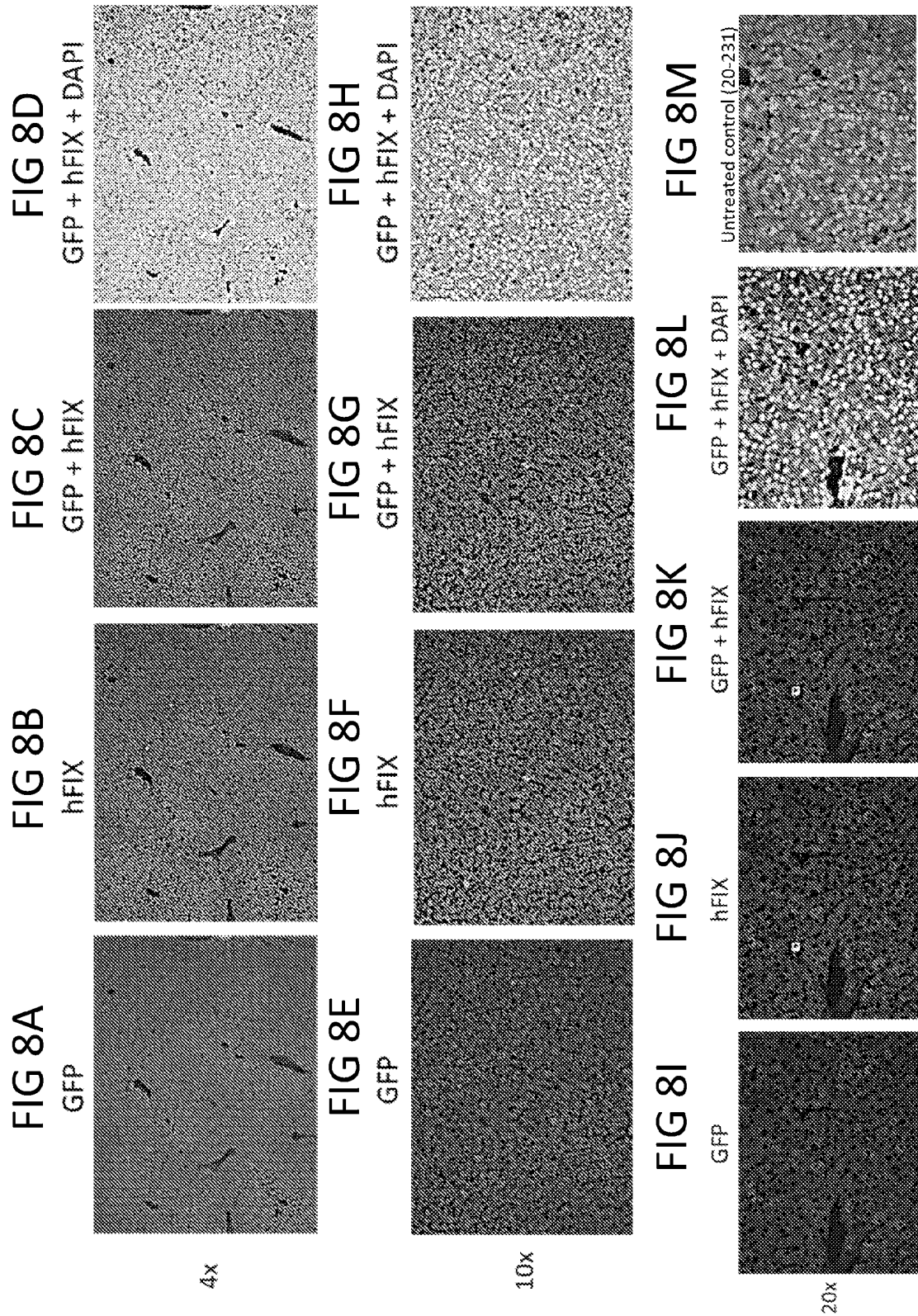


FIG 9

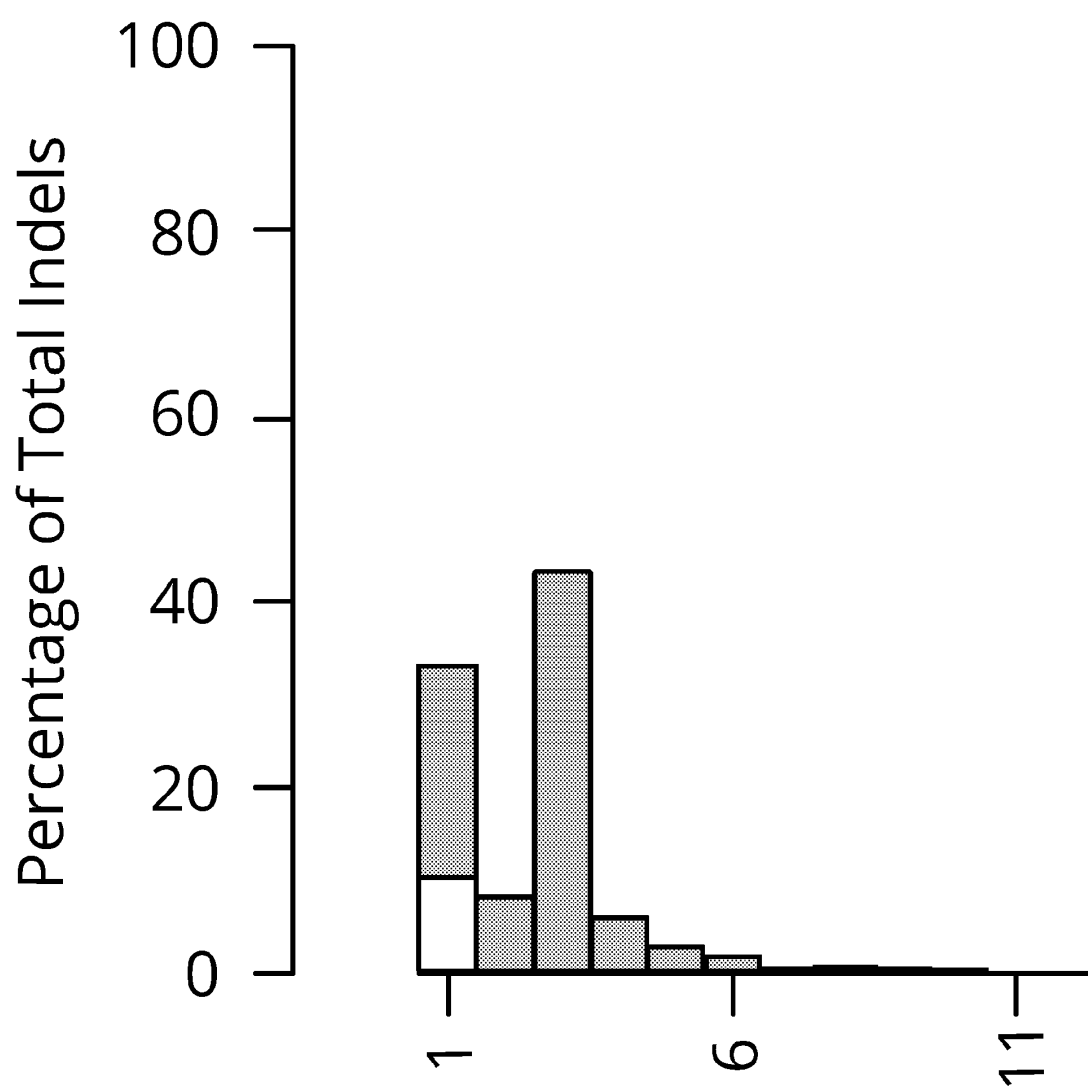


FIG 10A

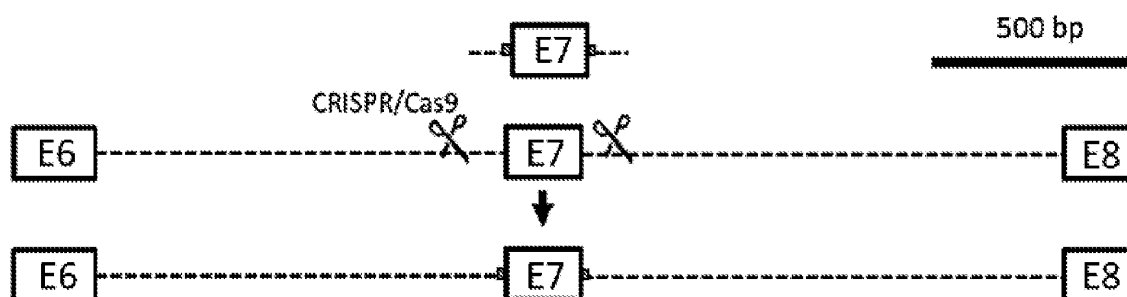


FIG 10B

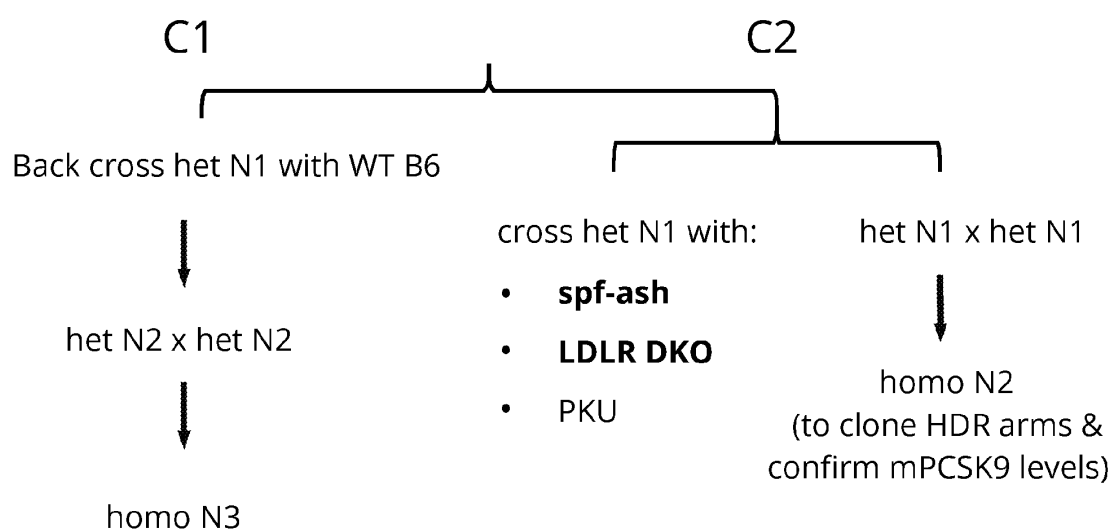


FIG 11A

HDR ARMS	Promoter (nuclease vector)	Serotype	Group	Animal ID	Sex	Age at dosing (day)	Anti-AAV Bab titer (on day 0)	Biopsy (day)	Transduction		Anglicon- seq	HTR- Seq
									OTC ISH	OTC IF	indel %	# of OT sites ^c
Long	-	AAVrh79	G1	21-180	M	13	50	85	0.1	0.6	0.09	0
				21-204	F	1	50	84	1.0	0.7	0.06	0; 0
Short	F113	AAVrh79	G5	21-146	F	7	50	84	2.3	1.3	1.5	0; 0
				21-113 ^a	F	15	1600	86	0	0	0.1	N.T.
	TBG	AAVrh79	G4	21-111 ^a	F	16	400	85	0	0	0.1	N.T.
				21-122 ^a	F	11	1600	85	0	0	0.1	N.T.
Long	F113	AAVhu37	G3	21-068	M	7	50	84	8.9	5.4	2.6	2; 2
				21-090	M	6	25	86	0.9	1.1	0.7	0; 0
		AAVrh79	G7	21-178	M	10	N.T. ^a	85	1.9	2.2	0.9	0; 0
				21-188	M	3	25	93	1.6	2.6	0.7	0; 1
	TBG	AAVhu37	G2	21-053	F	9	100	86	4.5	4.0	4.5	4; 3
				21-071	M	9	50	84	3.7	2.9	3.9	2; 0; 2
		AAVrh79	G6	21-157	F	6	25	84	16.9	18.6	12.8	27; 18
				21-175	F	11	<25	84	10.3	11.9	13.5	40; 27

