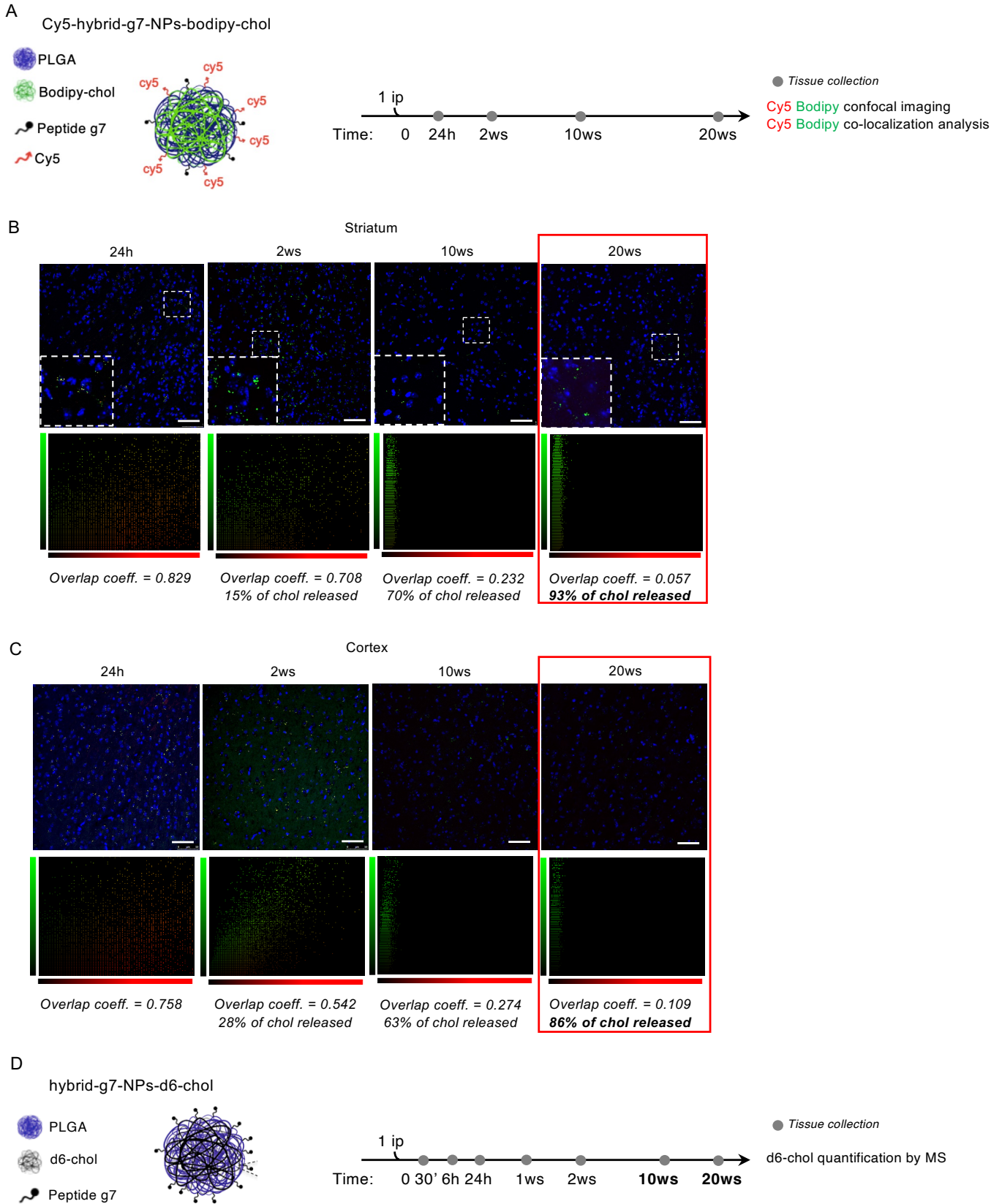


Supplementary Figure 1



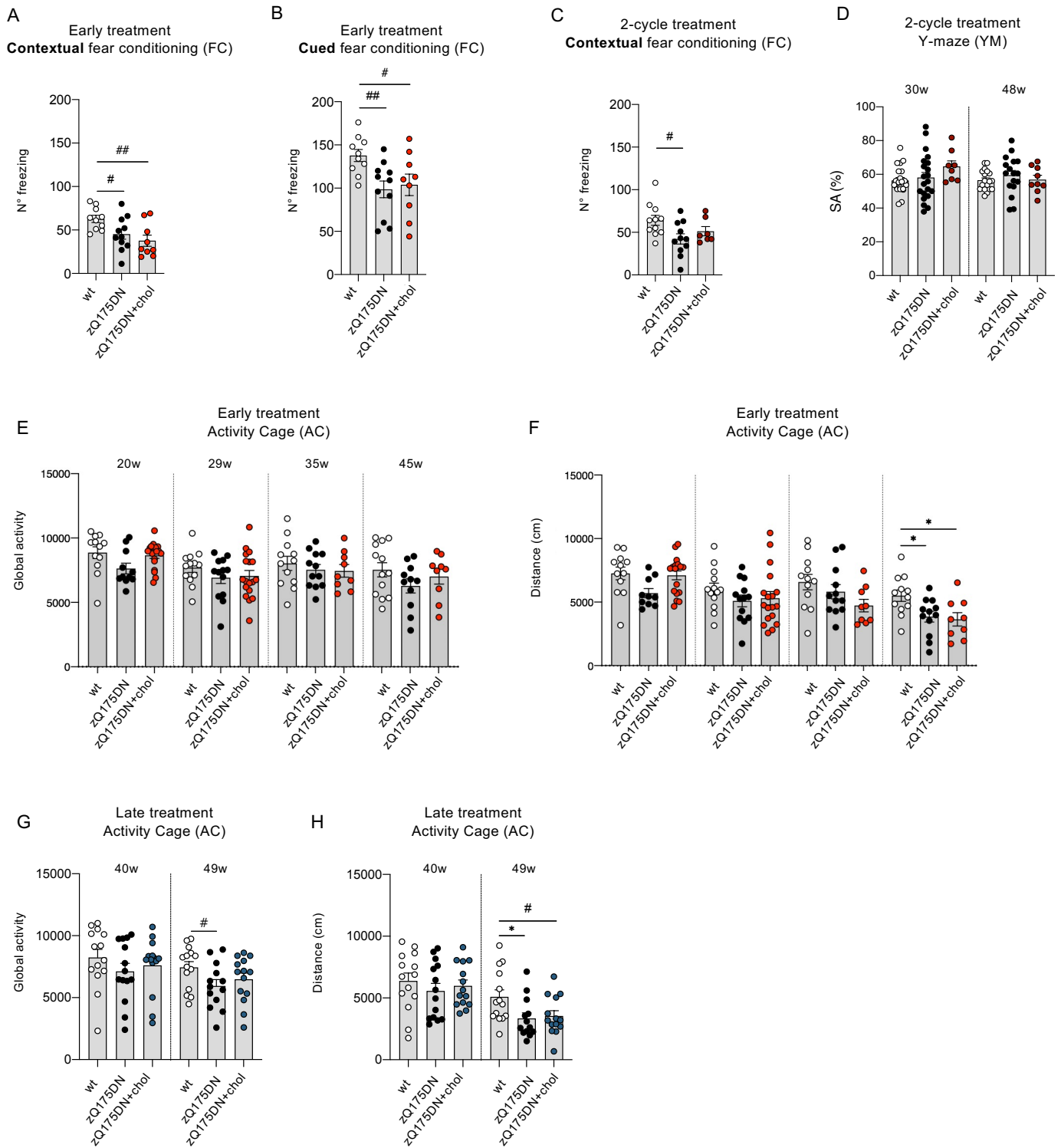
Supplementary Figure 1. Cholesterol release and quantification by hybrid-g7-NPs-chol in wt mice over time.

