HD Clinical Trials: ENROLL-HD, SIGNAL, and Others

Burton Scott MD
Duke HDSA Center of Excellence
Durham, NC

Enroll-HD

World-wide
Observational study
Started in 2012
Still recruiting

Goal: Accelerate discovery & development of new treatments for HD

As of Mar 2018 (enroll-hd.org): 15168 participants at 160 active sites in 17 nations

Sites in NC: Duke and Wake Forest Baptist

Candidates:

1) HD gene positive, with or without symptoms or official diagnosis
2) HD gene negative with FHx of HD
3) At risk for HD, and not yet tested
4) Children < age 18 w/ juvenile HD (w/ consent of parent / legal guardian)
5) Spouses/partners (not related by blood) of people with HD

ENROLL-HD

- Among 8714 with complete data collection through 2016:

  age 49.1 male 44.6%

  W 92.9%/ B 1.0%/ H 1.8%

- Stage (Total FC)

1	(11-13)	29%
2	(7-10)	36%
3	(3-6)	24%
4	(1-2)	8%
5	(0)	3%

Studies from ENROLL-HD

- Body weight is a robust predictor of clinical progression in HD (van der Burg et al, 2017) high baseline BMI → slower declines in function, movem't, cognition independent of mutant HTT CAG repeat size.
- Substance abuse hastens motor onset of HD (Schultz et al, 2017) Motor onset is 2.3 yrs earlier in tobacco users, 1.0 yr in alcohol users & 2.3 yrs in illicit drug users
- Health care delivery practices in HD specialty clinics (Frich et al, 2016) Most are multidisciplinary. 50-199 pts.
- Data analytics from Enroll-HD, a global clinical research platform for HD (Landwehrmeyer et al, Mov Disord Clin Practice)

Studies from ENROLL-HD

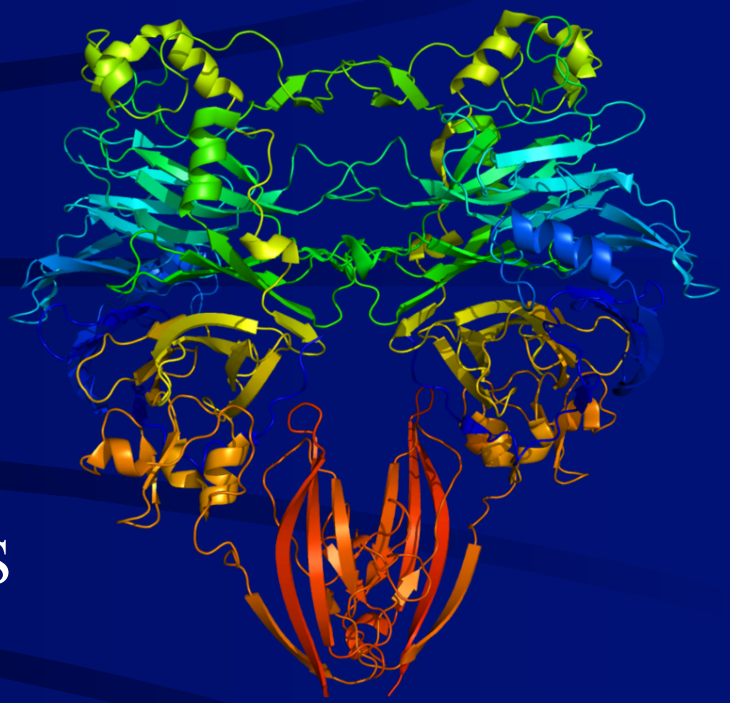
- Impact of FHx on clinical features of HD: 4.8% w/ -FHx for HD, 95.2% w/ +FHx HD. +FHx (awareness of HD) predicts 11.4 yr earlier onset depression & 6.7 yr earlier onset motor symp (Kringlen et al, 2017)
- Premanifest HD: Oculomotor abnlities. Horizontal ocular pursuits can be affected in premanifest HD. (Winder & Roos, 2018)
- Among HD patients w/ Type II DM, cognition slightly better in those taking metformin (Hervas et al, 2017)