FIG 11B-1

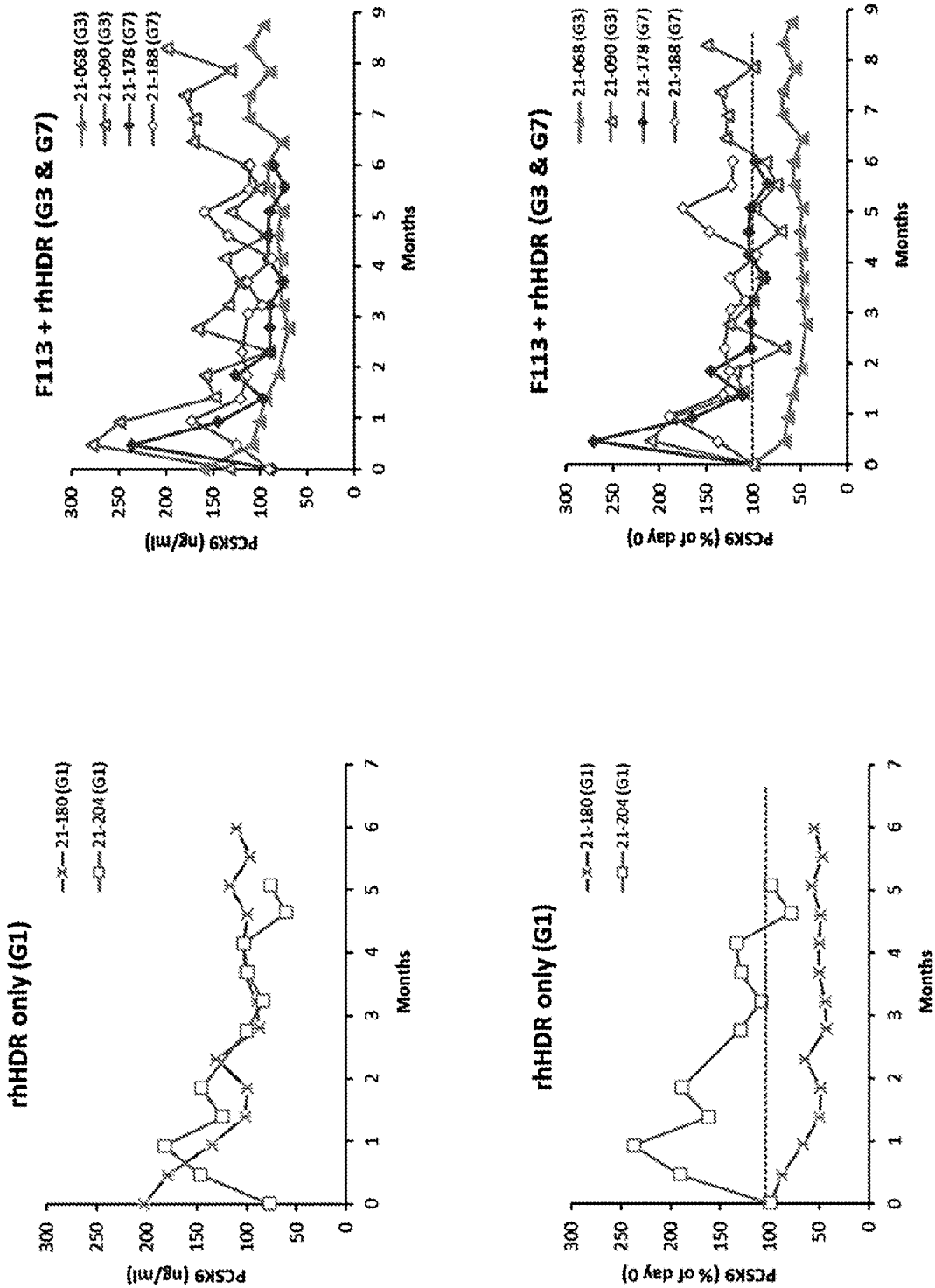


FIG 11B-2

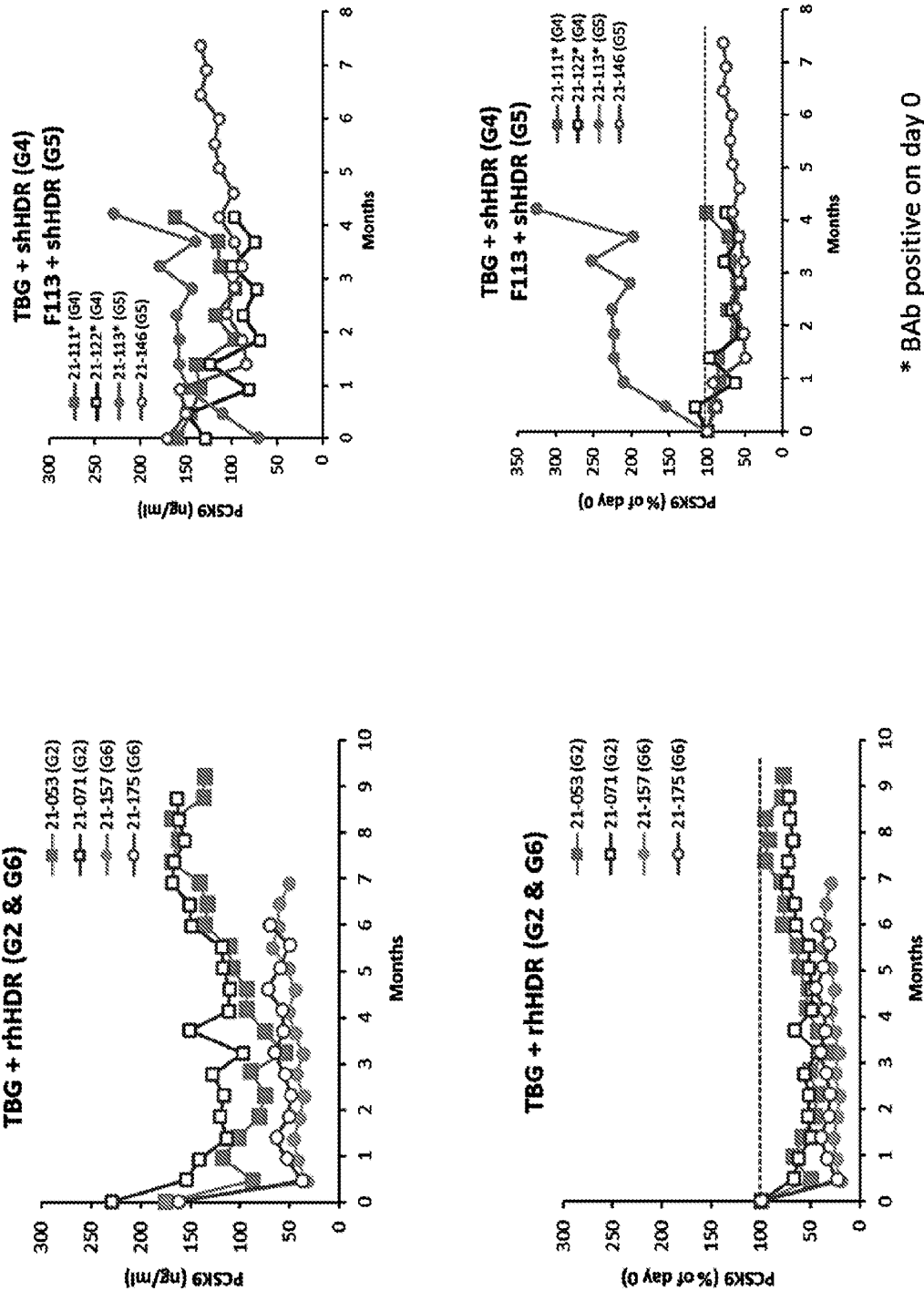


FIG 11C-1

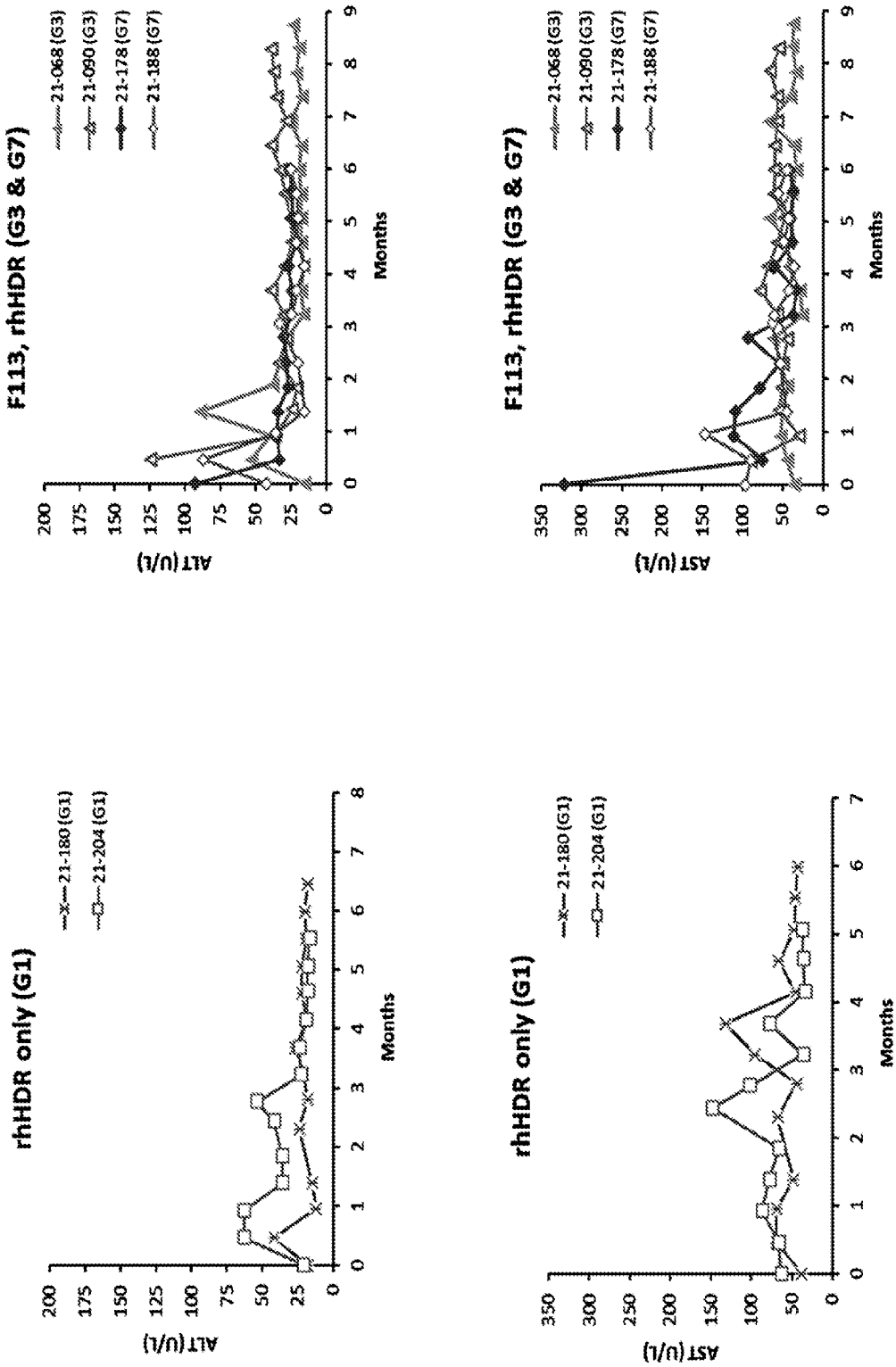


FIG 11C-2

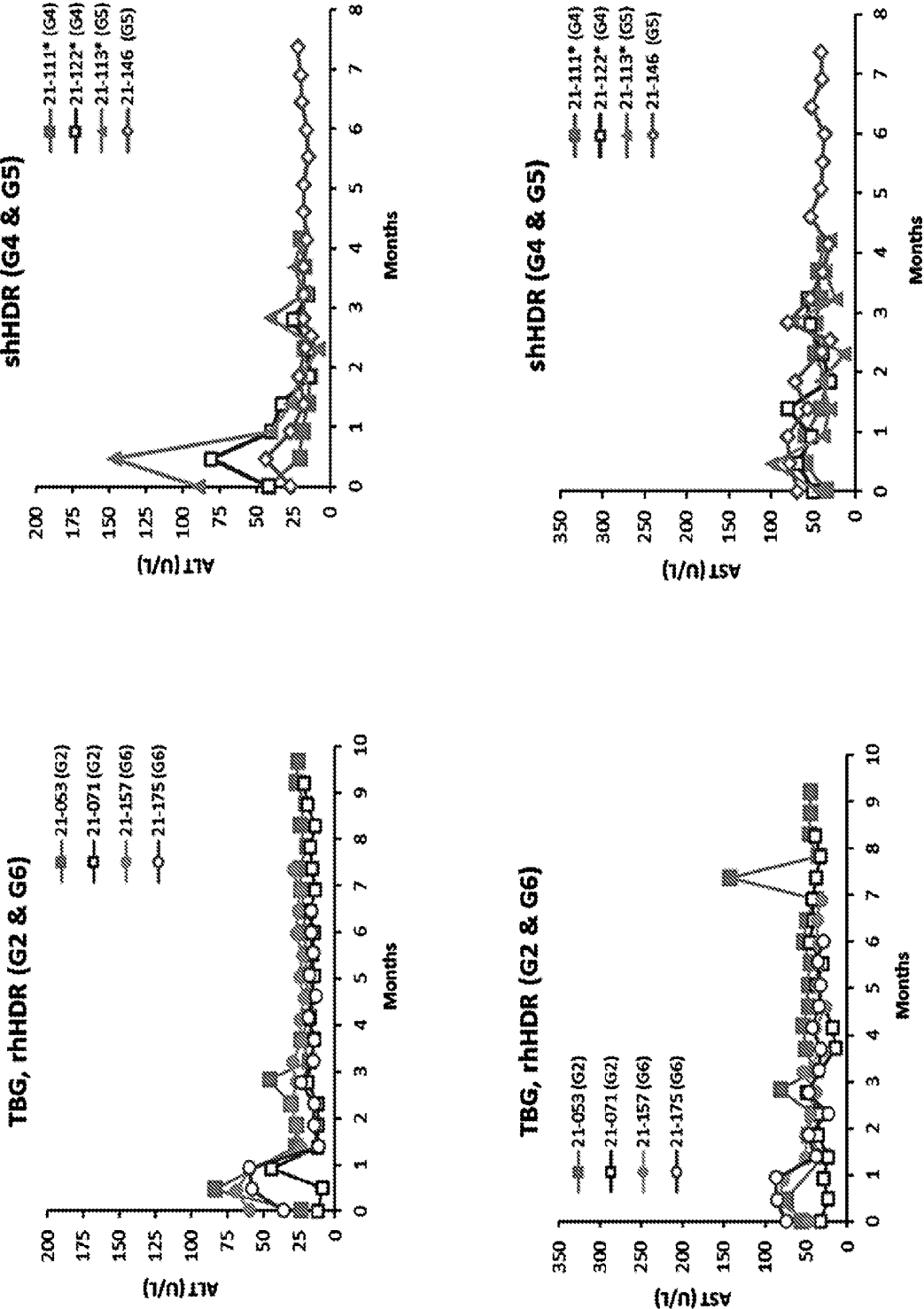


