**Supplementary Materials** 

Deregulation of mitochondrial reverse electron transport alters the metabolism of reactive oxygen species and NAD<sup>+</sup>/NADH and presents a therapeutic target in Alzheimer's disease

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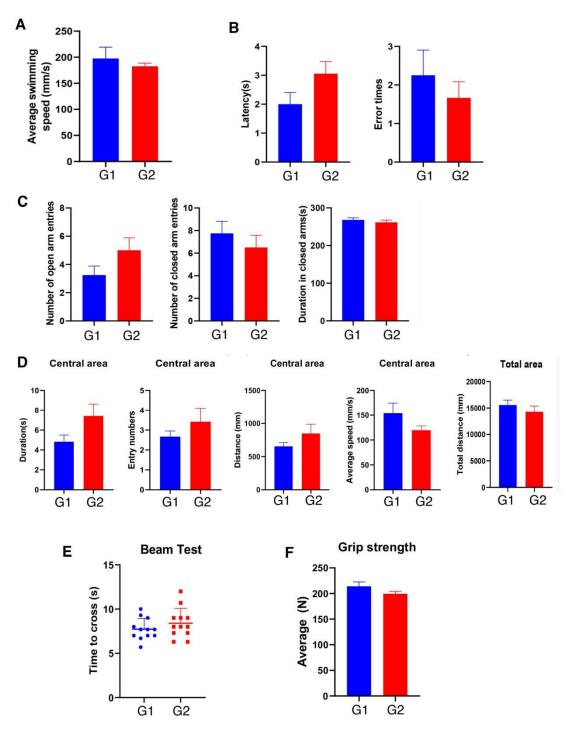
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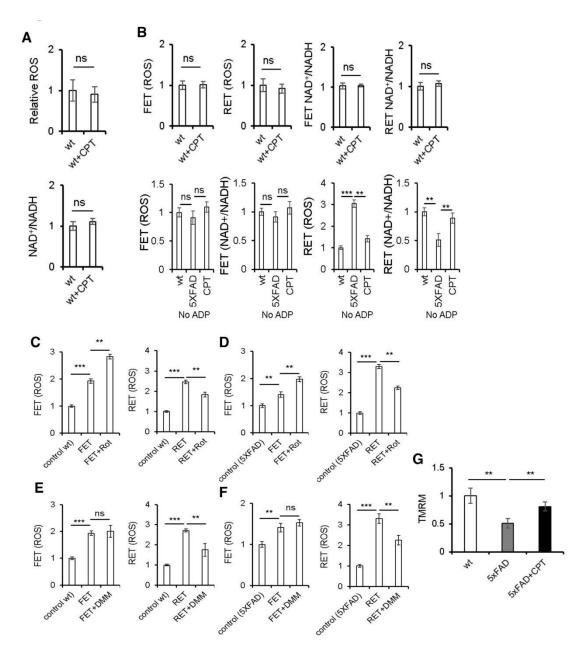
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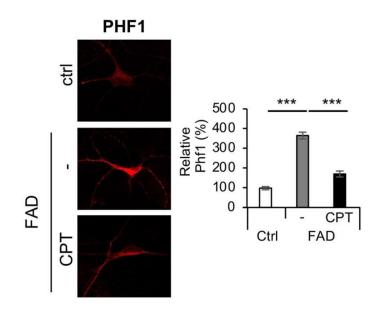
# **Supplementary Figures**



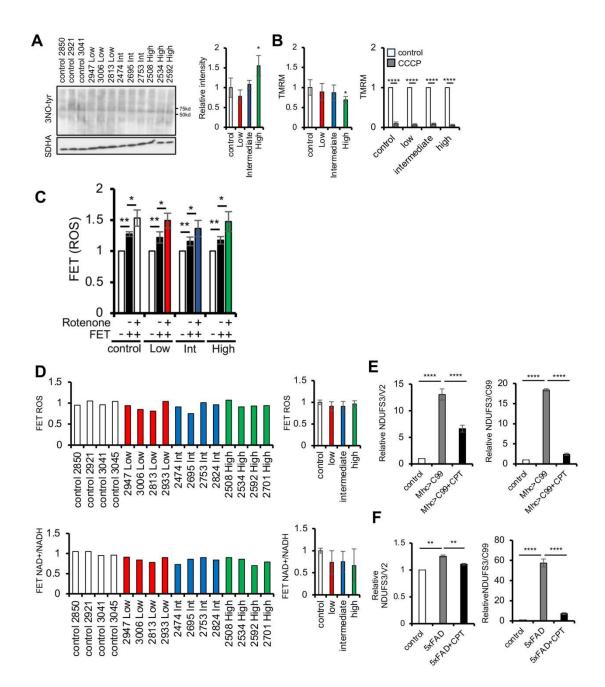
**Supplementary Figure 1.** 



Supplementary Figure 2.



