

RAW Data for Figure 1:

Dendritic spine density:

Tg2576-wt	non-tg	ArcA β -wt	non-tg	E22 Δ A β -wt	non-tg	ArcA β -wt +DAPT	non-tg +DAPT
1	0.42	0.78	0.5	1.08	1.18	0.97	0.9
1.05	0.43	0.86	0.4	0.95	1.09	0.9	0.84
0.97	0.3	0.82	0.34	1.15	1.06	1.02	1.22
1.08	0.49	1.2	0.36	1.18	1.14	1.03	1.43
0.47	0.36	1	0.4	1.08	0.88	1	0.89
1.39	0.64	1.28	0.63	1.03	1.1	1.17	1.23
1.34	0.62	0.99	0.64	0.91	1.09	1.01	1.06
0.85	0.37	1.17	0.66	0.88	0.85	1.1	0.97
1.17	0.59	1.29	0.89	0.8	0.93	1.09	1
0.96	0.47	1.08	0.8	0.86	0.87	1.04	0.94
1.21	0.87		0.81	0.94	0.91		
1.24	0.79		0.66	0.79	0.77		

**Statistical analysis for Figure 1:
one-way ANOVA with Tukey's multiple comparison test
GraphPad Prism 7.01**

Sample comparison	Mean Diff.	Significant?	Summary	Adjusted P Value
Tg2576-non-tg vs. Tg2576-tg	0.532	Yes	****	<0.0001
Tg2576-non-tg vs. ArcA β -non-tg	0.0138	No	ns	>0.9999
Tg2576-non-tg vs. ArcA β -tg	0.47	Yes	****	<0.0001
Tg2576-non-tg vs. E22 Δ A β -non-tg	0.09	No	ns	0.9079
Tg2576-non-tg vs. E22 Δ A β -tg	0.0717	No	ns	0.9717
Tg2576-non-tg vs. ArcA β -non-tg + DAPT	0.0278	No	ns	>0.9999
Tg2576-non-tg vs. ArcA β -tg + DAPT	0.0128	No	ns	>0.9999
Tg2576-tg vs. ArcA β -non-tg	-0.518	Yes	****	<0.0001
Tg2576-tg vs. ArcA β -tg	-0.0617	No	ns	0.988
Tg2576-tg vs. E22 Δ A β -non-tg	-0.442	Yes	****	<0.0001
Tg2576-tg vs. E22 Δ A β -tg	-0.46	Yes	****	<0.0001
Tg2576-tg vs. ArcA β -non-tg + DAPT	-0.504	Yes	****	<0.0001
Tg2576-tg vs. ArcA β -tg + DAPT	-0.519	Yes	****	<0.0001
ArcA β -non-tg vs. ArcA β -tg	0.456	Yes	****	<0.0001
ArcA β -non-tg vs. E22 Δ A β -non-tg	0.0762	No	ns	0.9696
ArcA β -non-tg vs. E22 Δ A β -tg	0.0578	No	ns	0.9939
ArcA β -non-tg vs. ArcA β -non-tg + DAPT	0.014	No	ns	>0.9999
ArcA β -non-tg vs. ArcA β -tg + DAPT	-0.001	No	ns	>0.9999
ArcA β -tg vs. E22 Δ A β -non-tg	-0.38	Yes	****	<0.0001
ArcA β -tg vs. E22 Δ A β -tg	-0.398	Yes	****	<0.0001
ArcA β -tg vs. ArcA β -non-tg + DAPT	-0.442	Yes	****	<0.0001
ArcA β -tg vs. ArcA β -tg + DAPT	-0.457	Yes	****	<0.0001
E22 Δ A β -non-tg vs. E22 Δ A β -tg	-0.0183	No	ns	>0.9999
E22 Δ A β -non-tg vs. ArcA β -non-tg + DAPT	-0.0622	No	ns	0.9905
E22 Δ A β -non-tg vs. ArcA β -tg + DAPT	-0.0772	No	ns	0.9673
E22 Δ A β -tg vs. ArcA β -non-tg + DAPT	-0.0438	No	ns	0.9989
E22 Δ A β -tg vs. ArcA β -tg + DAPT	-0.0588	No	ns	0.9932
ArcA β -non-tg + DAPT vs. ArcA β -tg + DAPT	-0.015	No	ns	>0.9999

Tg2576-non-tg refers to the non-transgenic littermates of the Tg2576-tg mice.
ArcA β -non-tg refers to the non-transgenic littermates of the ArcA β -tg mice.
E22 Δ A β -non-tg refers to the non-transgenic littermates of the E22 Δ A β -tg mice.