FIG 11D

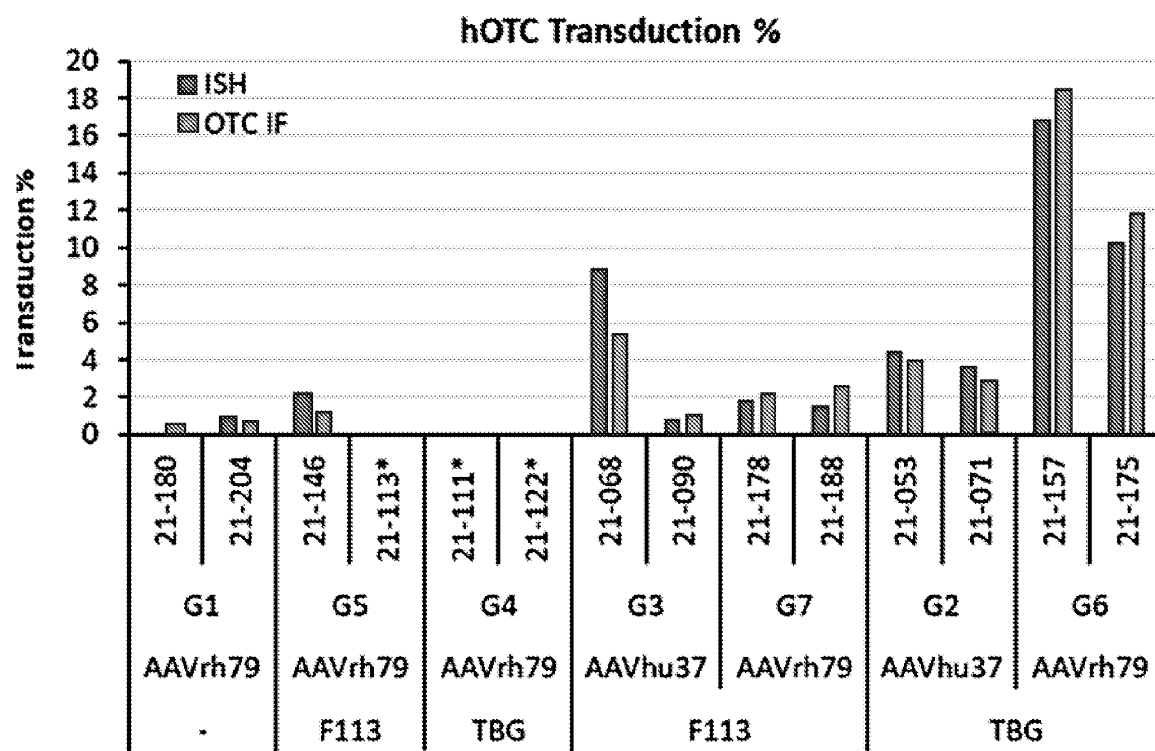


FIG 11E-1

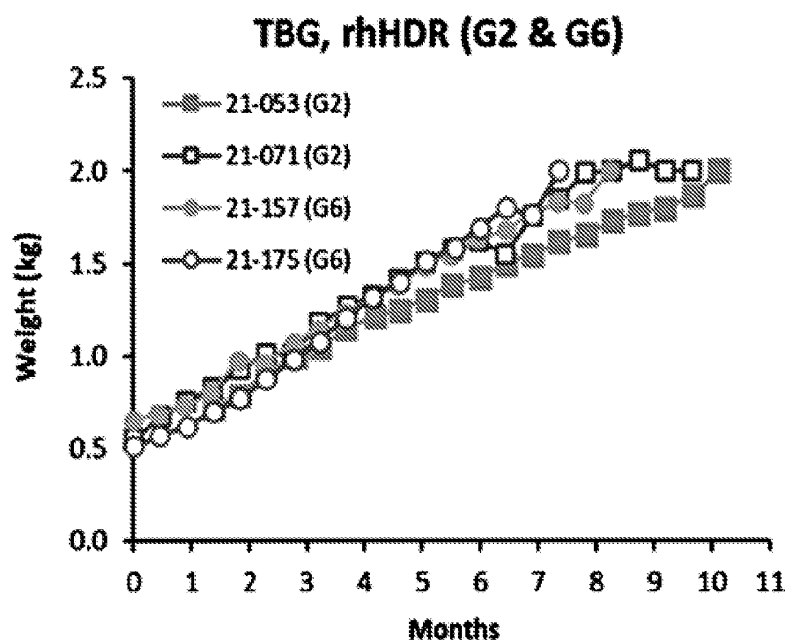
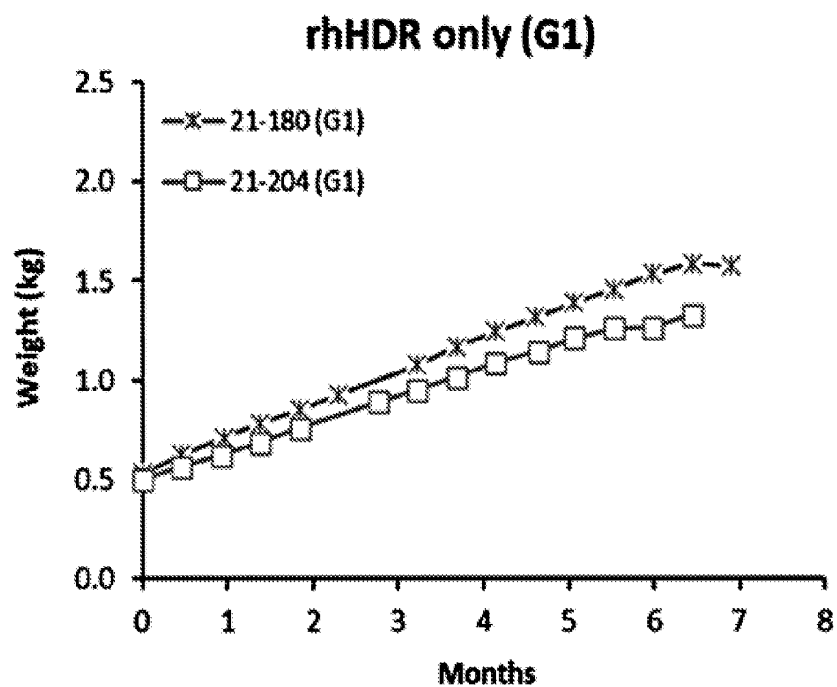
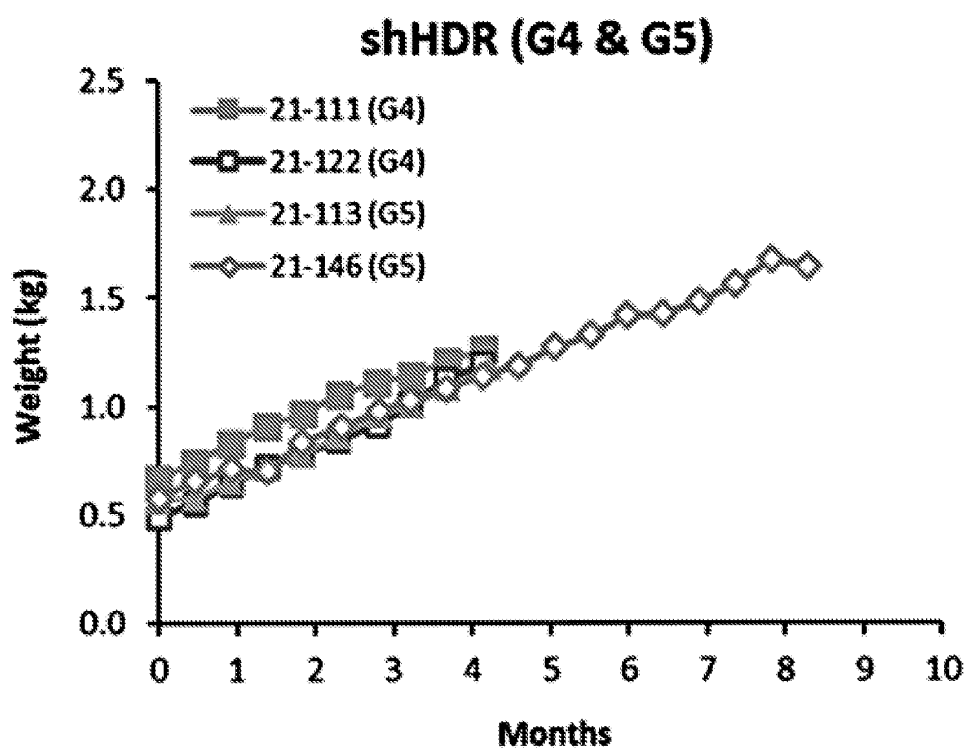