A Experimental paradigm: wt mice ($N = 4/\text{time point}$) were treated with a single ip injection of Cy5-hybrid-g7-NPs-bodipy-chol and sacrificed at different time points. Brains were collected for the analysis.

B–C Representative confocal images of brain slices (striatum in B, cortex in C) from wt mice after ip injection of hybrid-Cy5-g7-NPs-bodipy-chol sacrificed after 24 h, 2 weeks, 10 weeks or 20 weeks and relative co-localization of bodipy-chol and g7-NPs. Hoechst was used to counterstain nuclei (Ho, blue). Scale bar is 50 μm .

D Experimental paradigm: wt mice ($N = 4/\text{time point}$) were treated with a single ip injection of hybrid-g7-NPs-d6-chol and sacrificed at different time points. Different cerebral regions were collected for mass spectrometry analysis.

Supplementary Figure 2



Supplementary Figure 2. Cognitive and motor abilities of zQ175DN mice after the different treatments.

A-B N° of freezing in the fear conditioning (FC) test in the contextual (A) and cued paradigm (B) from the “early treatment” at 48 weeks of age.

C N° of freezing in the fear conditioning (FC) test in the contextual paradigm from the “2-cycle treatment” at 48 weeks of age.

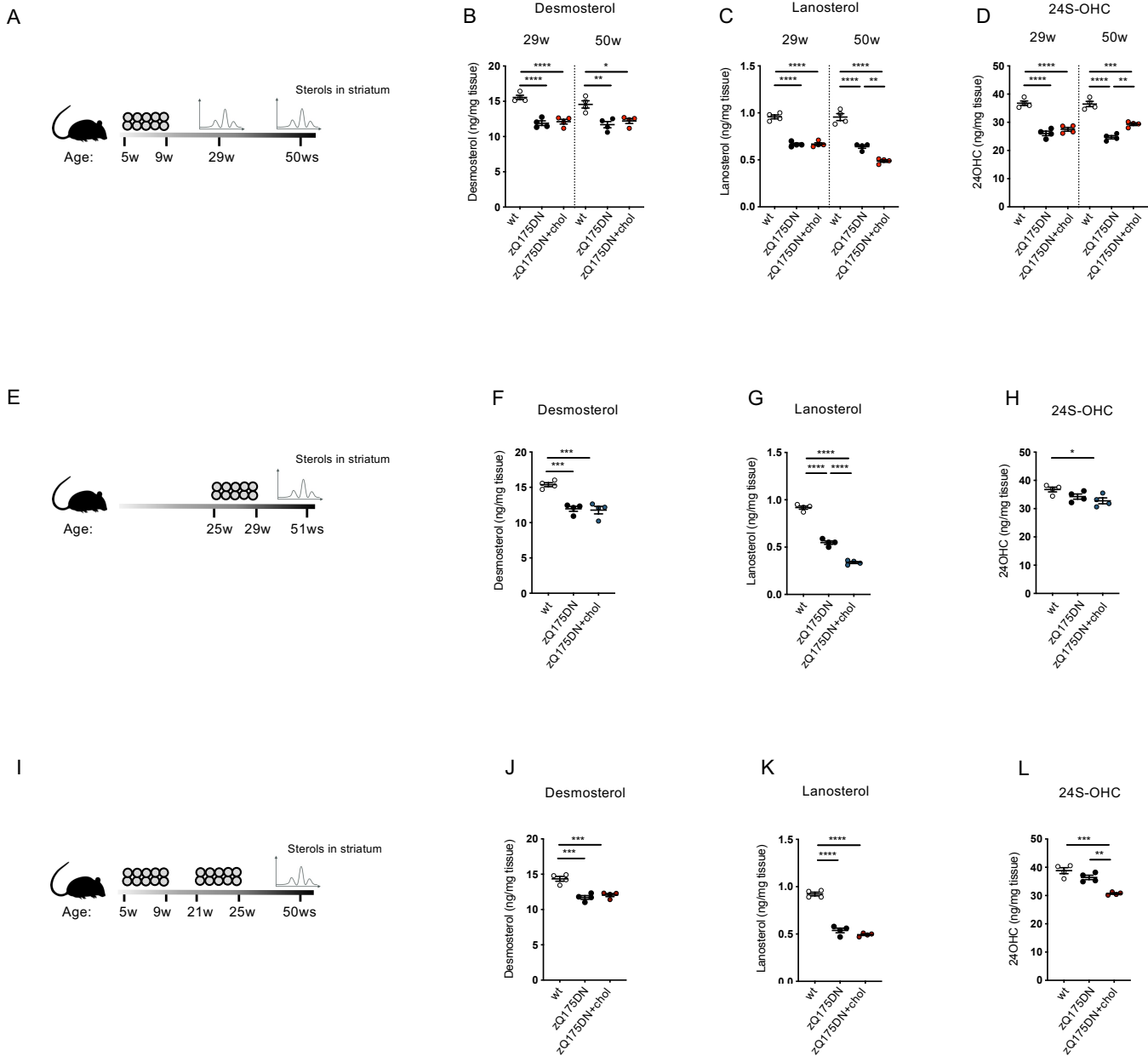
D Y-maze (YM) test from the “2-cycle treatment” at 30-48 weeks of age. Spontaneous alternation (SA) was calculated by dividing the n° of alternations by n° of possible triads x 100.

E-F Global motor activity (E) and total distance traveled (in cm) (F) in an Activity Cage (AC) test from the “early treatment”.

G-H Global motor activity (G) and total distance traveled (in cm) (H) in an Activity Cage (AC) test from the “late treatment”.