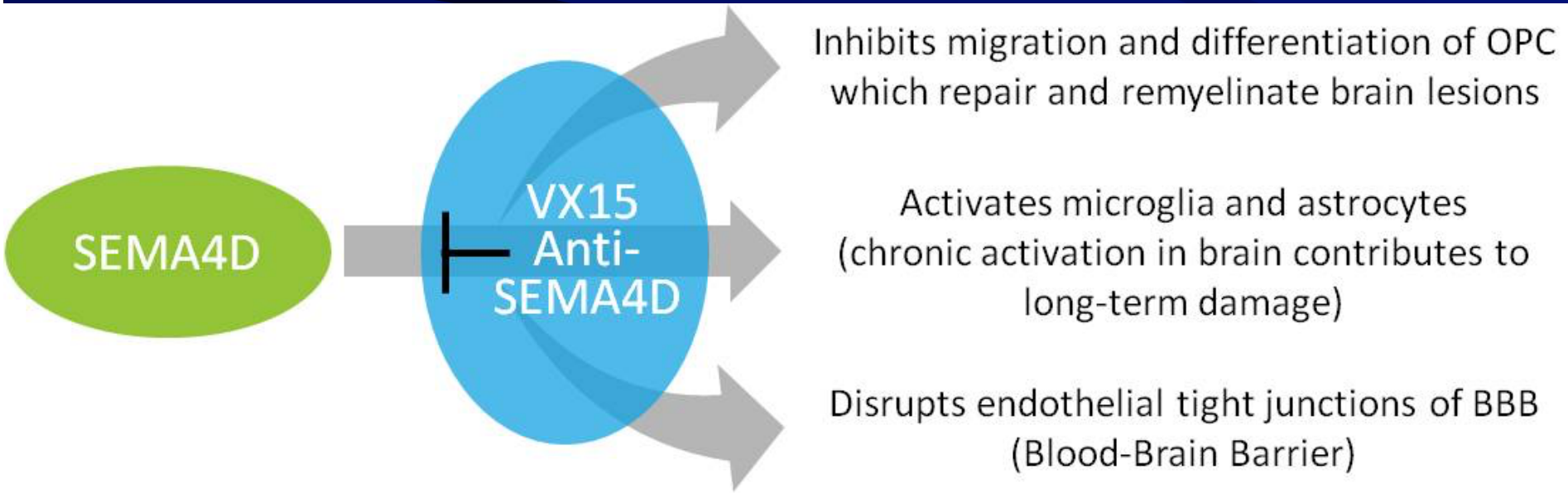
Studies from ENROLL-HD

- Assessing decline in HD. Can compare individual HD pts to a "clinical dashboard" of Total Motor Scores, Total Func Capacity score, Symbol Digit Modality score, controlling for age, CAGn. Can use to identify HD patients declining more rapidly than expected. For earlier potential intervention. (Walker et al, 2017).

