Combination anti-semaphorin4D immunotherapy and ASO-mediated total HTT lowering provide benefit beyond either individual therapy in humanized HD mice

Yuanyun Xie[1], Nalini Potluri[1], Vikas Mishra[2], Terrence Fisher[2], Morgan Rook[1], Casey Hart[1], Renee Ouellette[1], Kadambari Vyas[1], Ratnesh Kesineni[1], Maurice Zauderer[2], Elizabeth E Evans[2], Amber L Southwell[1]

[1]Burnett School of Biomedical Sciences, University of Central Florida, Orlando, FL.; [2]Vaccinex Inc., Rochester, NY.

ABSTRACT

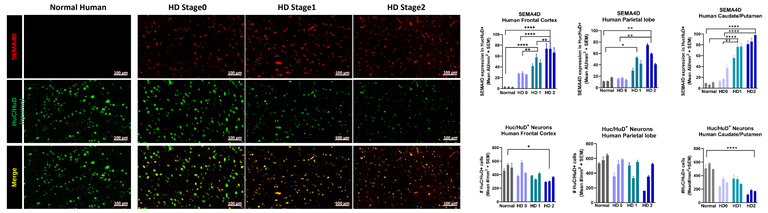
Genetic inactivation of mutant huntingtin (HTT) in symptomatic mice allows not only halting of neuropathological changes, but also some recovery from atrophy. However, therapeutic HTT lowering, particularly of both mutant and wild-type HTT, is likely to be less robust than this proof of concept and may not repair substantial damage to neurons and support cells that has occurred prior to treatment. These potential limitations suggest that combining HTT lowering with independent strategies to promote health and recovery of the damaged brain could provide more comprehensive benefit.

Anti-semaphorin4D (SEMA4D) immunotherapy has potential for combination therapy, as its target SEMA4D is elevated in brains of HD patients, and its proposed mechanisms may prevent loss of protective glial functions and restore vascular changes associated with neuronal dysfunction and degeneration in HD. The SIGNAL trial (NCT02481674) of anti-SEMA4D immunotherapy (pepinemab) did not meet its primary efficacy endpoints, however pre-specified exploratory assessments demonstrated significant benefit to the HD cognitive assessment battery composite score and caudate atrophy in individuals with early manifest disease. Similarly, we have previously demonstrated preclinical benefit of an anti-SEMA4D antibody (MAB67) in YAC128 HD mice (Southwell et al, Neurobiol Dis. 2015; 76:46–56), preventing white matter loss and some cognitive deficits, while positive trends were observed in grey matter loss and anxiety-like behavior that failed to reach statistical significance.

To evaluate the potential of anti-SEMA4D immunotherapy and HTT lowering combination therapy, Hu97/18 HD mice were treated with a total HTT lowering ASO at 6 weeks of age followed by weekly MAB67 treatment until 12 months of age. Consistent with previous studies, individual treatments prevented some cognitive deficits, while combination therapy also prevented anxiety-like behavior and hypoactivity, suggesting benefit beyond either therapy alone. Our findings support the potential use of combination anti-SEMA4D immunotherapy and HTT lowering for the treatment of HD.

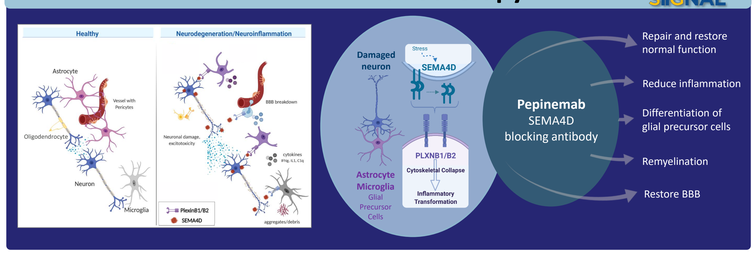
BACKGROUND

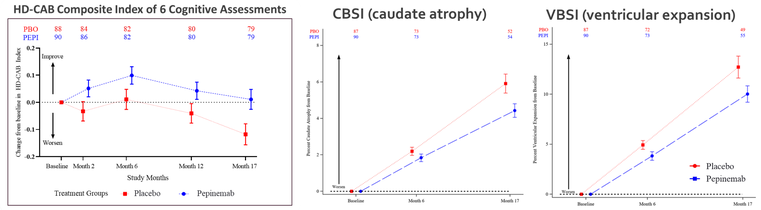
SEMA4D is progressively elevated in Human HD brain



Unpublished data. Evans et al. submitted manuscript under consideration.

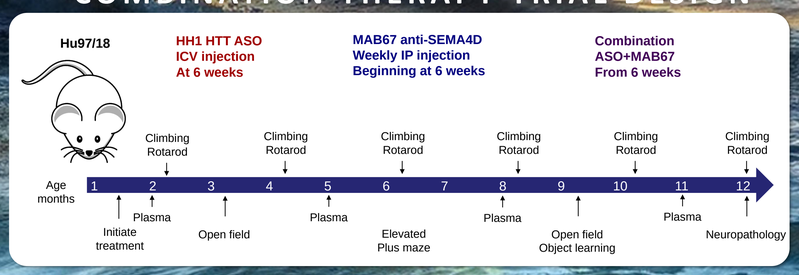
Anti-SEMA4D immunotherapy in HD





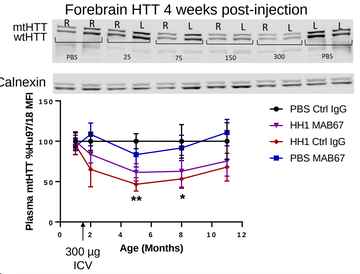
Unpublished data. Feigin et al submitted manuscript under consideration.