Data information: data in A–H are shown as scatterplot graphs with mean±SEM. Each dot corresponds to the value obtained from each animal. Statistics: one-way ANOVA with Tuckey post-hoc test (* $p < 0.05$); Student’s t-test ($\#p < 0.05$; $\#\#p < 0.01$).

Supplementary Figure 3



Supplementary Figure 3. Sterols in the striatum of zQ175DN mice after the different treatments.

A-D Mass spectrometry analysis performed in the striatum from the “early treatment” ($N = 4$ mice/group).

Scheme of the treatment (A); level of desmosterol (B), lanosterol (C), and 24S-OHC (D) in the striatum at 29 and 50 weeks.

E-H Mass spectrometry analysis performed in the striatum from the “late treatment” ($N = 4$ mice/group).

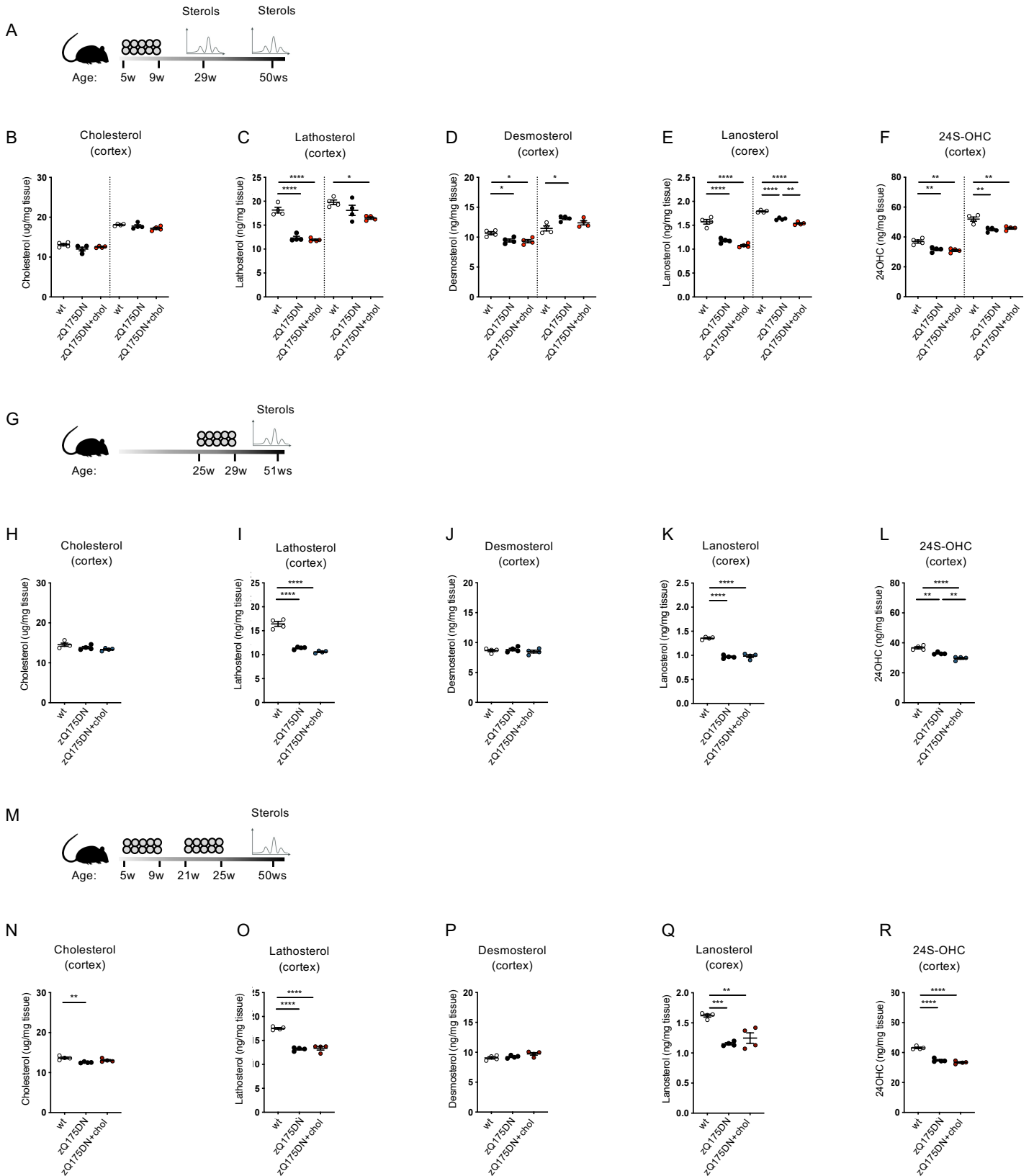
Scheme of the treatment (E); level of desmosterol (F), lanosterol (G), and 24S-OHC (H) in the striatum at 51 weeks.

I-L Mass spectrometry analysis performed in the striatum from the “2-cycle treatment” ($N = 4$ mice/group).

Scheme of the treatment (I); levels of desmosterol (J), lanosterol (K), and 24S-OHC (L) in the striatum at 50 weeks.

Data information: data in B–D, F–H, and J–L are shown as scatterplot graphs with mean±SEM. Each dot corresponds to the value obtained from each animal. Statistics: one-way ANOVA with Tuckey post-hoc test (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$).

Supplementary Figure 4



Supplementary Figure 4. Sterols in the cortex of zQ175DN mice after the different treatments.