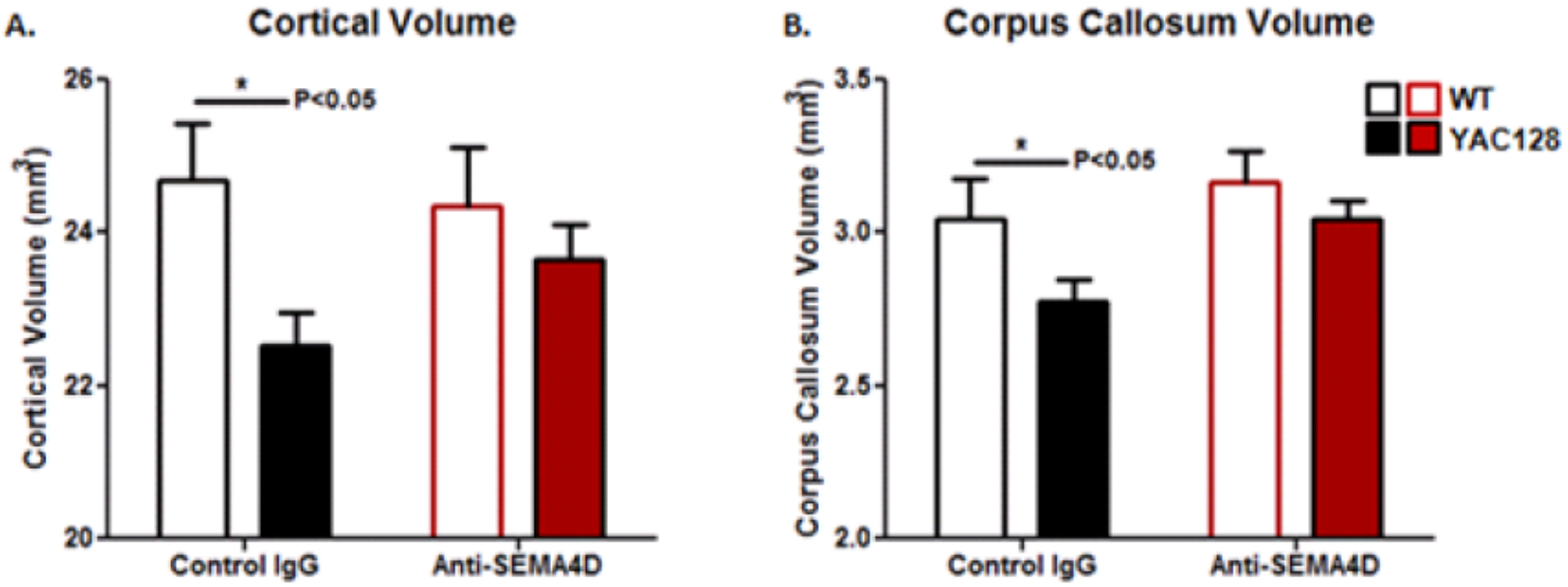
SIGNAL Study: Semaphorin-4 (SEMA4D)

- Axon guidance molecule
- Secreted by oligodendrocytes
- Induces growth cone collapse in CNS





Effect of Anti-Sema4D in HD mice



Anti-SEMA4D preserves brain grey and white matter in YAC128 Huntington's Disease mice. Free-floating brain tissue sections from 12 month-old MAb-treated YAC128 and wild type (WT) mice (n=13-21/group) were stained with anti-NeuN antibody. Cortical (**A**) and corpus callosum (**B**) volumes were determined by tracing the perimeter of the desired structure in serial sections using StereoInvestigator software (Microbrightfield) and volumes determined using the Cavalieri principle. Statistical significance was determined by ANOVA with Bonferroni's Multiple Comparison Test where *=p<0.05 and **=p<0.01.

SIGNAL Clinical Trial with VX 15

- Monoclonal Antibody against Semaphorin 4D.
- Evaluate safety & tolerability of monthly IV infusion of VX15/2503.
- 240 individuals, 21 yr of age or older, with late prodromal or early manifest HD
- Phase 2, multi-center, randomized, Double Blind, Placebo Controlled.

SIGNAL Clinical Trial with VX 15

- Efficacy endpts: brain volumes (MRI), FDG-PET, clinical features
- Now in Cohort B: 18 to 36 months of drug or placebo (1:1)
- Goal: Try to alter progression of Huntington's disease by reducing inflammation in the brain.
- On-going at Duke, Wake Forest, other sites
- Still recruiting.