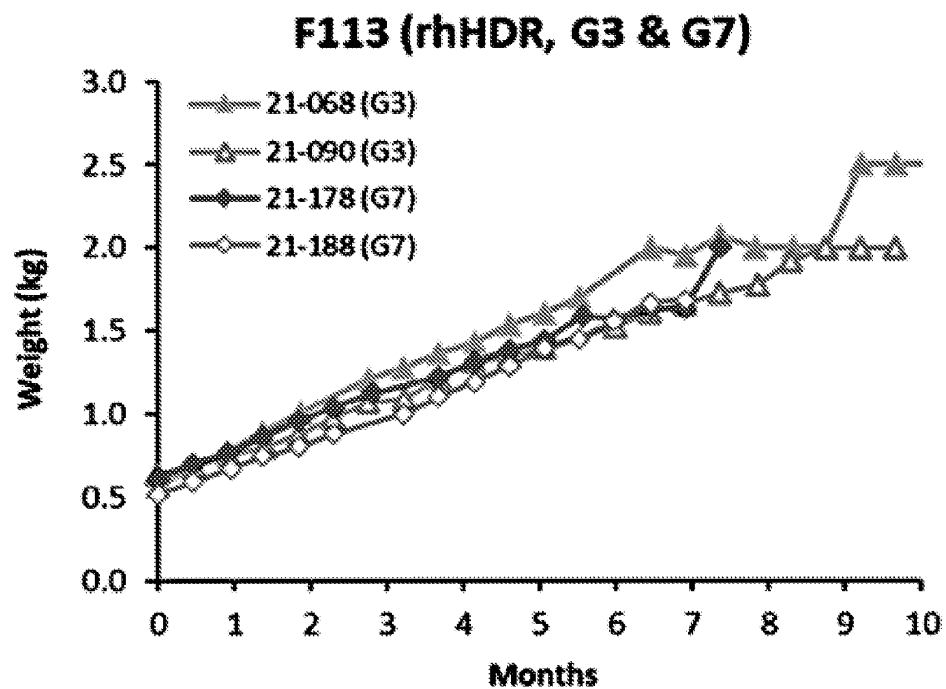


FIG 11E-2



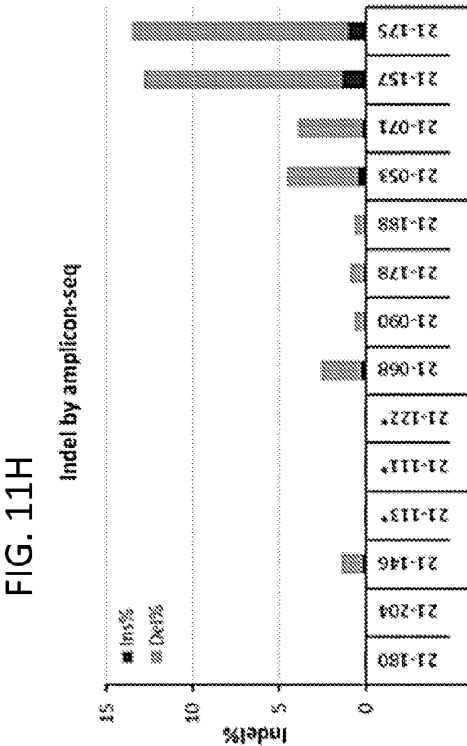
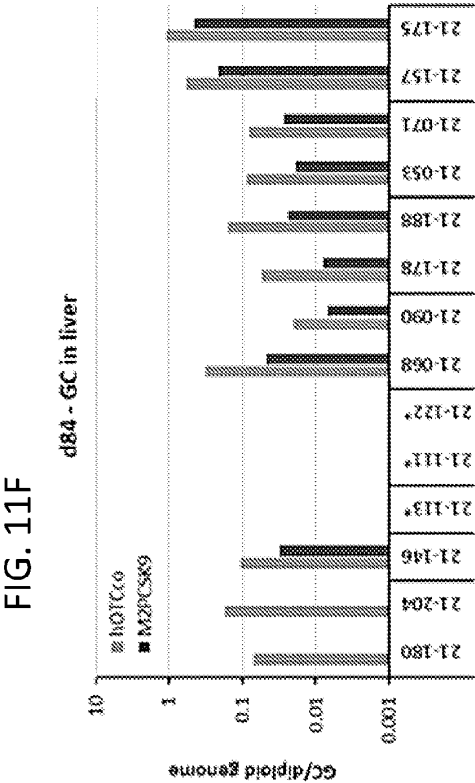
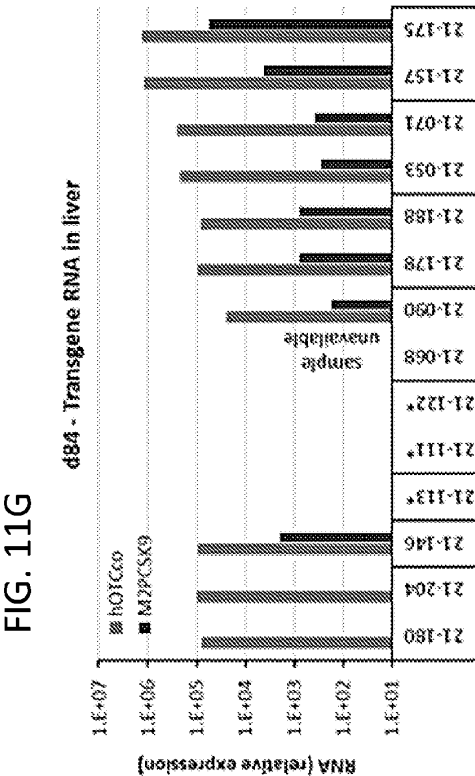
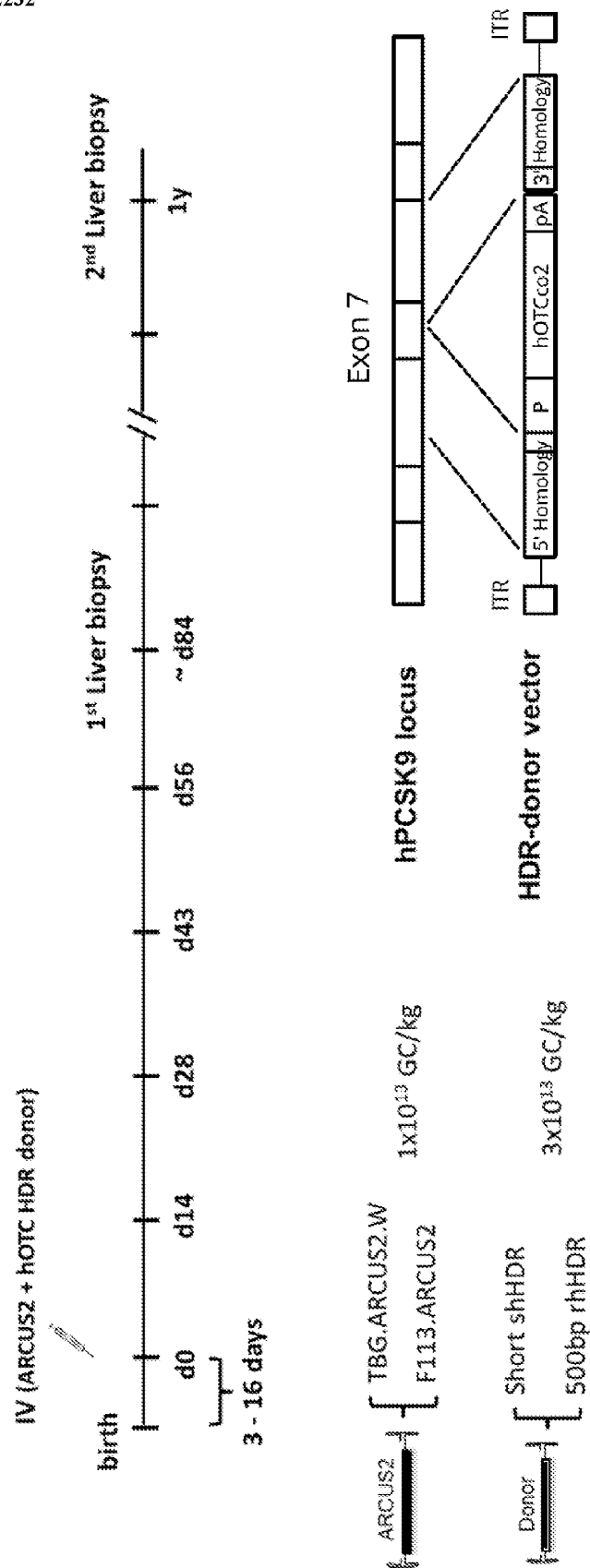