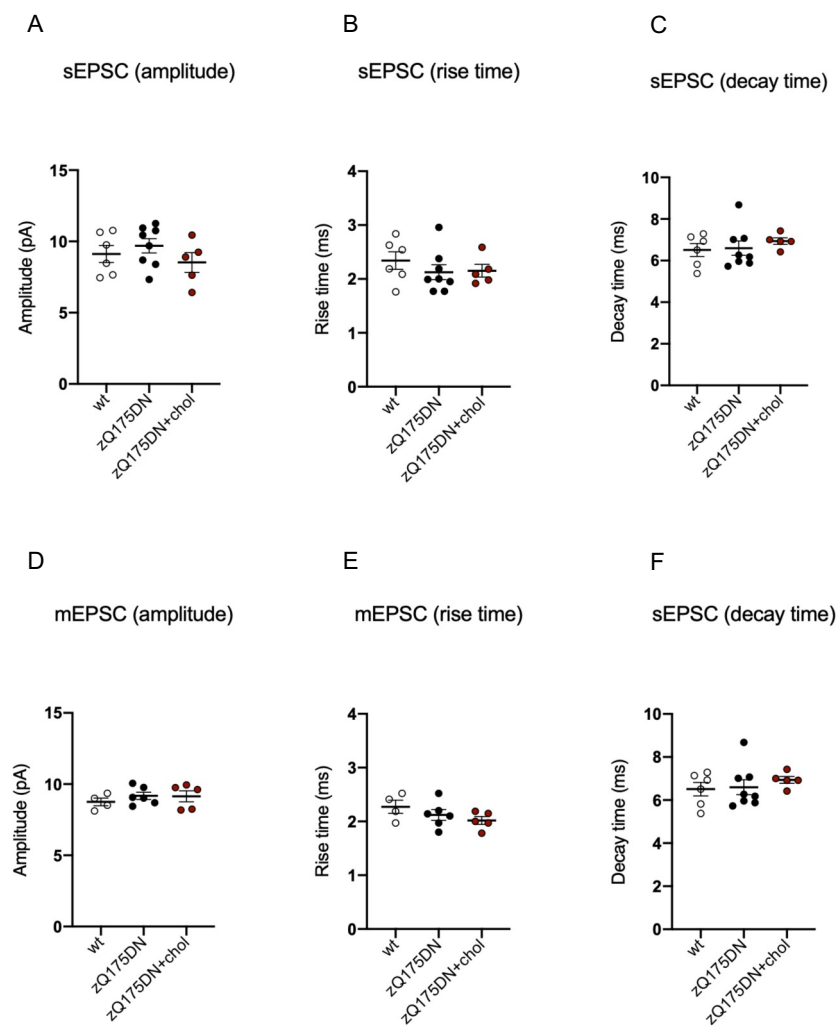
A-F Mass spectrometry analysis performed in the cortex from the “early treatment” ($N = 4$ mice/group). Scheme of the treatment (A); level of cholesterol (B), lathosterol (C), desmosterol (D), lanosterol (E), and 24-hydroxycholesterol (F) in the cortex at 29 and 50 weeks.

G-L Mass spectrometry analysis performed in the cortex from the “late treatment” ($N = 4$ mice/group). Scheme of the treatment (G); levels of cholesterol (H), lathosterol (I), desmosterol (J), lanosterol (K), and 24S-OHC (L) in the cortex at 51 weeks.

M-R Mass spectrometry analysis performed in the cortex from the “2-cycle treatment” ($N = 4$ mice/group). Scheme of the treatment (M); level of cholesterol (N), lathosterol (O), desmosterol (P), lanosterol (Q), and 24S-OHC (R) in the cortex at 50 weeks.

Data information: data in B–F, H–L, and N–R are shown as scatterplot graphs with mean±SEM. Each dot corresponds to the value obtained from each animal. Statistics: one-way ANOVA with Tuckey post-hoc test (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$).

Supplementary Figure 5



Supplementary Figure 5. Electrophysiological features of MSNs from zQ175DN mice after the “2-cycle treatment”.

A–F Average amplitude, rise time, and decay time of sEPSCs (A–C) and mEPSCs (D–F) recorded from MSNs of wt (6 cells from $N = 3$ mice), zQ175DN (8 cells from $N = 4$ mice) and zQ175DN+chol mice (5 cells from $N = 3$ mice).

Data information: data in A–F are shown as scatterplot graphs with mean \pm SEM. Each dot corresponds to the value obtained from each cell.

Supplementary Table 1

Level of d6-chol in striatum, cortex, cerebellum, liver, lung, kidney, and plasma measured by LC-MS ($N = 3/\text{group}$).

Data information: data are expressed as mean \pm SEM. Red boxes highlight values measured at 10 and 20 weeks after ip injection in each tissue. Data indicated with * were previously published (Birolini et al., JCR 2021).

Tissue	30* *	6h *	24h *	1w *	2w *	10w	20w
	Concentration (ng/mg)	Concentration (ng/mg)	Concentration (ng/mg)	Concentration (ng/mg)	Concentration (ng/mg)	Concentration (ng/mg)	Concentration (ng/mg)
Striatum	0,11 \pm 0,069	0,38 \pm 0,13	0,45 \pm 0,10	1,18 \pm 0,04	1,71 \pm 0,27	0,65 \pm 0,06	0,38 \pm 0,08
Cortex	0,00 \pm 0,00	0,24 \pm 0,06	0,36 \pm 0,07	1,04 \pm 0,16	1,38 \pm 0,55	0,55 \pm 0,03	0,38 \pm 0,09
Cerebellum	0,00 \pm 0,00	0,25 \pm 0,10	0,43 \pm 0,17	1,17 \pm 0,07	1,40 \pm 0,59	0,64 \pm 0,18	0,50 \pm 0,08
Liver	35,45 \pm 15,34	15,01 \pm 6,69	7,38 \pm 2,34	7,88 \pm 0,83	2,81 \pm 1,31	0,03 \pm 0,01	0,03 \pm 0,03
Lung	0,53 \pm 0,32	3,66 \pm 0,86	6,79 \pm 2,08	11,07 \pm 5,94	4,89 \pm 4,42	0,05 \pm 0,01	0,01 \pm 0,001
Kidney	1,85 \pm 1,00	4,47 \pm 2,42	6,30 \pm 4,72	8,80 \pm 0,12	5,02 \pm 2,01	0,07 \pm 0,01	0,06 \pm 0,05
Plasma	89,73 \pm 15,36	711,3 \pm 117,00	893,30 \pm 300,50	616,67 \pm 136,24	317,67 \pm 176,00	0,00 \pm 0,00	0,01 \pm 0,01

Supplementary Table 2

Number of animals used in each test performed in all the trials of this study.

	Early treatment												n. of tests performed (total)
	wt				zQ175DN				zQ175DN+chol				
	20w	29w	35w	45-48w	20w	29w	35w	45-48w	20w	29w	35w	45-48w	
Novel Object Recognition test (NOR)	13	13	12	12	10	13	12	12	18	18	9	9	151
Paw Clasp test (PC)	13	12	12	12	11	13	12	12	18	18	9	9	151
Grip Strength test (GC)	13	13	12	12	11	13	12	12	18	18	9	9	152
Activity Cage test (AC)	13	13	12	12	10	13	12	12	18	18	9	9	151
Rotarod test (RR)	-	-	-	13	-	-	-	13	-	-	-	9	35
Fear Conditioning test (FC)	-	-	-	10	-	-	-	11	-	-	-	9	30

	Late treatment						n. of tests performed (total)
	wt		zQ175DN		zQ175DN+chol		
	40w	49-51w	40w	49-51w	40w	49-51w	
Novel Object Recognition test (NOR)	14	14	14	13	14	14	83
Paw Clasp test (PC)	14	14	14	13	14	14	83
Grip Strength test (GC)	14	14	14	13	14	14	83
Activity Cage test (AC)	14	14	14	13	14	14	83
Rotarod test (RR)	-	14	-	13	-	14	41
Fear Conditioning test (FC)	-	13	-	13	-	13	39