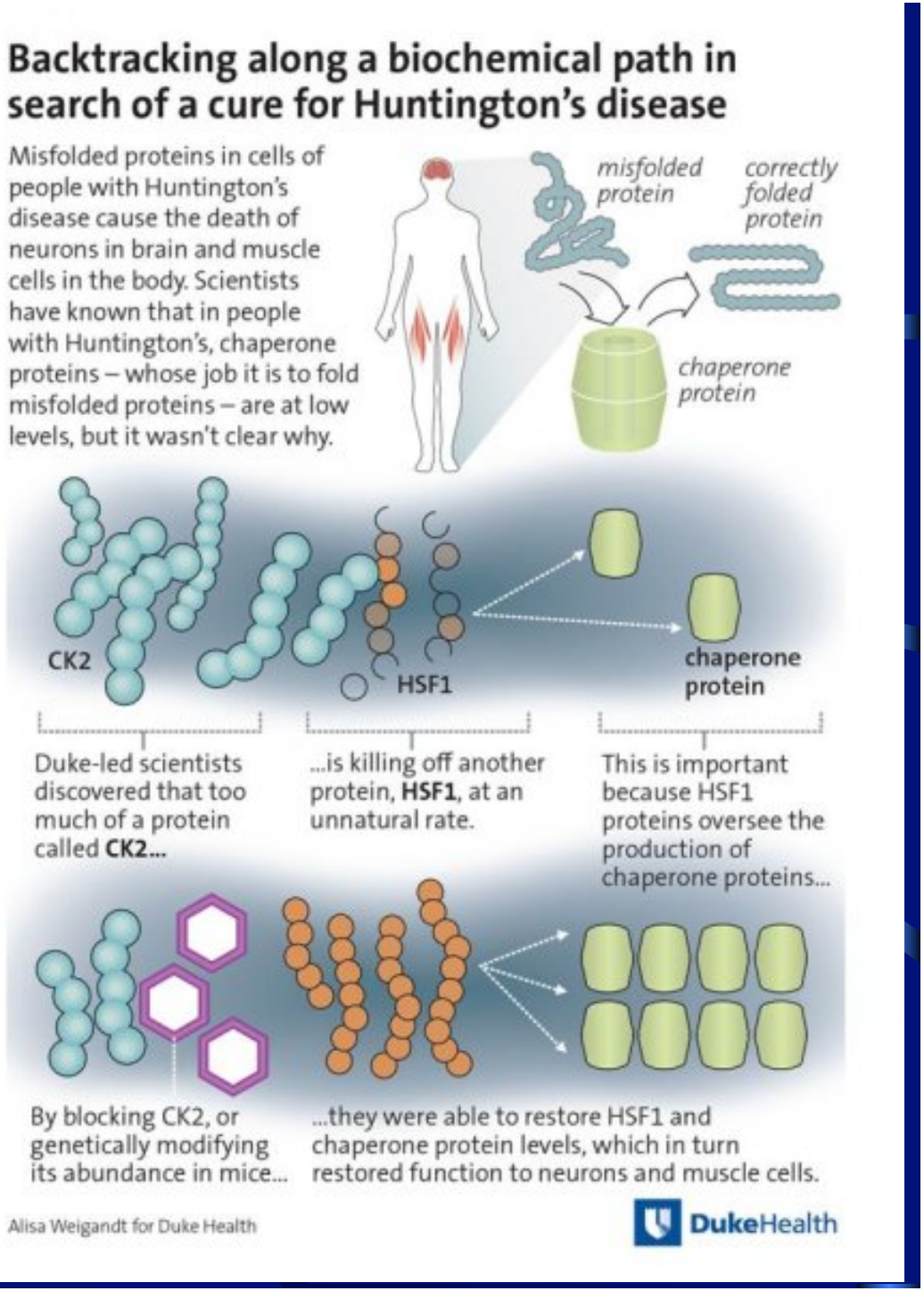
Role of the Immune System in Neurodegeneration – Dr. Donald Lo and Mr. Steven Marinero

- 20 adults with pre-manifest, early, & moderate HD. Also 20 controls and 20 w/ AD
- Peripheral blood mononuclear cells (PBMCs) isolated from whole blood by density gradient centrifugation
- CD14+ monocytes (previously found to be hyperactive in HD)
- Study interactions of monocytes with striatal medium spiny neurons (MSNs)

Abnormal Protein Folding in HD

- mHTT increases CK2 & E3 ligase, which reduces HSF1, which interferes with proper protein folding
- Blocking CK2 could provide a new therapeutic approach to HD.

Gomez-Pastor et al (& Donald Lo), 2016



Research in HD

- You and your family can help advance HD research by participating in clinical trials.

- Remember to register to vote and support government that advances HD research.