FIG 11I



Serotypes: AAVhu37 (n=4); AAVrh79 (n=10)

SUBSTITUTE SHEET (RULE 26)

FIG 13

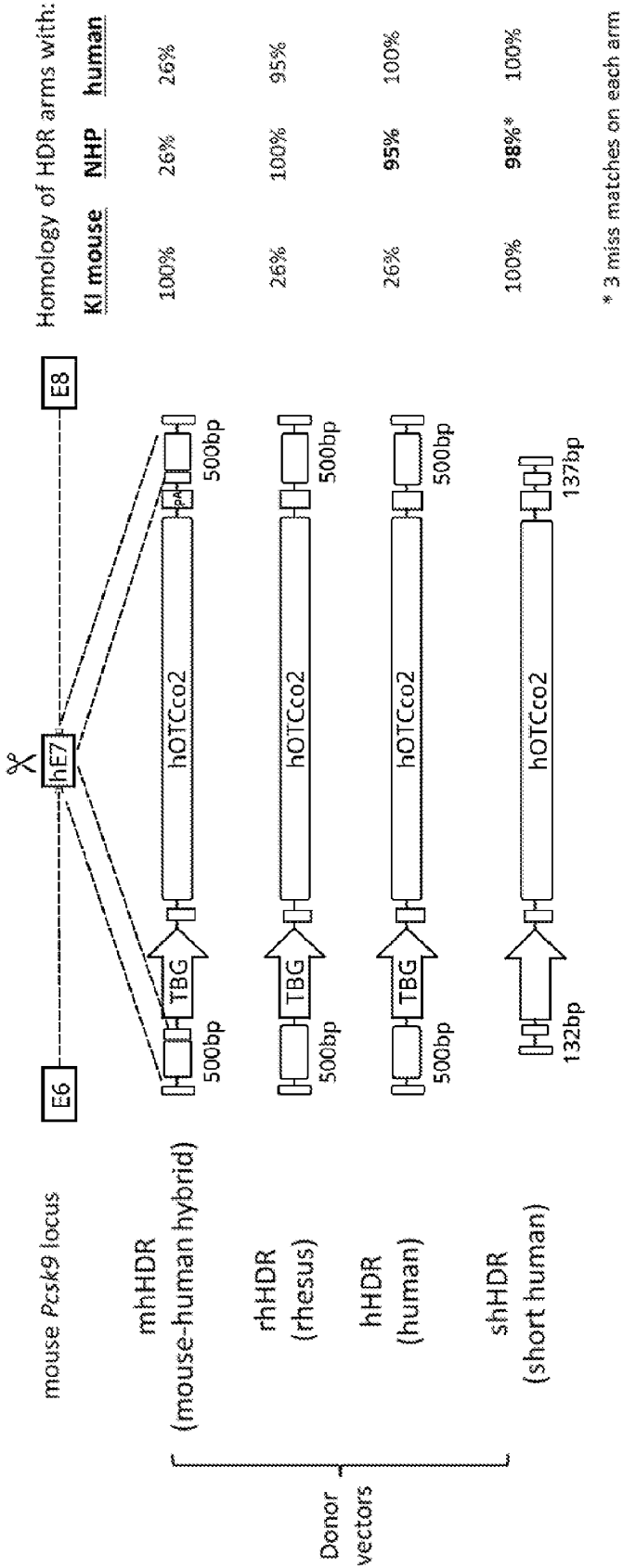


FIG 14A

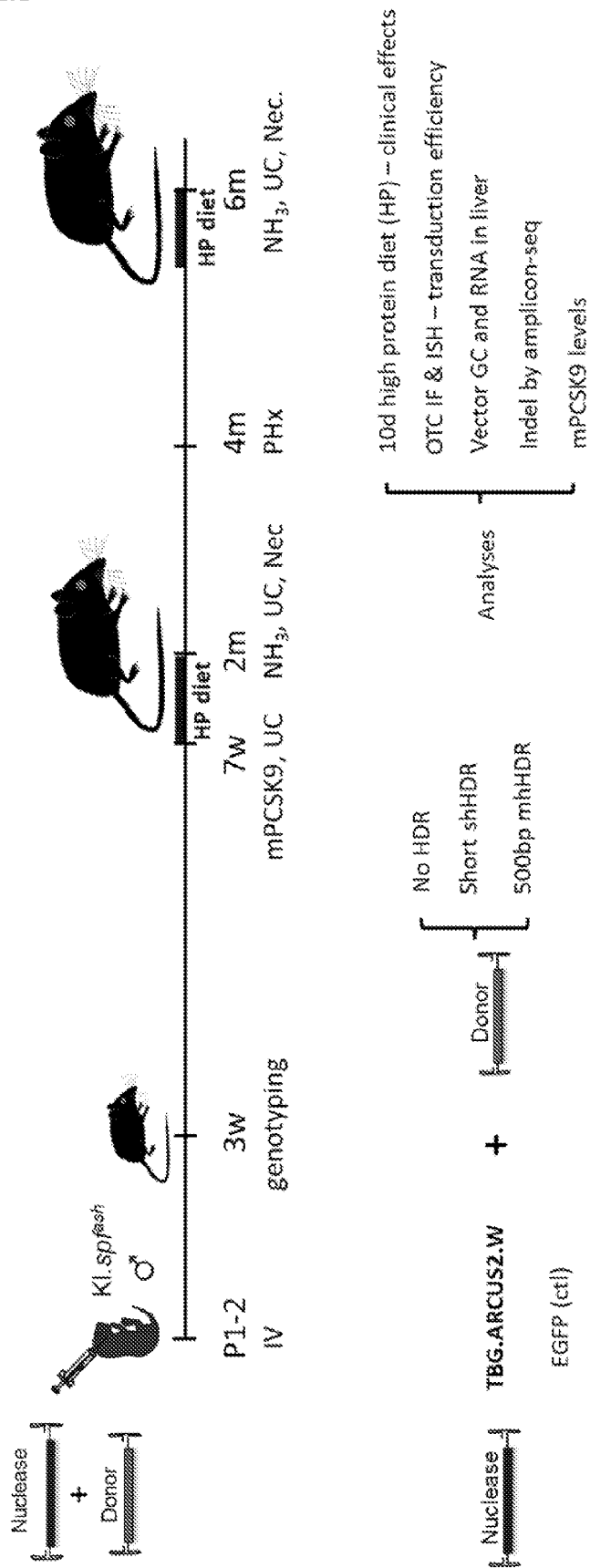


FIG 14B

Group	N	M2PCSK9 Meganuclease-Expressing AAV Vector (Targeting the <i>PCSK9</i> Gene)	Dose (GC/kg)	AAV Donor Vector	Dose (GC/kg)
1	20	AAVrh79.TBG.PI.M2PCSK9.WPRE.bGH	1.0×10^{13}	AAVrh79.mlhHDR.TBG.hOTCco.bGH	3.0×10^{13}
2	20	AAVrh79.TBG.PI.M2PCSK9.WPRE.bGH	1.0×10^{13}	AAVrh79.shHDR.TBG.hOTCco.bGH	3.0×10^{13}
3	20	AAVrh79.TBG.PI.M2PCSK9.WPRE.bGH	1.0×10^{13}	AAVrh79.TBG.hOTCco.bGH	3.0×10^{13}
4	20	AAVrh79.TBG.PIEGFP.WPRE.bGH (negative control)	1.0×10^{13}	AAVrh79.mlhHDR.TBG.hOTCco.bGH	3.0×10^{13}
5	20	NA	NA	NA	NA