	2-cycle treatment												n. of tests performed (total)
	wt				zQ175DN				zQ175DN+Chol				
	20w	29-30w	35w	45-48w	20w	29-30w	35w	45-48w	20w	29-30w	35w	45-48w	
Novel Object Recognition test (NOR)	15	18	19	18	13	17	18	18	17	17	17	17	204
Paw Clasp test (PC)	15	18	19	18	13	17	18	18	17	17	17	17	204
Grip Strength test (GC)	15	18	19	18	13	17	18	18	17	17	17	17	204
Activity Cage test (AC)	15	18	19	18	13	16	18	18	17	17	17	17	203
Rotarod test (RR)	-	-	-	17	-	-	-	13	-	-	-	17	47
Fear Conditioning test (FC)	-	-	-	11	-	-	-	11	-	-	-	7	29
Y-maze test (YM)	-	21	-	18	-	21	-	17	-	8	-	9	94

Supplementary Table 3

Quantification of the n° of muHTT aggregates in brain coronal slices of HD mice to measure the effect of the different strategies aimed at restoring cholesterol level/synthesis at the time points where a behavioural effect was observed. The mean values for each group were normalized to 100.

R6/2_SREBP2 gene therapy				R6/2_minipumps				R6/2_NPs		
R6/2 + AAV-Tom Contralateral hemisphere	R6/2 + AAV-Tom Infused hemisphere	R6/2 + AAV-hBHP2 Contralateral hemisphere	R6/2 + AAV-hBHP2 Infused hemisphere	R6/2 + ACSF Contralateral hemisphere	R6/2 + ACSF Infused hemisphere	R6/2 + Chol Contralateral hemisphere	R6/2 + Chol Infused hemisphere	R6/2 + saline	R6/2 + g7-PLGA-NPs- chol	R6/2 + g7-hybrid-NPs- chol
104	122	71	88	38	94	97	23	142	97	52
120	85	119	96	108	33	56	18	75	138	112
118	71	90	94	73	54	56	32	157	64	106
50	87	81	82	105	49	56	41	106	151	130
62	85	73	84	41	39	76	23	90	68	132
58	74	77	58	80	54	56	51	81	64	46
133	84	136	147	26	33	38	25	129	70	147
169	49	127	121	11	25	14	32	141	54	100
85	139	127	155	153	36	351	29	81	109	66
139	86	134	123	48	50	243	17	133	76	84
116	96	82	119	157	121	32	23	140	95	123
85	97	137	123	270	31	8	11	83	74	54
123	102	82	79	90	113	123	1	62	117	49
110	64	91	94	242	112	352	2	83	79	118
97	66	65	65	264	81	188	2	74	66	134
75	99	100	84	52	117	39	0	78	88	104
56	95	102	90	75	125	277	0	89	133	101
56	87	108	89	68	124	45	2	90	76	73
70	95	108	69	106	45	68	12	70	86	108
83	67	125	92	113	28	44	44	84	85	95
113	75	99	42	33	47	57	44	131	82	122
86	68	80	32	48	158	64	14	117	91	109
92	121	97	59	152	197	92	17	72	108	131
119	102	81	71	72	118	41	35	140	113	81
136	111	99	47	77	97	55	14	67	110	97
145	114	119	34		19	75	13	104	121	115
	141	94	28		165		22	80	111	130
		117	75							
		89	79							
		150	42							
		60	55							
		103	78							
		72	8							
		106	27							
		121	49							
		83	51							
		112	47							
		85	63							
		68	44							
		114	60							
		106	72							
		120	83							
		98	55							
		94	55							
		103								

zQ175DN_g7-hybrid-NPs- chol							
zQ175DN + saline Early treatment 29w	zQ175DN + NPs Early treatment 29w	zQ175DN + saline Early treatment 50w	zQ175DN + NPs Early treatment 50w	zQ175DN + saline Late treatment 51w	zQ175DN + NPs Late treatment 51w	zQ175DN + saline 2 cycles treatment 50w	zQ175DN + NPs 2 cycles treatment 50w
85	58	39	81	69	5	128	1
73	85	62	181	94	35	104	5
94	74	113	167	88	75	74	4
117	104	85	73	67	62	116	6
98	92	75	95	79	19	94	4
104	98	86	142	98	83	83	6
100	86	118	133	77	49	83	7
119	76	84	137	100	132	141	3
88	82	98	149	82	88	73	2
134	79	97	51	123	48	120	6
163	98	113	58	80	51	213	5
92	71	128	118	80	123	51	3
88	55	150	115	104	37	149	5
143	84	99	63	113	36	86	12
97	56	88	56	54	135	96	4
131	84	107	60	91	86	67	5
138	77	117	50	94	64	126	3
68	147	71	59	97	62	60	7
68	69	160	167	117	67	98	2
63	58	81	72	147	97	104	2
38	101	114	111	104	38	73	3
103	38	123	141	121	55	85	1
109	47	79	106	105	120	127	4
98	49	141	127	106	82	86	2
64	114	97	173	151	53	79	2
139	84	86	104	133	128	86	5
103	133	88		129	83		2
116	159						
133	5						
31	131						
85	80						
144	112						
83	100						
82	111						
77	66						
70	99						
92	85						
147	113						
98	92						
128	91						

Supplementary Table 4

Inflammatory response of HD mice following chronic injection of hybrid g7-NPs-chol ("2-cycle treatment", $N = 4/\text{group}$).

Analytes whose values are significantly different in zQ175DN+chol group compared to control group are in red boxes.

Data information: data are expressed as mean±SEM. Statistics: one-way ANOVA with Tuckey post-hoc test (* $p < 0.05$; ** $p < 0.01$).