Supplementary Figure 3.



**Supplementary Figure 4.** 

# Supplementary Tables

# Supplementary Table 1

Case	ADNC level	Sex	Age at	Clinical	Primary	Comorb	PMI (hrs)	Frozen	Frozen	Frozen	
P#			death		Neuropath	id		Block	Block	Block	
					Dx			Label	Side	Region	
P2850	Not	F	92	Control	None	AGD, limbic	8.0	Z6	L	ITG	
P2921	Not	F	82	Control	None	limbic			R	Superior parietal cortex	
P3041	Not	F	78	Control	None		11.6	Z15	Ľ,	Superior parietal cortex	
P3045	Not	F	84	Control	None	7.7		Z8 L		Superior parietal cortex	
P2947	Low	м	95	Control	None		9.6	Z3	L	ITG	
P3006	Low	М	91	Control	None		5.6	Z2	L	ITG	
P2813	Low	м	87	AD,Vascular	AD		30.5	Z2	L	ITG	
P2933	Low	М	87	MCI	ADNC, low		9.7	Z2	L	ITG	
P2474	Intermediate	F	87	MCI	AD,Braak IV	VBI	9.5	X7	L	ITG	
P2695	Intermediate	М	84		AD		28	Z3	L	ITG	
P2753	Intermediate	F	94	AD	AD		14.8	Z1	R	ITG	
P2824	Intermediate	М	89	MCI,Mixed	AD		9.1	Z2	L	ITG	
P2508	High	М	82	AD	AD		6.7	Z7	R	ITG	
P2534	High	F	75	AD	AD		6.9	Z7	R	ITG	
P2592	High	М	86	AD	AD		8.6	Z3	L	ITG	
P2701	High	F	76	AD	AD		18	Z1	L	ITG	

Μ	atrix	Р	lasma	Bra	nin					
Administ	ration Route	IV	РО	IV	РО					
Parameters	Unit	Values								
Dose Level	mg/kg	2	10	2	10					
$T_{1/2}$	h	4.22	3.33	6.98	3.33					
T <sub>max</sub>	h	0.25	2.00	0.08	1.00					
$\mathbf{C}_{\max}$	ng/mL, ng/g	1484.90	1611.23	1250.89	763.17					
Co	ng/mL, ng/g	1473.32	NA	1295.22	NA					
AUC <sub>(0-t)</sub>	h*ng/mL, h*ng/g	3056.62	14450.15	3680.33	7171.71					
AUC <sub>(0-∞</sub> )	h*ng/mL, h*ng/g	3085.50	14542.32	3870.56	7218.07					
MRT <sub>(0-t)</sub>	h	2.96	5.44	3.96	5.62					
$MRT_{(0-\infty)}$	h	3.21	5.59	5.44	5.77					
$V_{ss}$	mL/kg	2081.80	NA	2808.96	NA					
Vz	mL/kg	3942.86	NA	5206.47	NA					
Cl	mL/h/kg	648.19	NA	516.72	NA					
F	%	NA	94.55	NA	38.97					