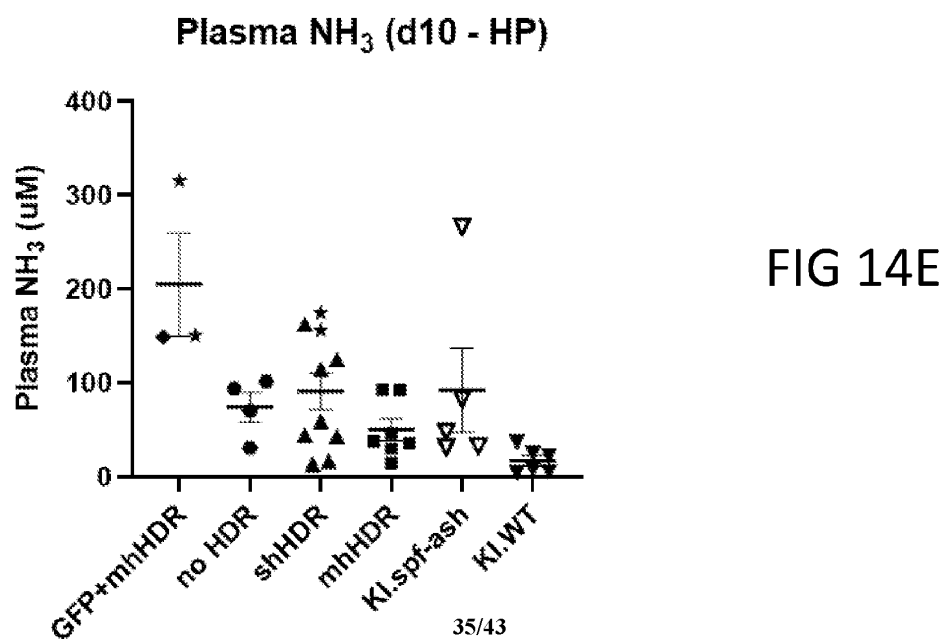
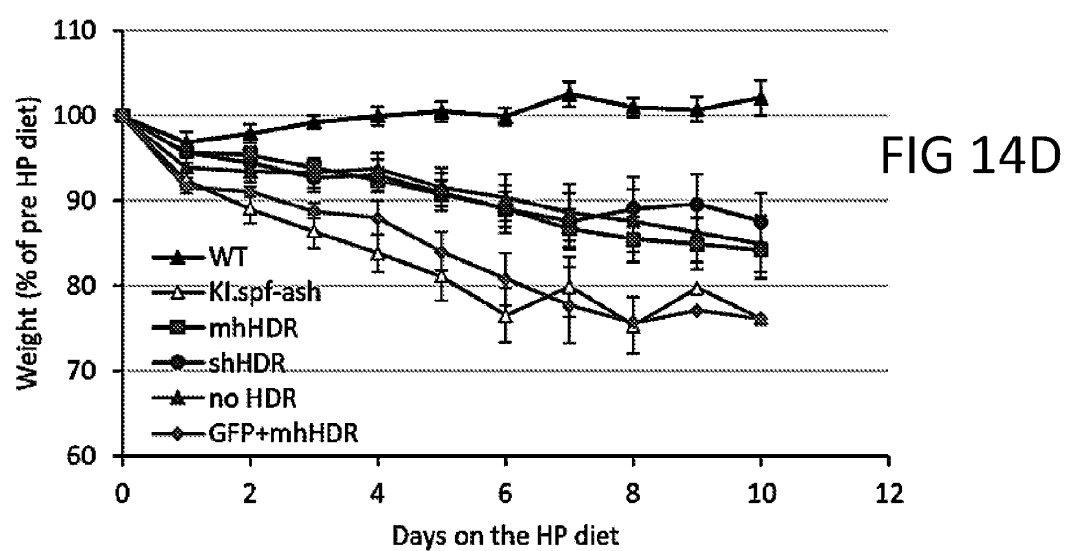
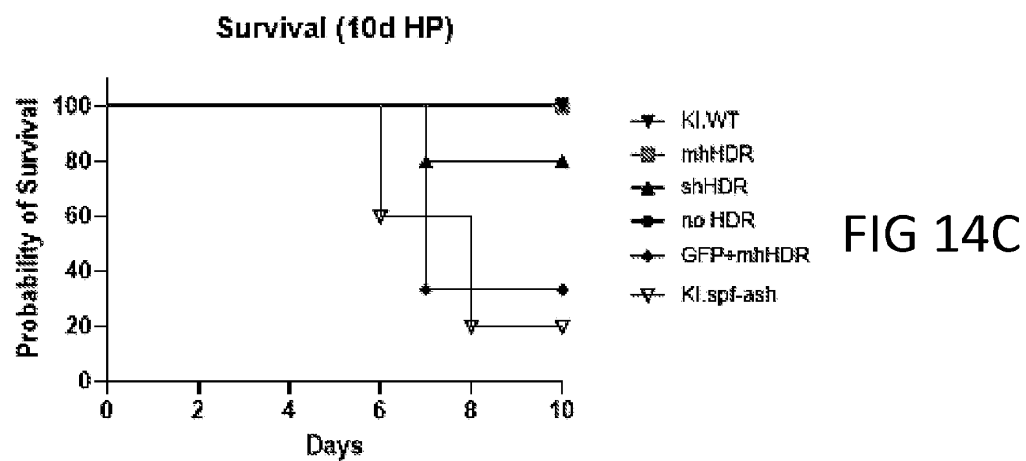