Analyte	Striatum (vs wt)				Cortex (vs wt)				Cerebellum (vs wt)			
	zQ175DN		zQ175DN+chol		zQ175DN		zQ175DN+chol		zQ175DN		zQ175DN+chol	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
IL-1a	0,722	0,056	0,667	0,000	0,778	0,064	0,556	0,064	0,895	0,053	1,053	0,086
IL-1b	0,909	0,105	0,546	0,105	0,700	0,100	0,650	0,126	1,600	0,432	1,500	0,100
IL-2	0,870	0,039	0,610	0,100	1,010	0,172	0,711	0,062	1,228	0,198	1,519	0,216
IL-3	N/D		N/D		N/D		N/D		N/D		N/D	
IL-4	N/D		N/D		N/D		N/D		N/D		N/D	
IL-5	1,000	0,577	1,000	0,000	0,500	0,289	0,333	0,333	0,857	0,286	0,429	0,143
IL-6	0,135	0,037	0,077	0,000	0,750	0,144	0,375	0,125	0,364	0,149	0,364	0,000
IL-9	0,770	0,068	0,892	0,126	0,641	0,078	0,719	0,131	0,761	0,043	0,682	0,049
IL-10	0,783	0,112	0,522	0,142	1,087	0,336	0,522	0,159	0,931	0,335	0,724	0,153
IL-12 (p40)	0,636	0,189	0,500	0,087	0,571	0,117	0,476	0,095	0,400	0,103	0,320	0,065
IL-12 (p70)	0,622	0,140	0,437	0,033	0,663	0,156	1,375	0,821	0,800	0,063	1,064	0,215
IL-13	0,625	0,052	0,627	0,103	0,896	0,176	0,701	0,033	1,452	0,131	1,305	0,223
IL-17	0,595	0,114	0,417	0,049	0,756	0,253	0,467	0,076	0,596	0,042	0,404	0,057
Eotaxin	0,719	0,060	0,469 *	0,031	0,722	0,106	0,639	0,070	0,878	0,138	0,781	0,040
G-CSF	0,849	0,121	0,636	0,091	0,500	0,000	0,750	0,250	0,467	0,128	0,533	-
GM-CSF	0,804	0,079	0,768	0,034	0,867	0,147	0,667	0,077	0,754	0,019	0,672	0,049
ING-gamma	0,500	0,084	0,466	0,028	0,897	0,119	0,588	0,120	0,607	0,031	0,533	0,050
KC	0,594	0,094	0,375 **	0,000	0,571	0,078	0,571	0,078	0,553	0,050	0,447 *	0,079
MCP-1	0,068	0,005	0,093	0,017	0,899	0,232	0,930	0,250	0,843	0,126	0,825	0,127
MIP-1a	1,047	0,114	1,043	0,117	1,167	0,271	0,892	0,113	0,713	0,116	0,629	0,117
MIP-1b	0,737	0,048	0,618	0,142	0,909	0,235	0,212	0,030	0,518	0,080	0,304	0,042
Rantes	0,680	0,067	0,530	0,075	0,983	0,178	1,017	0,144	1,388	0,194	1,327	0,212
TNF-a	0,610	0,028	0,695	0,198	0,725	0,180	0,975	0,170	0,559	0,093	0,509	0,081

Analyte	Lung (vs wt)				Liver (vs wt)				Kidney (vs wt)			
	zQ175DN		zQ175DN+chol		zQ175DN		zQ175DN+chol		zQ175DN		zQ175DN+chol	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
IL-1a	N/D		N/D		0,680	0,214	0,760	0,090	0,874	0,036	1,207	0,174
IL-1b	0,667	0,000	0,667	0,000	1,200	0,300	0,900	0,000	1,167	0,167	1,000	0,000
IL-2	0,692	0,000	1,578	0,451	1,447	0,417	1,303	0,224	0,919	0,193	0,730	-
IL-3	N/D		N/D		N/D		N/D		N/D		N/D	
IL-4	N/D		N/D		N/D		N/D		N/D		N/D	
IL-5	0,762	0,098	0,434	0,067	1,371	0,851	1,777	0,390	0,671	0,095	0,710	0,065
IL-6	0,718	0,271	1,231	0,774	0,913	0,126	0,543	0,174	0,752	0,068	1,282	0,600
IL-9	1,415	0,434	1,189	1,083	0,658	0,045	0,518	0,020	0,410	0,035	0,519	-
IL-10	1,000	0,406	0,878	0,378	0,734	0,008	0,677	0,000	1,104	0,203	0,816	0,190
IL-12 (p40)	0,998	0,000	0,998	0,003	0,992	0,001	0,986	0,015	0,996	0,005	0,993	0,006
IL-12 (p70)	0,858	0,024	1,135	0,256	1,028	0,054	0,942	0,111	0,818	0,091	0,679	0,032
IL-13	0,998	0,141	0,977	0,028	1,023	0,064	0,524	0,213	0,637	0,565	1,290	0,113
IL-17	0,889	0,222	0,833	0,096	0,583	0,083	1,000	0,250	0,667	0,000	0,778	0,111
Eotaxin	0,728	0,264	0,779	0,222	0,847	0,086	0,824	0,272	0,810	0,160	0,625	0,089
G-CSF	0,937	0,131	1,104	0,127	0,741	0,157	0,608	0,118	2,470	1,700	0,752	0,127
GM-CSF	0,815	0,074	0,926	0,134	1,193	0,153	1,105	0,158	1,279	0,154	0,930	0,000
ING-gamma	0,893	0,114	1,276	0,155	0,802	0,159	0,649	0,395	0,785	0,175	0,734	0,142
KC	0,639	0,083	0,635	0,035	0,654	0,116	0,438 *	0,132	0,646	0,098	0,813	0,018
MCP-1	1,153	0,133	1,063	0,509	0,905	0,171	0,947	0,213	0,924	0,104	0,930	0,174
MIP-1a	N/D		N/D		N/D		N/D		N/D		N/D	
MIP-1b	0,638	0,185	0,185	0,021	0,816	0,037	0,521	0,160	1,024	0,397	1,250	0,541
Rantes	0,743	0,257	1,004	0,075	0,944	0,100	0,738	0,310	1,141	0,131	1,227	0,272
TNF-a	0,881	0,346	1,220	0,409	1,191	0,409	0,454	0,331	0,917	0,027	0,684	-