RAW Data for Figure 2:

Dendritic spine density:

untreated	vehicle	wt A β 42	E22G A β 42	E22 Δ A β 42	wt A β 40	E22G A β 40	E22 Δ A β 42
1.27	0.8	0.66	0.38	1.3	0.72	0.89	1.23
1.02	1.23	0.41	0.41	0.71	0.85	0.85	0.83
1.29	1.19	0.79	0.64	1.07	0.94	0.89	0.97
1.09	1.1	0.92	0.77	0.99	1	0.89	1.05
1.15	1.12	0.56	0.65	1.26	0.84	0.83	0.76
1.1	0.92	0.35	0.46	1.03	0.94	1.11	1.32
1.19	1.02	0.82	0.31	1.24	0.96	0.94	0.86
1.15	1.19	0.68	0.73	1.3	0.91	0.91	0.9
1.02	1.02	0.79	0.31	1.21	0.89	0.66	1.16
0.99		0.85	0.87	0.88	1.07	0.69	0.87
1.17				1.33		1	1.18
1.09				1.39			1.17
				1.06			
				0.9			
				0.76			

**Statistical analysis for Figure 2:
one-way ANOVA with Tukey's multiple comparison test
GraphPad Prism 7.01**

Sample comparison	Mean Diff.	Significant?	Summary	Adjusted P Value
untreated vs. vehicle	0.0619	No	ns	0.9896
untreated vs. wt A β 42	0.445	Yes	****	<0.0001
untreated vs. E22GA β 42	0.575	Yes	****	<0.0001
untreated vs. E22 Δ A β 42	0.0322	No	ns	0.9996
untreated vs. wt 40	0.216	No	ns	0.0604
untreated vs. E22G40	0.249	Yes	*	0.0119
untreated vs. E22 Δ 40	0.103	No	ns	0.7964
vehicle vs. wt A β 42	0.383	Yes	****	<0.0001
vehicle vs. E22GA β 42	0.513	Yes	****	<0.0001
vehicle vs. E22 Δ A β 42	-0.0298	No	ns	0.9999
vehicle vs. wt 40	0.154	No	ns	0.4762
vehicle vs. E22G40	0.187	No	ns	0.203
vehicle vs. E22 Δ 40	0.0406	No	ns	0.9993
wt A β 42 vs. E22GA β 42	0.13	No	ns	0.6512
wt A β 42 vs. E22 Δ A β 42	-0.412	Yes	****	<0.0001
wt A β 42 vs. wt 40	-0.229	No	ns	0.0526
wt A β 42 vs. E22G40	-0.195	No	ns	0.1382
wt A β 42 vs. E22 Δ 40	-0.342	Yes	***	0.0002
E22GA β 42 vs. E22 Δ A β 42	-0.542	Yes	****	<0.0001
E22GA β 42 vs. wt 40	-0.359	Yes	***	0.0002
E22GA β 42 vs. E22G40	-0.325	Yes	***	0.0006
E22GA β 42 vs. E22 Δ 40	-0.472	Yes	****	<0.0001
E22 Δ A β 42 vs. wt 40	0.183	No	ns	0.1338
E22 Δ A β 42 vs. E22G40	0.217	Yes	*	0.0294
E22 Δ A β 42 vs. E22 Δ 40	0.0703	No	ns	0.9557
wt 40 vs. E22G40	0.0338	No	ns	0.9998
wt 40 vs. E22 Δ 40	-0.113	No	ns	0.7525
E22G40 vs. E22 Δ 40	-0.147	No	ns	0.4086

RAW Data for Figure 3:**A:****Cytotoy Assay (rel. Units):**

Tg2576-wt	non-tg	ArcA β -wt	non-tg	E22 Δ A β -wt	non-tg
21.00	45.00	27.36	30.62	29.98	36.16
23.00	48.00	27.36	39.91	30.87	40.57
15.00	38.00	26.71	29.96	28.22	36.16
19.00	39.00	24.75	31.27	22.93	20.28
26.00	36.00	24.75	31.27	23.81	22.05
28.00	38.00	25.40	31.92	22.93	21.17
23.00	40.00	24.10	31.92	17.64	14.99
26.00	38.00	23.45	32.57	18.52	17.64
30.00	44.00	24.10	31.92	30.87	35.28
32.00	40.00		39.08	29.10	44.10
29.00	36.00			28.22	39.69
32.00	37.00			22.05	24.69
				22.93	22.93
				22.93	23.81
				18.52	16.76
					17.64