FIG. 14H

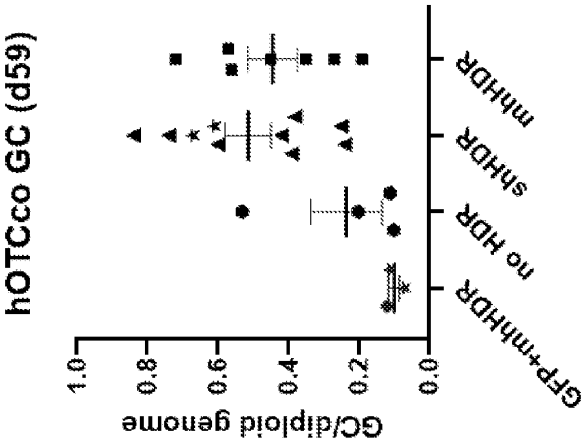


FIG 14G

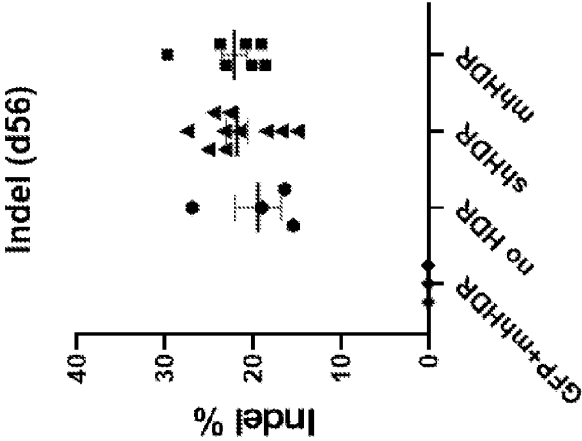


FIG 14F

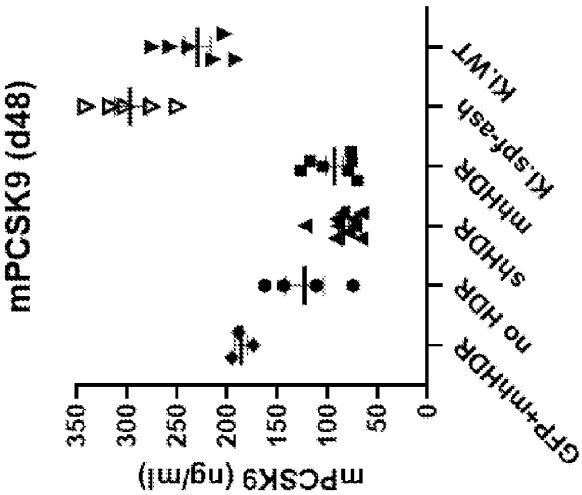


FIG 14I

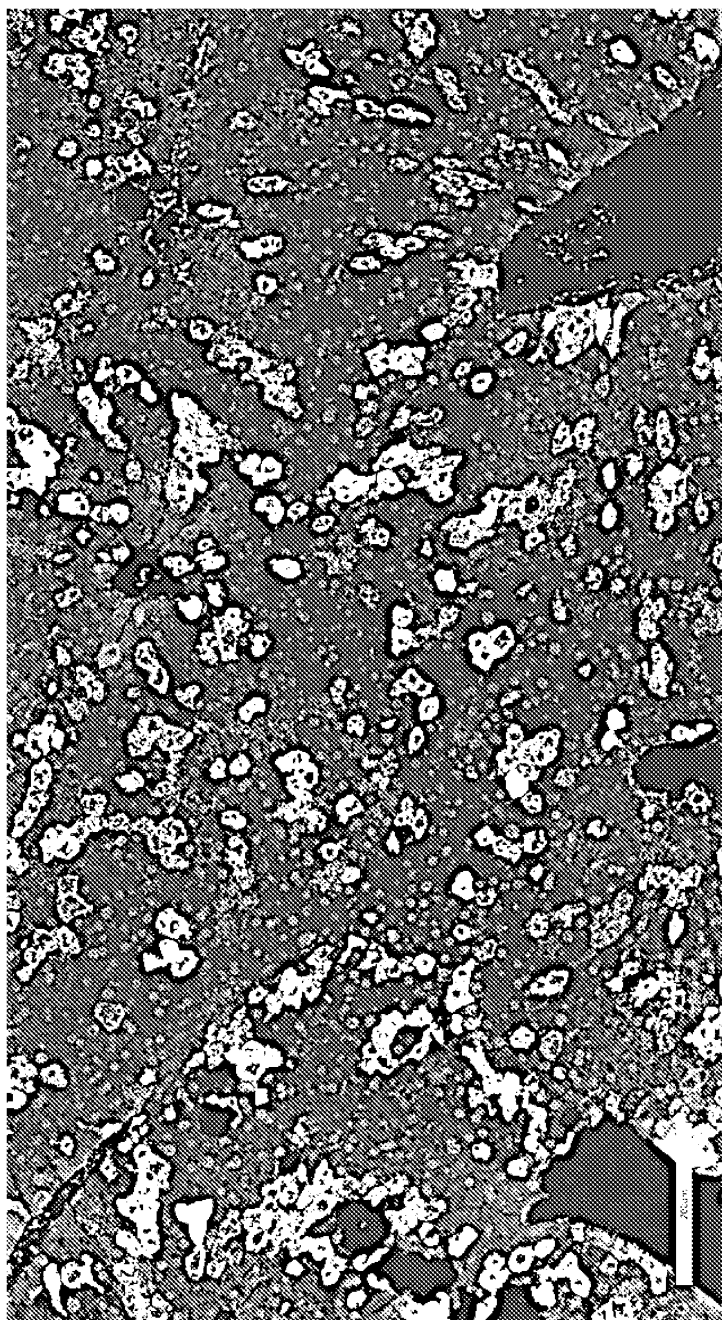
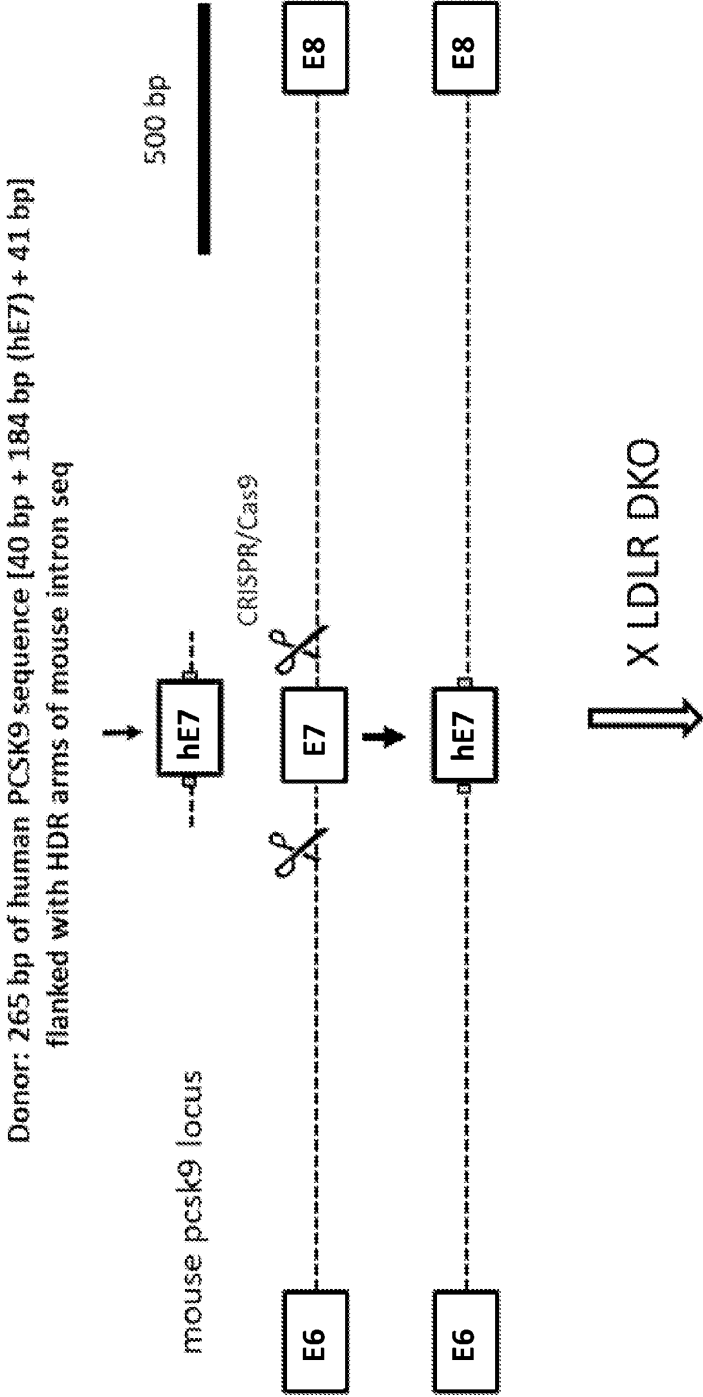


FIG 15



PCSK9-hE7-KI.LDLR DKO Mouse Model

hE7^{KI}/hE7^{KI}.Idlr⁻.Idlr⁻.apobec1⁻/apobec1⁻ (hoFH disease model)

