Washington University in St. Louis
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ALPHA-SYNUCLEIN LIGANDS AS SPECIFIC PET IMAGING PROBES FOR PARKINSON'S DISEASE AND OTHER DISORDERS

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Technology Description

A team of researchers at Washington University have developed and optimized highly potent PET imaging probes which are specific for the misfolded protein that is the hallmark of Parkinson's disease and related disorders. This family of molecules was designed based on structure activity relationship analysis to quantify alpha-synuclein aggregation in the brain and provide an objective method for identifying patients with early stage disease. The resulting compounds have a high affinity for alpha-synuclein but do not bind to similar misfolded proteins found in Alzheimer's disease (amyloid, tau). The imaging agents could also be used to diagnose other synucleinopathies such as dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). These probes could be used by physicians or in clinical trials for early stage diagnosis/identification as well as monitoring disease progression and response to therapy.

Stage of Research

- **In vitro binding** – The inventors initially identified several first generation compounds with high specificity and affinity (K_i < 100 nM) for alpha-synuclein. This was further confirmed by ex vitro autoradiography.
- **Optimization** – The inventors further optimized the agents and have identified a lead compound with K_i <10nM
- **In vivo** –MicroPET studies in nonhuman primate showing the lead compounds can penetrate the blood brain barrier and have high cortical uptake withfavorable pharmacokinetics in the brain. Human studies planned.

Applications

- **PET imaging of alpha-synuclein** – radiolabeled probes to quantify the level and distribution of aggregated protein in patients with Parkinson's disease, DLB or MSA; end user applications include:
  - clinical trials – patient selection and surrogate marker for efficacy
  - monitoring – tracking disease progression and response to therapy
  - diagnostics – objective early stage disease detection

Key Advantages

- **Specific –** binds alpha-synuclein but does not bind amyloid or tau fibrils and other markers of

Alzheimer's disease
- **High affinity binding –** optimized compound with K_i < 10 nM
- **Quantitative marker for monitoring and early diagnosis:**
  - could be used to quantify aggregated protein
  - could lead to early treatment which could slow disease progression

Publications

- Yue, X., Dhavale, D. D., Li, J., Luo, Z., Liu, J., Yang, H., ... & Tu, Z. (2018). Design, synthesis, and in vitro evaluation of quinolinyl analogues for α-synuclein aggregation. *Bioorganic & medicinal chemistry letters*, 28(6), 1011-1019.

Patents

- U.S. Patent Application Pending
- Related Intellectual Property: Alpha-synuclein ligands (U.S. Patent Application, Publication No. US2017189566; WUSTL Case No. T-014558)