Lieberman Andrew (Orcid ID: 0000-0001-9032-580X)

A PET ligand for mutant huntingtin sheds light on disease

Andrew P. Lieberman, MD, PhD[1,*] and Roger L. Albin, MD[2,3]

Departments of Pathology[1] and Neurology[2], University of Michigan Medical School,

Ann Arbor, MI 48109

Neurology Service and Geriatrics Research, Education, and Clinical Center[3], VAAAHS,

Ann Arbor, MI, 48105

*Corresponding author:
3510 MSRB1
1150 W. Medical Center Dr.
Ann Arbor, MI 48109
Email: liebermn@umich.edu

Word Count: 407

Financial Disclosure/Conflict of interest declaration: The authors declare no financial disclosure or conflicts of interest related to this manuscript.

Funding sources for this study: None

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/mds.29019

Bertoglio D, Bard J, Hessmann M, Liu L, et al. Development of a ligand for in vivo imaging of mutant huntingtin in Huntington's disease. *Sci. Transl. Med.* 2022; doi: 10.1126/scitranslmed.abm3682.

Huntington disease, a rare dominant degenerative disorder, manifests with neuropsychiatric changes and progressive cognitive and motor impairments. These diverse clinical manifestations reflect neurodegeneration initially in striatal medium spiny neurons and progressing to involve the entire brain. Disease-causing expansions of a CAG/polyglutamine tract in the gene encoding huntingtin (HTT) protein trigger protein misfolding underlying the occurrence of histopathologically visible intranuclear and cytoplasmic inclusion bodies. As is likely for the eight other polyglutamine expansion disorders, proteotoxicity, and possibly RNA toxicity, underlie significant aspects of the pathogenic cascade, providing the rationale for HTT lowering therapeutics.

While HTT levels measured in CSF correlate well with brain expression, visualization of mutant HTT in patients, particularly those entering trials of HTT lowering therapeutics, would provide insight into the regional distribution of pathology, assess target engagement, and permit *in vivo* evaluation of regional durability of therapeutic effects. A significant step forward is the development of a positron emission tomography (PET) imaging radioligand with high affinity and selectivity for mutant HTT.[1,2] The radioligand described by Bertoglio and colleagues, dubbed CHDI-180, binds mutant but not wild type HTT with low nanomolar affinity and recognizes a nonmonomeric species distinct from intranuclear inclusion bodies. CHDI-180 identified age- and region-specific pathology in three mouse models and detected pharmacological effects of two intervention paradigms: direct striatal delivery of AAV-expressing zinc finger protein

repressors of mutant HTT and genetic suppression of mutant HTT in a regulatable mouse model. Lowering of HTT in these models was associated with positive effects on imaging markers of striatal neuron dysfunction.

These findings reveal a promising step toward development of a mutant HTT-specific PET ligand. As with other neurodegenenerative proteinopathies, the identity of the relevant toxic protein species is unclear.[3] Further studies are needed to define the precise HTT species recognized by CHDI-180, to determine whether this is the optimal target for PET imaging, and to establish if reported binding of CHDI-180 to beta-amyloid[2] confounds results in patients. Beta-amyloid binding may not be an issue in this largely younger to middle-aged population. Additional PET ligands for mutant HTT are in development[2,4] and may offer complementary tools. The efficacy of any PET ligand depends on the abundance of the target protein. Murine models tend to have less overt neurodegeneration than humans with relative persistence of inclusion-expressing neurons. Whether murine-human differences present a significant challenge for imaging Huntington disease patients is yet to be established. This PET tracer holds significant promise for translational studies, particularly evaluating HTT-lowering therapeutics.

Acknowledgements

Author Roles: APL and RLA wrote the manuscript.

Financial disclosure of all research funding for the previous 12 months:
APL: NIH (R01 NS055746, R01 NS122746, R01 NS119873, R03 NS11708, P30 AG072931, P30 AG053760, T32 GM141840, R21 NS111191, R01 NS106302-01A1, R21 NS112974-01A1); Arvinas, Inc; Firefly Fund; Dana's Angel's Research Trust
RLA: NIH (P50 NS123067; R21 NS114749; P30 AG072931, P30 AG053760); Parkinson's Foundation; Farmer Family Foundation.

References

1. Bertoglio D, Bard J, Hessmann M, et al. Development of a ligand for in vivo imaging of mutant huntingtin in Huntington's disease. Sci Transl Med 2022; 14, eabm3682.

2. Herrmann F, Hessmann M, Schaertl S, et al. Pharmacological characterization of mutant huntingtin aggregate-directed PET imaging tracer candidates. Sci Rep 2021; 11:17977.

3. Ramdzan YM, Trubetskov MM, Ormsby AR, et al. Huntingtin inclusions trigger cellular quiescence, deactivate apoptosis, and lead to delayed necrosis. Cell Rep 2017;19:919-927.

4. Kaur T, Brooks AF, Lapsys A, et al. Synthesis and evaluation of a fluorine-18 radioligand for imaging Huntingtin aggregates by positron emission tomographic imaging. Front Neurosci 2021; 15:766176.