### Supplementary Table 2 PK parameters of CPT in rats after IV and PO administration

NA: not applicable

# Supplementary Table 3

			CPT(M3) PO Plasm	na Pharmaco	kinetic Prof	ile in APP/PS1 mice		
O(G2) Plasma concent	ration time data							
PO(G2) Flasma concenti PO(G2) I								
Time			Concentration (ng/mL)		1	Mean	SD	CV
								(%)
(h)	Mous		Mouse 13 Mouse 1		Mouse 22	(ng/mL)	(ng/mL)	
	336		29100 38500		36400	32967	4075	12.4
			CPT(M3) PO Liver F	harmacokin	etic Profile i	n male APP/PS1 mice		
(G2) Liver concentrat								
PO(G2)								
Time			Concentration (ng/g)			Mean	SD	CV
(h)	Mous 642		Mouse 13 Mouse 1 68400 73200		Mouse 22 61200	(ng/g) 68300	(ng/g) 5223	(%)
	042	00 07800	00400 73200	75000	01200	08300	3223	7.05
				Liver/Plasma	Ratio Profi	e		
(G2) Dose				Erronn hushin	a reactor rom			
(G2) Dose Time			Liver/Plasma Ratio Profi	le				CV
(h)	Mous	se 8 Mouse 9	Mouse 13 Mouse 1		Mouse 22	Mean	SD	
(14)	1.9		2.35 1.90	2.68	1.68	2.10	0.36	(%) 17.1
						in male APP/PS1 mice	1	
(G2) Kidney concentr	ration time data							
PO(G2)								
Time			Concentration (ng/g)		1	Mean	SD	CV
(h)	Mous		Mouse 13 Mouse 1		Mouse 22	(ng/g)	(ng/g)	(%)
	276	600 22560	29520 25980	26220	28020	26650	2382	8.94
			ł	Kidney/Plasm	a Ratio Prof	file		
(G2) Dose								
Time			Kidney/Plasma Ratio Pro			Mean	SD	CV
(h)	Mous		Mouse 13 Mouse 1	17 Mouse 18	Mouse 22			(%) 16.3
00000	0.8	21 0.701	1.01 0.675		0.770	0.82	0.13	16.3
			PO Heart Phan	macokinetic	Profile in ma	ale APP/PS1 mice		
O(G2) Heart concentrat	tion-time data							
PO(G2)	Dose							
Time			Concentration (ng/g)			Mean	SD	CV
(h)	Mous		Mouse 13 Mouse 1	17 Mouse 18	Mouse 22	(ng/g)	(ng/g)	(%)
	168	300 18120	25800 18660		22140	20700	3407	16.5
				Heart/Plasma	a Ratio Profi	le		
(G2) Dose							50 - 24-	
Time			Heart/Plasma Ratio Profi		100 000	Mean	SD	CV
(h)	Mous 0.50	se 8 Mouse 9 00 0.563	Mouse 13 Mouse 1 0.887 0.485		Mouse 22 0.608	0.642	0.168	(%) 26.1
	0.50	JU 0.505				ale APP/PS1 mice	0.100	20.1
			PO Lung Phan	macokinetic	Profile in ma	lie APP/PS1 mice		
D(G2) Lung concentrat								
PO(G2) I Time	Jose		Concentration (ng/g)			Mean	SD	CV
(h)	Mous	se 8 Mouse 9	Mouse 13 Mouse 1	17 Mouse 18	Mouse 22			
(n)	132		9420 25860		13260	(ng/g) 14550	(ng/g) 5737	(%) 39.4
	132	12240		Lung/Plasma			0.01	30.4
V(00) Deer				Eurig/1 lasing	a Ratio From	16		
D(G2) Dose Time			Lung/Plasma Ratio Profi	6				CV
(h)	Mous	se 8 Mouse 9	Mouse 13 Mouse 1		Mouse 22	Mean	SD	
(1)	0.3		0.324 0.672			0.435	0.126	(%) 29.1
	1 0.00	0.000			Profile in m	ale APP/PS1 mice		
D(G2) uterus concentr	ration-time data							
PO(G2) uterus concentr PO(G2) I								
Time			Concentration (ng/g)			Mean	SD	CV
(h)	Mous	se 8 Mouse 9	Mouse 13 Mouse	17 Mouse 18	Mouse 22	(ng/g)	(ng/g)	
	212		14300 21000	19800	17000	17633	3650	(%) 20.7
				<b>Jterus</b> /Plasm	- Detis Desi	file		
			ι	Jterus /Plasn	ha Ratio Pro			
			ı	Jterus /Plash	ha Ratio Pro			
			Uterus /Plasma Ratio Pro	file	na Katio Pro		sp.	CV
(G2) Dose	Mous		Uterus /Plasma Ratio Pro Mouse 13 Mouse 1	file 17 Mouse 18	Mouse 22	Mean	SD	(%)
(G2) Dose Time			Uterus /Plasma Ratio Pro Mouse 13 Mouse 1 0.491 0.545	file 17 Mouse 18 0.707	Mouse 22 0.467	<b>Mean</b> 0.538	SD 0.116	
(G2) Dose Time	Mous		Uterus /Plasma Ratio Pro Mouse 13 Mouse 1 0.491 0.545	file 17 Mouse 18 0.707	Mouse 22 0.467	Mean		(%)
(G2) Dose Time (h)	Mous 0.6		Uterus /Plasma Ratio Pro Mouse 13 Mouse 1 0.491 0.545	file 17 Mouse 18 0.707	Mouse 22 0.467	<b>Mean</b> 0.538		(%)