Analyte	Spleen (vs wt)				Heart (vs wt)				Plasma (vs wt)			
	zQ175DN		zQ175DN+chol		zQ175DN		zQ175DN+chol		zQ175DN		zQ175DN+chol	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
IL-1a	0,772	0,140	0,579	0,101	0,750	0,205	1,071	0,327	1,250	0,433	1,125	0,389
IL-1b	1,208	0,386	1,198	0,361	0,735	0,062	0,525	0,149	1,387	-	0,465	0,070
IL-2	0,750	0,076	0,804	0,103	0,928	0,226	0,978	0,125	0,546	-	1,455	-
IL-3	N/D		N/D		N/D		N/D		N/D		N/D	
IL-4	N/D		N/D		N/D		N/D		N/D		N/D	
IL-5	N/D		N/D		0,750	0,000	1,250	0,500	0,476	0,095	0,476	0,286
IL-6	0,144	0,011	0,167	0,056	1,350	0,150	0,900	0,000	0,800	0,267	0,978	0,470
IL-9	1,250	0,250	0,889	0,111	0,667	0,000	0,945	0,278	0,750	0,250	0,500	-
IL-10	N/D		N/D		1,115	0,366	0,847	0,191	0,667	0,273	0,404	-
IL-12 (p40)	N/D		N/D		N/D		N/D		N/D		N/D	
IL-12 (p70)	1,520	0,843	0,423	0,141	1,386	0,486	0,477	0,000	2,291	1,264	1,156	0,345
IL-13	1,018	0,296	0,718	0,131	1,091	0,105	0,909	0,065	0,788	0,290	0,575	0,084
IL-17	1,905	0,780	0,643	0,270	1,071	0,643	0,643	0,000	0,333	-	0,556	0,222
Eotaxin	N/D		N/D		N/D		N/D		N/D		N/D	
G-CSF	0,500	0,000	0,688	0,120	3,000	2,000	1,000	0,000	0,366	-	1,162	0,791
GM-CSF	1,282	0,303	1,016	0,071	0,989	0,033	0,935	0,042	1,062	0,122	0,943	0,035
ING-gamma	0,866	0,082	0,698	0,119	3,118	-	1,482	0,581	0,779	0,095	0,945	0,025
KC	0,885	0,128	0,695	0,320	0,826	0,242	0,776	0,064	0,558	0,315	0,781	0,439
MCP-1	0,921	0,020	0,927	0,091	0,919	0,029	0,740	0,048	0,619	0,095	0,582	0,018
MIP-1a	1,000	0,250	0,656	0,054	N/D		N/D		0,667	0,381	0,429	0,143
MIP-1b	0,956	0,163	1,014	0,330	0,801	0,082	0,852	0,048	2,652	0,967	1,605	0,310
Rantes	2,097	0,768	0,247	-	0,741	0,158	0,685	0,067	1,667	0,500	2,500	0,536
TNF-a	1,087	0,513	1,017	0,402	0,845	0,027	0,938	0,177	1,229	0,263	0,836	0,296

Supplementary Table 5

Complete blood count of wt and HD mice following systemic and chronic injection of hybrid g7-NPs-cholesterol ("2-cycle treatment", $N = 5-6$ /group). R.I.= reference intervals.

Statistics: Kruskal-Wallis followed by Mann-Whitney test.

Group	Mouse ID	Sex	RBC ($10^4/\mu\text{L}$)	HGB (g/L)	HCT ($10^{\wedge}(-1)\%$)	MCV ($10^{\wedge}(-1)\text{fL}$)	MCH ($10^{\wedge}(-1)\text{pg}$)	MCHC (g/L)	Erythrolysis	Anisocytosis
wt	4264	Male	5,76	7,7	27,2	47,2	13,4	28,3	+	
wt	4266	Male	7,68	10,7	36,4	47,4	13,9	29,4	n.o.	
wt	4267	Male	8,18	11,7	40,1	49	14,3	29,2	n.o.	
wt	4269	Female	8,84	12,4	41,7	47,2	14	29,7	n.o.	
wt	4271	Male	7,92	11,1	38	48	14	29,2	n.o.	
wt	4276	Female	8,11	11,2	37,9	46,7	13,8	29,6	n.o.	
zQ175DN	4268	Female	8,27	11,2	40,3	48,7	13,5	27,8	n.o.	
zQ175DN	4274	Female	8,51	11,2	39,3	46,2	13,2	28,5	n.o.	
zQ175DN	4277	Female	5,83	7,8	28,1	48,2	13,4	27,8	+	
zQ175DN	4278	Male	7,86	11	38,6	49,1	14	28,5	+	
zQ175DN	4279	Male	8,5	11,6	40,6	47,8	13,6	28,6	n.o.	
zQ175DN	4280	Male	8,69	12,1	42,2	48,6	13,9	28,7	+	slight
zQ175DN+chol	4389	Male	8,68	11,5	41,4	47,7	13,2	27,8	n.o.	
zQ175DN+chol	4390	Male	9,05	12,1	42,7	47,2	13,4	28,3	n.o.	
zQ175DN+chol	4391	Male	7,89	11	38,9	49,3	13,9	28,3	+	
zQ175DN+chol	4394	Female	9,18	12,2	41,8	45,5	13,3	29,2	+	
zQ175DN+chol	4411	Female	8,13	10,6	37,6	46,8	13	28	n.o.	

RI male	8.27-9.91	12.20-15.00	40.30-48.50
RI female	8.60-9.67	12.80-14.40	42.80-46.80

n.o.= not observed

Group	Mouse ID	Sex	PLT ($10^3/\mu\text{L}$)	PLT aggregates	RDW-CV ($10^{\wedge}(-1)\%$)	WBC ($10^3/\mu\text{L}$)	Neutrophils ($\times 10^3/\mu\text{L}$)	Lymphocytes ($\times 10^3/\mu\text{L}$)	Monocytes ($\times 10^3/\mu\text{L}$)	Eosinophils ($\times 10^3/\mu\text{L}$)	Epithelial cells
wt	4264	Male	437	+	16,2	4,45	0,49	3,56	0,40	0,00	n.o.
wt	4266	Male	268	+	19,2	8,16	0,24	7,83	0,08	0,00	n.o.
wt	4267	Male	407	+++	19,7	3,03	0,67	2,27	0,06	0,03	n.o.
wt	4269	Female	170	-/+	18,9	0,83	0,09	0,63	0,11	0,00	+
wt	4271	Male	129	-/+	19,1	3,36	0,60	2,65	0,10	0,00	n.o.
wt	4276	Female	189	+++	18,7	1,3	0,16	1,14	0,00	0,00	+
zQ175DN	4268	Female	197	-	19,9	3,96	0,71	3,17	0,08	0,00	n.o.
zQ175DN	4274	Female	198	++	19	2,27	0,32	1,93	0,02	0,00	n.o.
zQ175DN	4277	Female	203	+++	16,4	2,91	0,44	2,33	0,15	0,00	+
zQ175DN	4278	Male	157	+++	18,3	6,92	1,11	5,67	0,14	0,00	n.o.
zQ175DN	4279	Male	492	++	19,2	5,27	0,58	4,37	0,26	0,05	+
zQ175DN	4280	Male	184	n.o.	19,4	5,68	0,6248	4,9984	0	0,0568	+
zQ175DN+chol	4389	Male	1426	+	19,7	8,3	0,25	7,97	0,08	0,00	+
zQ175DN+chol	4390	Male	598	-/+	19,9	1,88	0,11	1,77	0,00	0,00	n.o.
zQ175DN+chol	4391	Male	885	+	20,4	11,11	0,33	10,55	0,22	0,00	+
zQ175DN+chol	4394	Female	651	++	21,7	1,2	0,00	1,15	0,05	0,00	+
zQ175DN+chol	4411	Female	260	-/+	19,7	9,62	1,84	7,50	0,48	0,00	+

418.00-1187.00
157.00-939.00

2.70-14.00
2.70-10.50

n.o.= not observed

Supplementary Table 6

Blood chemistry of wt and HD mice following systemic and chronic injection of hybrid g7-NPs-chole (“2-cycle treatment”, $N = 5-6/\text{group}$).
CBC = complete blood count; R.I.= reference intervals.

