IDENTIFICATION OF NEW PHARMACODYNAMIC BIOMARKERS OF CT1812 THAT CORRELATE WITH FAVORABLE FUNCTIONAL CONNECTIVITY OF THE BRAIN

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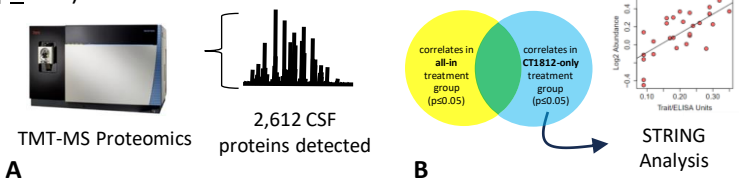
INTRODUCTION

Synaptic function and brain functional connectivity is impaired in Alzheimer's disease (AD). Recently, in the SEQUEL phase 2 clinical trial (NCT04735536) in AD patients, we have shown that our drug candidate, CT1812, can favorably impact the functional connectivity as measured by the quantitative EEG measure Amplitude Envelope Correction (AECc p=0.034)[1]. To identify synaptic markers of CT1812 associated with this favorable change, we performed Pearson correlation analyses between multiple EEG parameters and the CSF proteome from SEQUEL.

METHODS

Participants (n=16) received 29 days of either CT1812 (300 mg, PO, qD) or placebo following a two-week washout, then switched treatment for another 29 days period. TMT mass spectrometry proteomics was performed on CSF at baseline and after both treatment periods. Previous correlation analyses were performed to identify molecular correlates of theta and alpha wave power and functional connectivity irrespective of treatment[2]. Here to identify CT1812-driven correlates that may be pharmacodynamic biomarkers of CT1812 linked to EEG parameters, we performed Pearson correlation analyses on change from baseline values across multiple EEG parameters and each protein in the CSF proteome ($p \leq 0.05$) from CT1812 treated only patients. Comparative analyses were performed across EEG parameters followed by pathway analysis using STRING ($p \leq 0.05$).



Schema 1. (A) Following CSF sample analysis via TMT-proteomics (B) Pearson correlation analyses were performed between multiple AECc parameters and each protein in the CSF proteome . Proteins determined to be correlates only in the CT1812-treated group (outer portion of blue circle) were subject to pathway analyses.

RESULTS

Sets of Proteins and Biological Processes Associated with Global Alpha AECc

A

Gene	Prot ID	p value	cor	Gene	Prot ID	p value	cor
HBG1	P69891	1.71E-03	0.88	**PIK3IP1**	Q96FE7	2.35E-04	-0.83
SLC4A1	P02730	2.70E-03	0.86	**MALRD1**	Q5VYJ5	9.07E-03	-0.77
ALDH1A1	P00352	7.04E-04	0.79	BTN2A2	Q8WVV5	1.28E-03	-0.77
MATN2	O00339	1.37E-03	0.77	BAMBI	Q13145	2.73E-03	-0.74
NDRG1	Q92597	1.65E-02	0.76	METRNL	Q641Q3	2.93E-03	-0.73

B

term ID	term description	strength	p value
GO:0005584	Collagen type I trimer	2.25	2.19E-02
GO:0019773	Proteasome core complex, alpha-subunit complex	1.83	5.00E-03
GO:0005583	Fibrillar collagen trimer	1.65	1.06E-02
GO:0005839	Proteasome core complex	1.55	2.20E-03
GO:0005788	Endoplasmic reticulum lumen	0.66	4.50E-02
GO:0034774	Secretory granule lumen	0.65	4.89E-02
GO:0031012	Extracellular matrix	0.63	3.50E-03
GO:0062023	Collagen-containing extracellular matrix	0.6	4.89E-02
GO:0070062	Extracellular exosome	0.53	7.87E-10

Fig 1. (A) Topmost directly (red) and inversely (blue) CSF proteins correlated to global alpha AECc are listed ($p \leq 0.05$). In bold are proteins associated with AD phenotype. B) STRING pathway analysis to identify top biological processes associated to global alpha AECc was performed for a list of 160 proteins ($p \leq 0.05$) correlated only in the CT1812-treated group. GO terms sorted by strength.

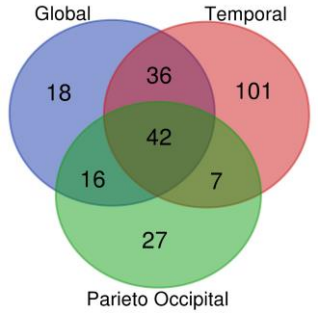
CONCLUSION

Potential CT1812 molecular correlates to parameters of brain activity as assessed via EEG and may be surrogate candidate biomarkers of an impact of CT1812 on brain activity were identify

These findings may support the clinical development of therapeutics that impact functional connectivity or synaptic activity.

Proteins Commonly Associated Across Multiple alpha AECc Parameters

A



B

ALDH1A1	HIBADH	**PRDX2**
ALDH9A1	JAM2	PRG2
BAMBI	LRRN1	**PSMA1**
BTN2A2	LYPLA1	PSMA4
CHST7	MATN2	PSMA6
COL1A2	METRNL	**PSMB7**
EIF4B	NHLRC3	SECTM1
FAHD1	NOTCH1	SLC4A1
FZD3	NTM	SLIT3
FZD6	OAF	SNX12
GAS1	PCDH9	ST6GAL2
GRIA3	PGLS	TKT
GXYLT1	PIK3IP1	UBE2N
HBG1	PNP	**WNT4**

C

term ID	term description	strength	p value
GO:0005615	Extracellular space	0.44	2.60E-03
GO:0019773	Proteasome core complex, alpha-subunit complex	2.25	4.30E-04
GO:0070062	Extracellular exosome	0.58	4.30E-04
GO:0031982	Vesicle	0.44	4.30E-04
GO:0005576	Extracellular region	0.43	4.30E-04
GO:0005839	Proteasome core complex	1.97	3.70E-04

Fig 2. Venn diagram (A) and list of 42 (B) commonly correlated proteins across global, temporal and parieto-occipital alpha AECc ($p \leq 0.05$). (C) STRING Pathway analysis indicated an impact on proteasomal (PSMA, PSMB), extracellular exosomal (WNT4, ALDH1A1) and vesicular (PRDX2) biologies.

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