Y(G2) Dose Time (h)	Mous 0.63		Uterus /Plasma Ratio Pro Mouse 13 Mouse 1 0.491 0.545 PO Brain Phar	file 17 Mouse 18 0.707	Mouse 22 0.467	<b>Mean</b> 0.538		(%)
2(G2) Dose Time (h) D(G2) Brain concentral PO(G2) I Time	tion-time data	31 0.388	Uterus /Plasma Ratio Pro Mouse 13 Mouse 1 0.491 0.545 PO Brain Phan Concentration (ng/g)	file 17 Mouse 18 0.707 macokinetic	Mouse 22 0.467 Profile in ma	Mean 0.538 ale APP/PS1 mice Mean		(%) 21.5
D(G2) Dose Time (h) D(G2) Brain concentrat PO(G2) I	e Mous 0.6 tion-time data Dose S Mous	31 0.388 se 8 Mouse 9	Uterus /Plasma Ratio Pro Mouse 13 Mouse 1 0.491 0.545 PO Brain Phar Concentration (ng/g) Mouse 13 Mouse 1	file 17 Mouse 18 0.707 macokinetic 17 Mouse 18	Mouse 22 0.467 Profile in ma Mouse 22	Mean 0.538 ale APP/PS1 mice Mean	0.116 SD (ng/g)	(%) 21.5
2(G2) Dose Time (h) D(G2) Brain concentral PO(G2) I Time	tion-time data	31 0.388 se 8 Mouse 9	Uterus /Plasma Ratio Pro Mouse 13 Mouse 1 0.491 0.545 PO Brain Phan Concentration (ng/g)	file 17 Mouse 18 0.707 macokinetic 17 Mouse 18	Mouse 22 0.467 Profile in ma	Mean 0.538 ale APP/PS1 mice	0.116	(%) 21.5
V(G2) Dose Time (h) D(G2) Brain concentrat PO(G2) I Time	e Mous 0.6 tion-time data Dose S Mous	31 0.388 se 8 Mouse 9	Uterus /Plasma Ratio Pro       Mouse 13     Mouse 1       0.491     0.545       PO Brain Phar       Concentration (ng/g)       Mouse 13     Mouse 1       27240     17880	file 17 Mouse 18 0.707 macokinetic 17 Mouse 18 17700	Mouse 22 0.467 Profile in ma Mouse 22 16920	Mean 0.538 ale APP/PS1 mice Mean (ng/g) 19480	0.116 SD (ng/g)	(%) 21.5
V(G2) Dose Time (h) D(G2) Brain concentrat PO(G2) I Time	e Mous 0.6 tion-time data Dose S Mous	31 0.388 se 8 Mouse 9	Uterus /Plasma Ratio Pro       Mouse 13     Mouse 1       0.491     0.545       PO Brain Phar       Concentration (ng/g)       Mouse 13     Mouse 1       27240     17880	file 17 Mouse 18 0.707 macokinetic 17 Mouse 18	Mouse 22 0.467 Profile in ma Mouse 22 16920	Mean 0.538 ale APP/PS1 mice Mean (ng/g) 19480	0.116 SD (ng/g)	(%) 21.5
(G2) Dose Time (h) 2(G2) Brain concentrat PO(G2) I Time (h) (G2) Dose	Mous 0.63 bose Mous 177 100	31 0.388 se 8 Mouse 9	Uterus /Plasma Ratio Pro       Mouse 13     Mouse 1       0.491     0.545       PO Brain Phan       Concentration (ng/g)       Mouse 13     Mouse 1       27240     17880	file 17 Mouse 18 0.707 macokinetic 17 Mouse 18 17700 Brain/Plasma	Mouse 22 0.467 Profile in ma Mouse 22 16920	Mean       0.538       ale APP/PS1 mice       (ng/g)       19480	0.116 SD (ng/g) 3890	(%) 21.5 CV (%) 20.0
X(G2) Dose Time (h) D(G2) Brain concentrat PO(G2) L Time (h) X(G2) Dose Time	Mous O.6 tion-time data Dose Mous 100	31 0.388 se 8 Mouse 9 00 19440 mg/kg	Uterus /Plasma Ratio Proi Nouse 13 Mouse 1 0.491 0.545 PO Brain Phar Concentration (ng/g) Mouse 13 Mouse 27240 17880 Brain/Plasma Ratio Profi	file 17 Mouse 18 0.707 macokinetic 17 Mouse 18 17700 Brain/Plasma Ie	Mouse 22 0.467 Profile in ma Mouse 22 16920 a Ratio Profi	Mean 0.538 ale APP/PS1 mice Mean (ng/g) 19480	0.116 SD (ng/g)	(%) 21.5 CV (%) 20.0 CV
(G2) Dose Time (h) D(G2) Brain concentrat PO(G2) I Time (h) X(G2) Dose	Mous 0.63 bose Mous 177 100	31 0.388 se 8 Mouse 9 000 19440 mg/kg se 8 Mouse 9	Uterus /Plasma Ratio Pro       Mouse 13     Mouse 1       0.491     0.545       PO Brain Phan       Concentration (ng/g)       Mouse 13     Mouse 1       27240     17880	file 17 Mouse 18 0.707 macokinetic 17 Mouse 18 17700 Brain/Plasma Ie	Mouse 22 0.467 Profile in ma Mouse 22 16920	Mean       0.538       ale APP/PS1 mice       (ng/g)       19480	0.116 SD (ng/g) 3890	(%) 21.5 CV (%) 20.0