FIG. 16

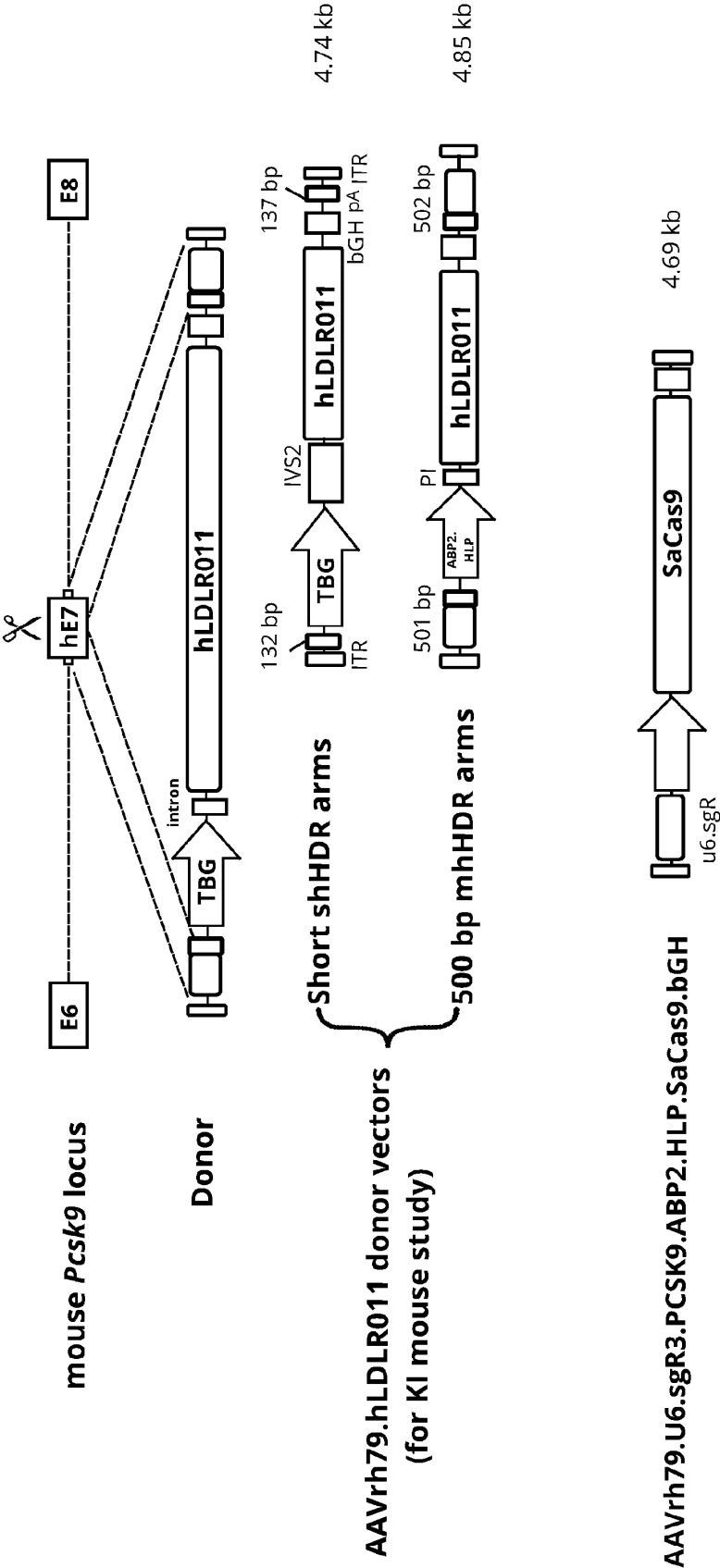


FIG 17

W3448- Study Design

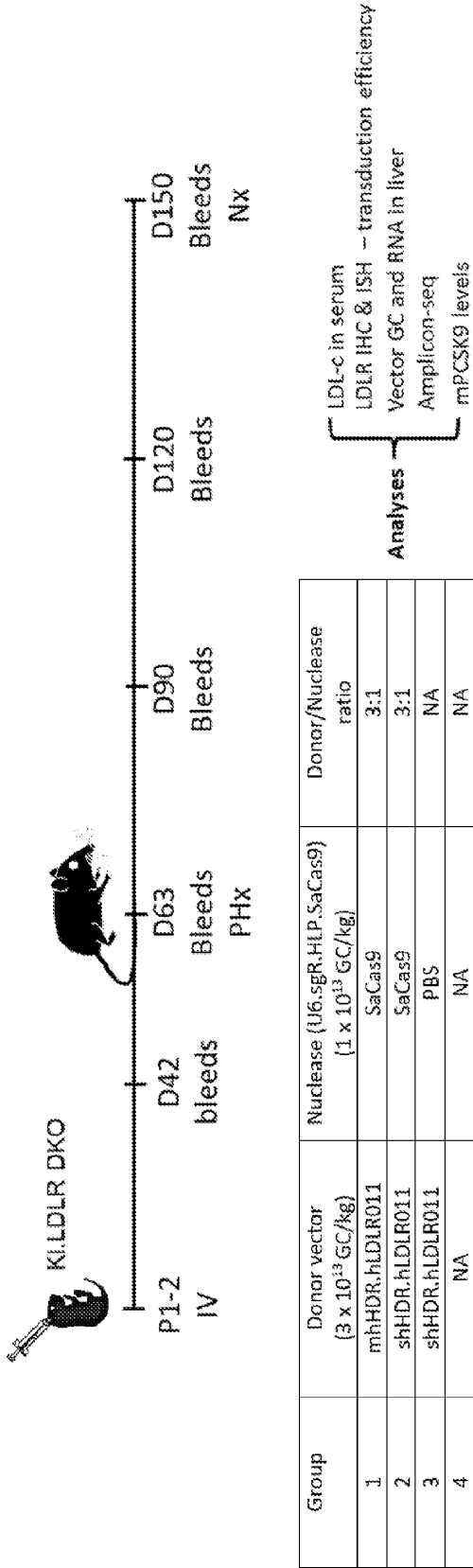


FIG. 18A

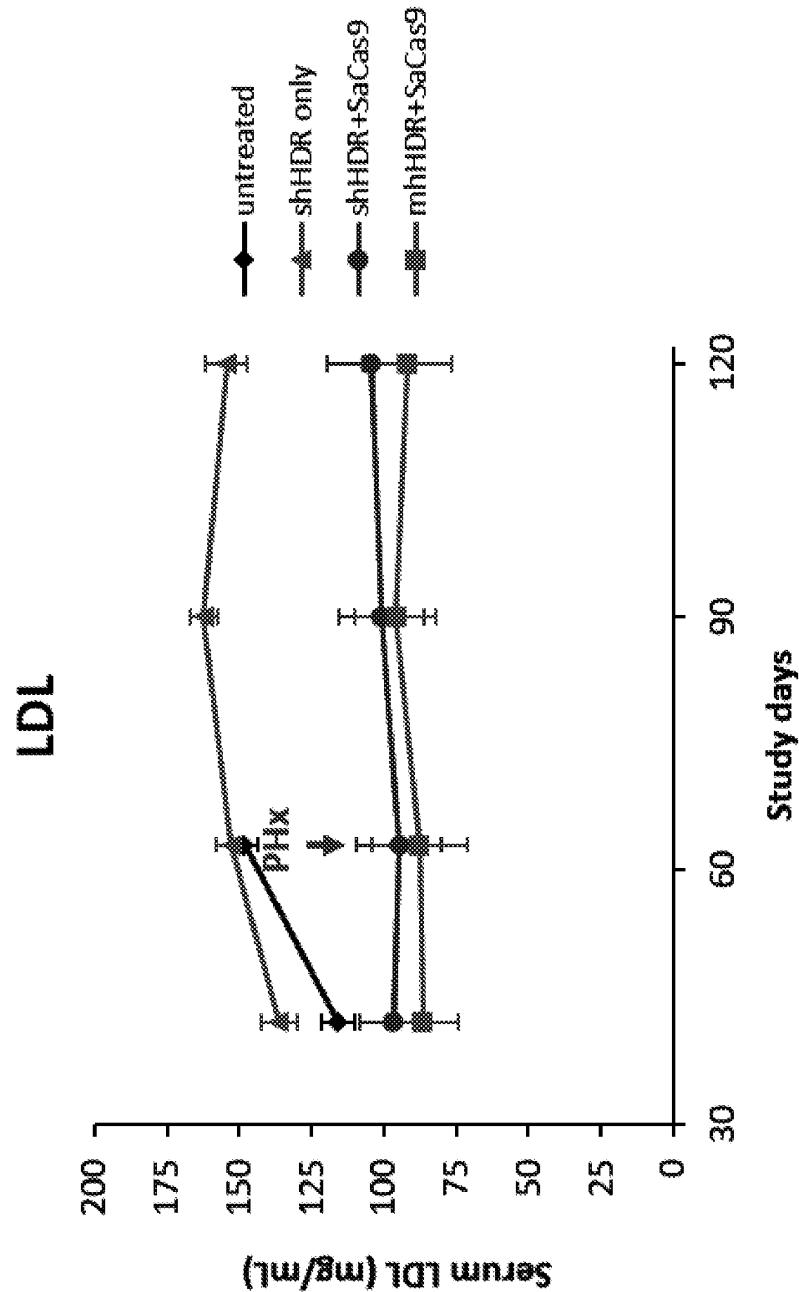


FIG. 18D

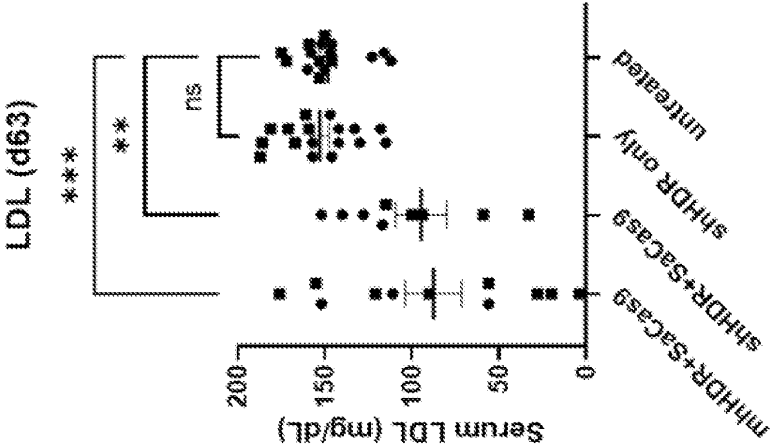


FIG. 18C

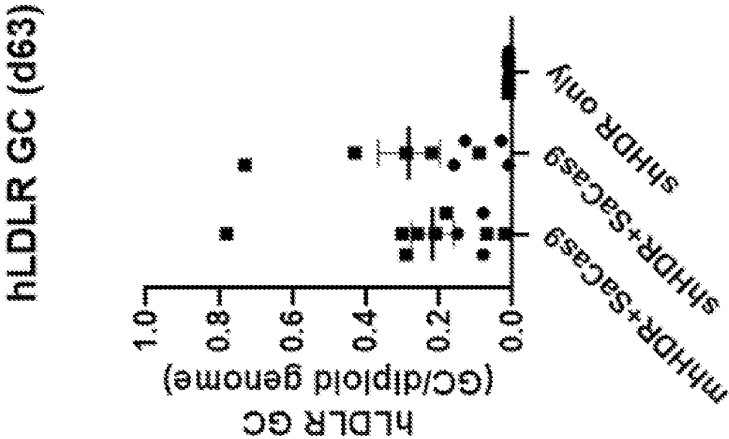


FIG. 18B

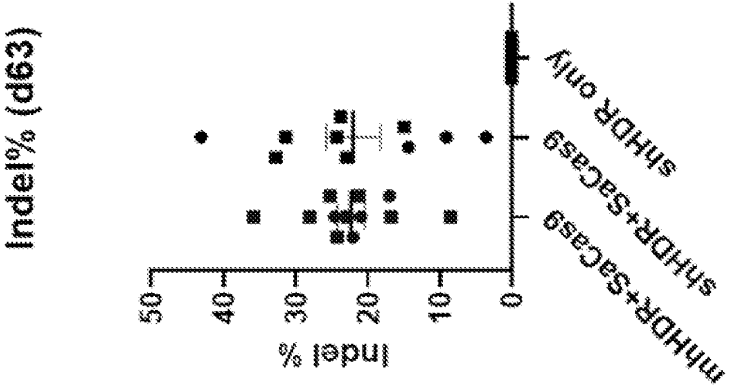
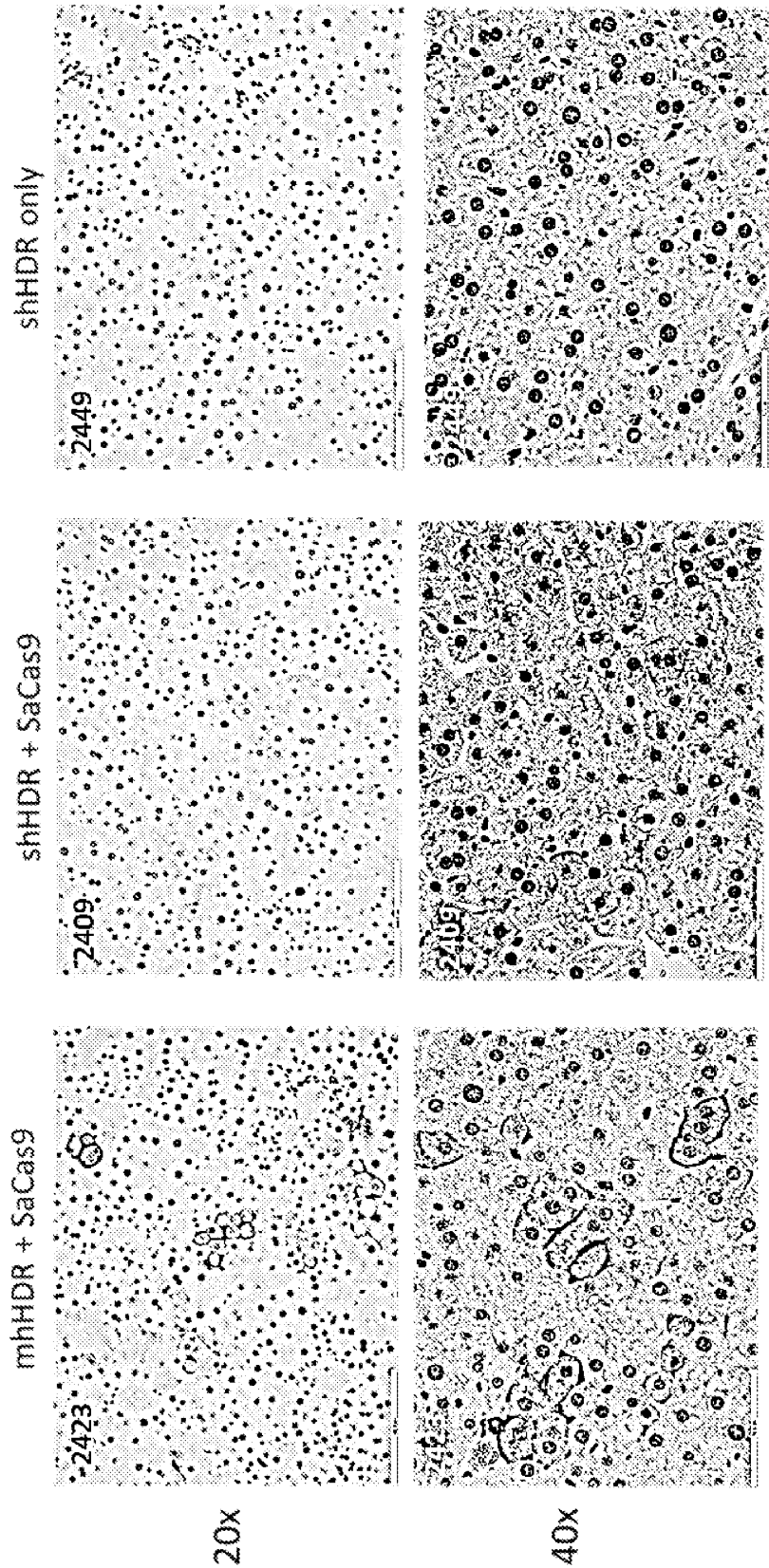


FIG. 19

Day 63 liver from partial hepatectomy



Animals will be necropsied on day 150. Transduction will be compared before and after d63 PHx