COMBINATION THERAPY TRIAL DESIGN

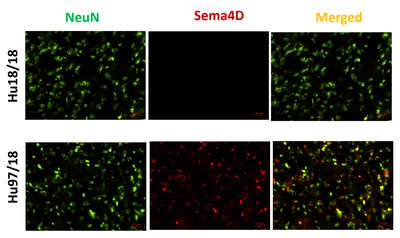


TARGETS AND ENGAGEMENT

HH1 ASO suppresses HTT



SEMA4D in Hu97/18 striatum



MOTOR BEHAVIOR

ASO and Combination therapy improves bodyweight in females

ASO and combination therapy improves motor performance

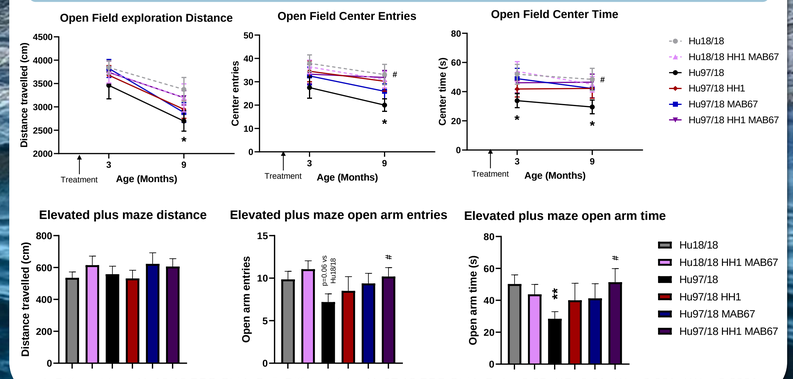
COGNITIVE BEHAVIOR

Individual and combination therapy prevents cognitive deficits

*=Difference between trial 1 and trial 2, #=Different from Hu97/18 PBS Ctrl IgG trial 2; *p<0.05, **P<0.01, ***p<0.001

PSYCHIATRIC BEHAVIOR

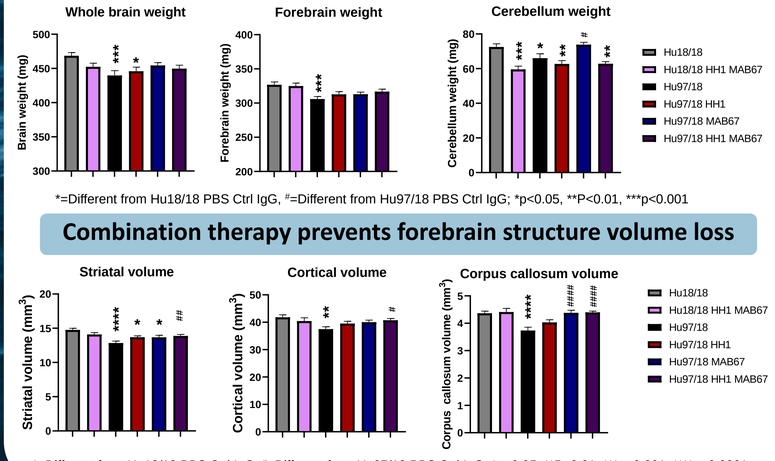
Combination therapy prevents hypoactivity and anxiety-like behavior



*=Different from Hu18/18 PBS Ctrl IgG, #=Different from Hu97/18 PBS Ctrl IgG; *p<0.05, **P<0.01, ***p<0.001, ****p<0.0001

NEUROPATHOLOGY

Individual and combination therapy ameliorates forebrain atrophy



*=Different from Hu18/18 PBS Ctrl IgG, #=Different from Hu97/18 PBS Ctrl IgG; *p<0.05, **P<0.01, ***p<0.001

Combination therapy prevents forebrain structure volume loss

*=Different from Hu18/18 PBS Ctrl IgG, #=Different from Hu97/18 PBS Ctrl IgG; *p<0.05, **P<0.01, ***p<0.001, ****p<0.0001

SUMMARY

-SEMA4D is upregulated in neurons of Hu97/18 HD mice
-ASO HH1 suppresses human HTT in the brain and circulation of Hu97/18 mice
-Compared to Hu18/18 control mice, Hu97/18 mice are overweight and display motor deficits. ASO and combination therapy normalizes body weight of female Hu97/18 mice and improve motor performance.
-Consistent with previous reports, MAB67 and ASO therapy individually prevent object learning deficits, and combination therapy is similar to individual therapies.
-Hu97/18 mice display hypoactivity during exploratory activity that is prevented by combination therapy, but not by individual therapies.
-Consistent with previous reports, a trend toward reduced anxiety-like behavior was observed with either MAB67 or ASO therapy, while combination therapy prevents anxiety.
-Consistent with previous reports, a trend toward increased forebrain weight was observed with either MAB67 or ASO therapy. Combination therapy was similar to individual therapies.
-Consistent with previous reports, a trend toward increased striatal and cortical volume was observed with either MAB67 or ASO therapy, and MAB67 prevents corpus callosum volume loss. Combination therapy prevents loss of striatal, cortical, or corpus callosum volume.
-Combination anti-SEMA4D and HTT lowering therapy provide benefit beyond individual therapies

Disclosures: VM, TF, EE, MZ are employees of Vaccinex Inc.
Vaccinex Inc provided MABs as well as financial, technical, and intellectual support for the work performed in the laboratory of Amber L. Southwell.