# Supplementary Table 4

		01-1	6-63						61-2 61-2							Group								
APP/PS1 mice + CPT (W)								APP/PS1 mice + Vehicle											Treatment					
35	30	29	28	26	24	22	18	17	13	9	8	36	34	33	32	27	25	19	15	14	12	6	3	Ð
I	1	1	I	1	1	T	I	I	I	1	I	1	I	t	I	L	I	I	I	1	t.	I	1	Brain
ï	I	Î	I	ĩ	ĩ	L	I	I	)	I	I	I	I	I	I	L	I	I	I	J	Ĺ	1	1	Spine
1	1	1	1	I	1	I	I	1	I	1	1	1	1	I	1	I	I	1	I	1	L	1	1	Thymus gland
1	I	1	1	I	I	I	ï	ī	I	I	I	I	I	I	1	T	I	1	1	I	L	I	I	Thymus gland Thyroid gland Esophagus Stomach
ī	1	Ĩ.	1	T,	Ĩ	L	ī	1	1	I	I	ī	I	L	1	Ľ	I	1	1	I	Ē	1	I	Esophagus
1	I	I	I	L	1	T	I	1	I	I	T	1	I	t	1	L	I	I	I	1	t	1	1	Stomach
1	I.	I	1	L	intestinal tympanites	I	I	intestinal tympanites	ī	I	1	I	I	I	intestinal tympanites	ī	ī	I	I	1	Ĺ	ī	intestinal tympanites	Intestine
1	I	1	1	I.	1	1	1	I	I	I	1	I	1	I.	1	T.	1	I	I	T	I,	1	I	Liver and pancreas
1	1	1	1	1	1	1	1	1	1	1	1	1	1	T	1	ı	1	1	1	1	ı	1	1	Kidneys
1	I	Ĭ.	T	L	1	I.	1	1	1	I	I	1	I	I.	1	I,	1	1	I.	1	Ľ,	j.	I	Spleen
1	1	ï	1	L	i	1	I	1	I	1	I	1	I	I	1	L	ī	1	I	1	1	1	1	Heart
1	I	1	1	1	J	1	I	1	Ţ	1	T	1	I	t	1	T	1	1	T	1	t	1	1	Trachea
ï	T	ĩ	1	ĩ	ï	I	ï	1		ı	1	I	I	t	1	I.	I	1	I	1	Ĺ	1	T	Lung
1	hydrometra	1	ı	hydrometra	1	1	I	ı	uterine length abn-ormal	ı	ı	1	ı	<u>I</u>	1	ı	ı	ı	I	1	Ę	1	1	Uterus
I	1	ī	1	ī	I	1	ï	1		I	I	ī	I	¢	1	ı	ı	1	ī	1	î,	1	1	Ovary
1	T	I	1	I,	I	1	I	1	ļ	1	I	1	1	I	1	Ľ	1	I	I	1	I.	1	1	Mammary glands

Note: "---" means the organs were normal by visual observation.