Statistics: Kruskal-Wallis followed by Mann-Whitney test.

Group	Mouse ID	Sex	Quantity of plasma (ul)	Severity of hemolysis	Cholesterol	Triglycerids	Albumin	Total proteins	Glucose	Creatinine	ALT	AST	
wt	4264	Male	120	+	2,09	0,80	15	39	5,27	2,59	11	28	
wt	4266	Male	135	+	1,99	0,88	26	45	8,72	4,28	21	36	
wt	4267	Male	250	++	2,07	1,35	28	53	8,60	4,22	42	86	
wt	4269	Female	190	++	1,78	1,13	27	49	10,66	5,23	45	83	
wt	4271	Male	160	++	2,22	1,07	27	48	9,55	3,62	44	96	
wt	4276	Female	150	++	1,68	1,03	34	46	10,05	4,93	63	107	
zQ175DN	4268	Female	180	+	2,04	0,60	32	48	12,93	6,35	50	87	
zQ175DN	4274	Female	65	++	2,15	0,99	28	38	5,16	2,53	39	84	
zQ175DN	4277	Female	whole sample used for CBC				insuff. sample						
zQ175DN	4278	Male	65	++	2,38	1,00	36	41	10,05	4,93	36	189	
zQ175DN	4279	Male	260	++	2,30	0,63	24	49	10,05	4,93	33	111	
zQ175DN	4280	Male	175	++	2,74	1,41	31	62	6,33	3,11	45	95	
zQ175DN+chol	4389	Male	260	+	2,28	0,70	42	54	13,32	6,54	37	99	
zQ175DN+chol	4390	Male	250	+	2,20	0,54	41	48	10,49	5,15	52	110	
zQ175DN+chol	4391	Male	175	+	1,89	0,86	insuff. sample	51	7,94	3,90	138	253	
zQ175DN+chol	4394	Female	450	+	1,71	0,51	47	51	9,49	4,66	36	73	
zQ175DN+chol	4411	Female	80	+	2,51	1,16	insuff. sample	45	9,10	4,47	45	187	

RI male	1.6-2.3	0.8-1.2	23-25	57-60	6.3-10.5	8.8-17.7	39-65	56-104
RI female	1.3-1.8	0.5-0.9	22-25	54-59	6.2-11.6	7.9-9.7	45-58	66-120

Supplementary Table 7

Body weight and weight of organs in grams of wt and HD mice following systemic and chronic injection of hybrid g7-NPs-chol ("2-cycle treatment", $N = 5-6/\text{group}$).

Statistics: Kruskal-Wallis followed by Mann-Whitney test.

Group	Mouse ID	Sex	Weight (g)							
			Body	Liver	Spleen	Left kidney	Right kidney	Heart	Left testis	Right testis
wt	4264	Male	28,7	1,680	0,107	0,348	0,773	0,215	0,083	0,090
wt	4266	Male	31,1	1,603	0,087	0,207	0,190	0,159	0,090	0,086
wt	4267	Male	32,2	1,715	0,096	0,226	0,220	0,205	0,093	0,087
wt	4269	Female	27,7	1,554	0,120	0,182	0,176	0,153	/	/
wt	4271	Male	36,4	1,910	0,092	0,238	0,235	0,243	0,102	0,113
wt	4276	Female	26,7	1,455	0,112	0,141	0,161	0,187	/	/
zQ175DN	4268	Female	22,3	1,087	0,117	0,126	0,140	0,136	/	/
zQ175DN	4274	Female	22,2	1,129	0,096	0,133	0,132	0,144	/	/
zQ175DN	4277	Female	22,8	1,168	0,113	0,141	0,142	0,130	/	/
zQ175DN	4278	Male	26,7	1,417	0,072	0,167	0,168	0,139	0,092	0,092
zQ175DN	4279	Male	29,3	1,542	0,083	0,171	0,182	0,144	0,100	0,108
zQ175DN	4280	Male	32,0	1,637	0,080	0,197	0,208	0,191	0,096	0,091
zQ175DN+chol	4389	Male	26,3	1,375	0,063	0,144	0,150	0,141	0,088	0,111
zQ175DN+chol	4390	Male	25,4	1,415	0,094	0,162	0,170	0,149	0,100	0,091
zQ175DN+chol	4391	Male	25,4	1,021	0,095	0,205	0,221	0,165	0,090	0,090
zQ175DN+chol	4394	Female	20,8	1,180	0,116	0,127	0,127	0,124	/	/
zQ175DN+chol	4411	Female	20,8	1,158	0,096	0,129	0,129	0,116	/	/

Supplementary Table 8

Summary of gross and histological lesions of wt and HD mice following systemic and chronic injection of hybrid g7-NPs-cholesterol ("2-cycle treatment", *N* = 5-6/group).

	wt	zQ175DN	zQ175DN+chol
Heart, myocardial mineralizations	1/6	2/6	0/5
Lung, perivascular/peribronchial lymphoplasmacytic infiltrate	6/6	4/6	5/5
Lung, acidophilic macrophage pneumonia	3/6	3/6	5/5
Testes, residual bodies	2/4	3/3	3/3
Uterus, cystic endometrial hyperplasia	2/2	3/3	2/2
Ovary, periovaric lymphocytic infiltrates	0/2	2/3	1/2
Liver, multifocal neutrophilic and lymphoplasmacytic infiltrate	6/6	5/6	4/5
Kidney, hydronephrosis	1/6	0/6	0/5
Kidney, polycystic	1/6	0/6	0/5
Kidney, peripelvic lymphoplasmacytic infiltrates	5/6	4/6	3/5
Kidney, interstitial lymphoplasmacytic infiltrates	3/6	1/6	0/5
Kidney, intratubular hyaline casts	1/6	4/6	2/5
Spleen, white pulp hyperplasia	5/6	6/6	4/5
Spleen, hemosiderosis	2/6	2/6	2/5
Spleen, extramedullary hematopoiesis	3/6	3/6	3/5
Salivary glands, lymphoplasmacytic infiltrates	5/6	6/6	5/5
Lymph nodes, hyperplasia	4/6	6/6	2/5
Lymph nodes, sinus histiocytosis	3/6	5/6	3/5

Supplementary Table 9

Foreign body granuloma analysis of HD mice following systemic and chronic injection of hybrid g7-NPs-chol for all the treatments.

Type of NPs	N° of IP injections	Weeks after the last IP	N° of nodules	Concretions diameter
g7-hybrid-NPs	10	20	1 (not in all mice)	1-2 mm
g7-hybrid-NPs	10	40	1-2 (not in all mice)	1-2 mm
g7-hybrid-NPs	10 + 10 (2 cycles)	20	5-6 (in all mice)	2-3 mm