B:**Cytotoy Assay:**

untreated	vehicle	wt A β 42	E22G A β 42	E22 Δ A β 42	wt A β 40	E22G A β 40	E22 Δ A β 42
18.20	20.01	26.20	26.36	20.32	23.46	24.99	14.79
19.32	19.20	27.11	25.92	18.00	23.46	17.34	13.26
22.33	21.69	26.79	24.00	22.96	21.93	25.50	20.40
21.05	22.33	27.43	21.85	19.77	23.46	24.48	18.36
18.43	19.28	27.85	25.28	21.00	15.81	20.40	19.89
18.00	18.85	28.28	25.71	21.43	17.85	21.93	18.87
18.85	21.00	25.71	27.42	24.00	22.44	20.40	20.91
19.28	20.14	24.85	26.14	21.43	21.42	19.38	22.95
21.43	22.28	26.14		24.00	20.40	13.26	23.46
21.43	21.85	26.57		23.14	17.85	14.79	24.48

C:

Cytotox Assay:

untreated	vehicle	wt A β 42	E22G A β 42	E22 Δ A β 42
16.0	18.0	18.0	17.0	17.0
17.0	20.0	18.0	16.0	20.0
20.8	17.6	15.1	16.4	17.0
17.0	15.8	16.4	18.3	17.0
17.0	17.0	15.8	18.3	18.9

D:

Western blot (rel. Units):

untreated	vehicle	wt A β 42	E22G A β 42	E22 Δ A β 42
0.10252457	0.09637935	0.5991973	0.3733438	0.09514805
0.08933795	0.22133976	0.24085441	0.25506339	0.08536898
0.09015963	0.0845228	0.48206893	0.43752766	0.07526084
0.06408804	0.06545653	0.26741373	0.23066941	0.05850462

**Statistical analysis for Figure 3:
one-way ANOVA with Tukey's multiple comparison test
GraphPad Prism 7.01**

A:

Sample comparison	Mean Diff.	Significant?	Summary	Adjusted P Value
Tg2576-non-tg vs. Tg2576-tg	-14.6	Yes	****	<0.0001
Tg2576-non-tg vs. ArcA β -non-tg	0.00111	No	ns	>0.9999
Tg2576-non-tg vs. ArcA β -tg	-7.71	Yes	*	0.0339
Tg2576-non-tg vs. E22 Δ -non-tg	0.699	No	ns	0.9996
Tg2576-non-tg vs. E22 Δ -tg	-1.79	No	ns	0.9666
Tg2576-tg vs. ArcA β -non-tg	14.6	Yes	****	<0.0001
Tg2576-tg vs. ArcA β -tg	6.87	No	ns	0.0792
Tg2576-tg vs. E22 Δ -non-tg	15.3	Yes	****	<0.0001
Tg2576-tg vs. E22 Δ -tg	12.8	Yes	****	<0.0001
ArcA β -non-tg vs. ArcA β -tg	-7.71	No	ns	0.0583
ArcA β -non-tg vs. E22 Δ -non-tg	0.698	No	ns	0.9997
ArcA β -non-tg vs. E22 Δ -tg	-1.79	No	ns	0.977
ArcA β -tg vs. E22 Δ -non-tg	8.41	Yes	**	0.0095
ArcA β -tg vs. E22 Δ -tg	5.93	No	ns	0.1341
E22 Δ -non-tg vs. E22 Δ -tg	-2.48	No	ns	0.8436

Tg2576-non-tg refers to the non-tragengenic littermates of the Tg2576-tg mice.

ArcA β -non-tg refers to the non-tragengenic littermates of the ArcA β -tg mice.

E22 Δ A β -non-tg refers to the non-tragengenic littermates of the E22 Δ A β -tg mice.

B:

Sample comparison	Mean Diff.	Significant?	Summary	Adjusted P Value
untreated vs. vehicle	-0.831	No	ns	0.9956
untreated vs. wt A β 42	-6.86	Yes	****	<0.0001
untreated vs. E22GA β 42	-5.5	Yes	***	0.0005
untreated vs. E22 Δ A β 42	-1.77	No	ns	0.7666
untreated vs. wt A β 40	-0.976	No	ns	0.9883
untreated vs. E22GA β 40	-0.415	No	ns	>0.9999
untreated vs. E22 Δ A β 40	0.095	No	ns	>0.9999
vehicle vs. wt A β 42	-6.03	Yes	****	<0.0001
vehicle vs. E22GA β 42	-4.67	Yes	**	0.0051
vehicle vs. E22 Δ A β 42	-0.942	No	ns	0.9905
vehicle vs. wt A β 40	-0.145	No	ns	>0.9999
vehicle vs. E22GA β 40	0.416	No	ns	>0.9999
vehicle vs. E22 Δ A β 40	0.926	No	ns	0.9914
wt A β 42 vs. E22GA β 42	1.36	No	ns	0.9471
wt A β 42 vs. E22 Δ A β 42	5.09	Yes	***	0.0007
wt A β 42 vs. wt A β 40	5.89	Yes	****	<0.0001
wt A β 42 vs. E22GA β 40	6.45	Yes	****	<0.0001
wt A β 42 vs. E22 Δ A β 40	6.96	Yes	****	<0.0001
E22GA β 42 vs. E22 Δ A β 42	3.73	No	ns	0.0516
E22GA β 42 vs. wt A β 40	4.53	Yes	**	0.0075
E22GA β 42 vs. E22GA β 40	5.09	Yes	**	0.0016
E22GA β 42 vs. E22 Δ A β 40	5.6	Yes	***	0.0004
E22 Δ A β 42 vs. wt A β 40	0.797	No	ns	0.9966
E22 Δ A β 42 vs. E22GA β 40	1.36	No	ns	0.9287
E22 Δ A β 42 vs. E22 Δ A β 40	1.87	No	ns	0.7164
wt A β 40 vs. E22GA β 40	0.561	No	ns	0.9996
wt A β 40 vs. E22 Δ A β 40	1.07	No	ns	0.98
E22GA β 40 vs. E22 Δ A β 40	0.51	No	ns	0.9998

C:

Sample comparison	Mean Diff.	Significant?	Summary	Adjusted P Value
untreated vs. vehicle	-0.118	No	ns	>0.9999
untreated vs. wt A β 42	0.912	No	ns	0.8572
untreated vs. E22GA β 42	0.378	No	ns	0.9936
untreated vs. E22 Δ A β 42	-0.422	No	ns	0.9903
vehicle vs. wt A β 42	1.03	No	ns	0.7959
vehicle vs. E22GA β 42	0.496	No	ns	0.9822
vehicle vs. E22 Δ A β 42	-0.304	No	ns	0.9972
wt A β 42 vs. E22GA β 42	-0.534	No	ns	0.9767
wt A β 42 vs. E22 Δ A β 42	-1.33	No	ns	0.6065
E22GA β 42 vs. E22 Δ A β 42	-0.8	No	ns	0.9054

D:

Sample comparison	Mean Diff.	Significant?	Summary	Adjusted P Value
untreated vs. vehicle	-0.0304	No	ns	0.9903
untreated vs. wt A β 42	-0.311	Yes	**	0.0025
untreated vs. E22GA β 42	-0.238	Yes	*	0.0209
untreated vs. E22 Δ A β 42	0.00796	No	ns	>0.9999
vehicle vs. wt A β 42	-0.28	Yes	**	0.0061
vehicle vs. E22GA β 42	-0.207	Yes	*	0.0495
vehicle vs. E22 Δ A β 42	0.0384	No	ns	0.9772
wt A β 42 vs. E22GA β 42	0.0732	No	ns	0.8073
wt A β 42 vs. E22 Δ A β 42	0.319	Yes	**	0.002
E22GA β 42 vs. E22 Δ A β 42	0.246	Yes	*	0.0166

RAW Data for S1Figure:

A:

Dendritic spine density:

wt A β 42	wt A β 40	E22G A β 42	E22G A β 40	E22 Δ A β 42	E22 Δ A β 42
0.66	0.72	0.38	0.89	1.3	1.23
0.41	0.85	0.41	0.85	0.71	0.83
0.79	0.94	0.64	0.89	1.07	0.97
0.92	1	0.77	0.89	0.99	1.05
0.56	0.84	0.65	0.83	1.26	0.76
0.35	0.94	0.46	1.11	1.03	1.32
0.82	0.96	0.31	0.94	1.24	0.86
0.68	0.91	0.73	0.91	1.3	0.9
0.79	0.89	0.31	0.66	1.21	1.16
0.85	1.07	0.87	0.69	0.88	0.87
			1	1.33	1.18
				1.39	1.17
				1.06	
				0.9	
				0.76	

B:

Cytotox Assay

wt A β 42	wt A β 40	E22G A β 42	E22G A β 40	E22 Δ A β 42	E22 Δ A β 42
26.2	23.46	26.36	24.99	20.32	14.79
27.11	23.46	25.92	17.34	18	13.26
26.79	21.93	24	25.5	22.96	20.4
27.43	23.46	21.85	24.48	19.77	18.36
27.85	15.81	25.28	20.4	21	19.89
28.28	17.85	25.71	21.93	21.43	18.87
25.71	22.44	27.42	20.4	24	20.91
24.85	21.42	26.14	19.38	21.43	22.95
26.14	20.4		13.26	24	23.46
26.57	17.85		14.79	23.14	24.48

**Statistical analysis for S1 Figure:
one-way ANOVA with Tukey's multiple comparison test
GraphPad Prism 7.01**

A:

Sample comparison	Mean Diff.	Significant?	Summary	Adjusted P Value
wt A β 42 vs. wt A β 40	-0.229	No	ns	0.0586
wt A β 42 vs. E22GA β 42	0.13	No	ns	0.58
wt A β 42 vs. E22GA β 40	-0.1952	No	ns	0.1369
wt A β 42 vs. E22 Δ A β 42	-0.4123	Yes	****	<0.0001
wt A β 42 vs. E22 Δ A β 40	-0.342	Yes	***	0.0004
wt A β 40 vs. E22GA β 42	0.359	Yes	***	0.0004
wt A β 40 vs. E22GA β 40	0.03382	No	ns	0.9979
wt A β 40 vs. E22 Δ A β 42	-0.1833	No	ns	0.1331
wt A β 40 vs. E22 Δ A β 40	-0.113	No	ns	0.6762
E22GA β 42 vs. E22GA β 40	-0.3252	Yes	**	0.0012
E22GA β 42 vs. E22 Δ A β 42	-0.5423	Yes	****	<0.0001
E22GA β 42 vs. E22 Δ A β 40	-0.472	Yes	****	<0.0001
E22GA β 40 vs. E22 Δ A β 42	-0.2172	Yes	*	0.0354
E22GA β 40 vs. E22 Δ A β 40	-0.1468	No	ns	0.3674
E22 Δ A β 42 vs. E22 Δ A β 40	0.07033	No	ns	0.9093

B:

Sample comparison	Mean Diff.	Significant?	Summary	Adjusted P Value
wt A β 42 vs. wt A β 40	5.885	Yes	***	0.0003
wt A β 42 vs. E22GA β 42	1.358	No	ns	0.9086
wt A β 42 vs. E22GA β 40	6.446	Yes	****	<0.0001
wt A β 42 vs. E22 Δ A β 42	5.088	Yes	**	0.0022
wt A β 42 vs. E22 Δ A β 40	6.956	Yes	****	<0.0001
wt A β 40 vs. E22GA β 42	-4.527	Yes	*	0.0153
wt A β 40 vs. E22GA β 40	0.561	No	ns	0.9976
wt A β 40 vs. E22 Δ A β 42	-0.797	No	ns	0.9877
wt A β 40 vs. E22 Δ A β 40	1.071	No	ns	0.9554
E22GA β 42 vs. E22GA β 40	5.088	Yes	**	0.0045
E22GA β 42 vs. E22 Δ A β 42	3.73	No	ns	0.0724
E22GA β 42 vs. E22 Δ A β 40	5.598	Yes	**	0.0014
E22GA β 40 vs. E22 Δ A β 42	-1.358	No	ns	0.8857
E22GA β 40 vs. E22 Δ A β 40	0.51	No	ns	0.9985
E22 Δ A β 42 vs. E22 Δ A β 40	1.868	No	ns	0.6717