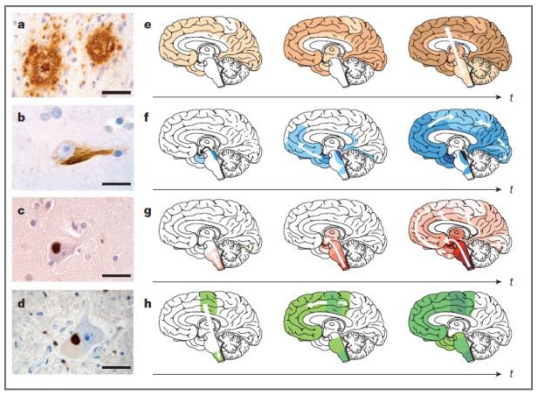
Alzheimer disease, Dementia with Lewy bodies, Parkinson disease, ALS

Cellular and Animal Models of Neurodegenerative diseases

～ efficient evaluation of medicine～

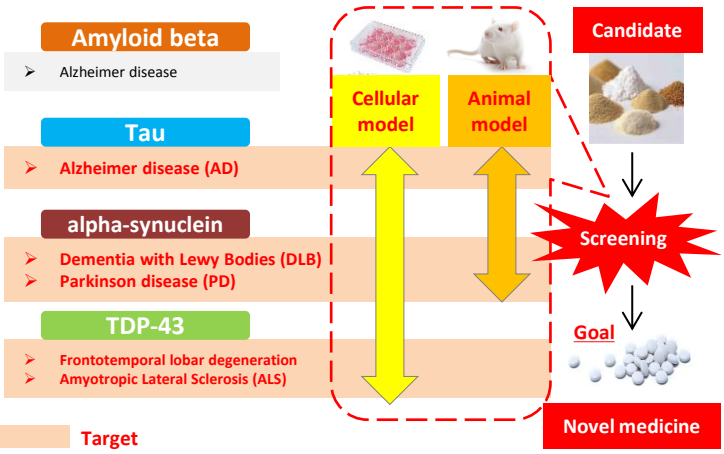
- Accumulation of abnormal protein that cause neurodegeneration
- Useful for the development and evaluation of medicines

◆ Neurodegenerative diseases: Aging and spread of abnormal protein



(Jucker M. & Walker L. C., Nature, 2013)

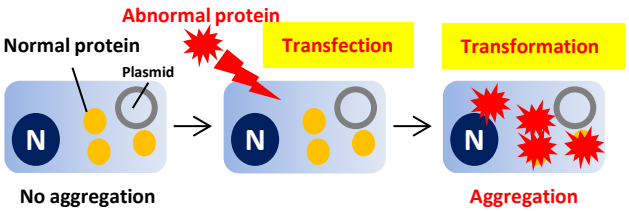
◆ Our disease models for screening

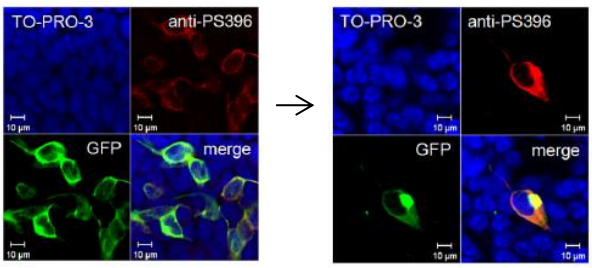


◆ Cellular models

"Accumulation" of abnormal protein as seen in patient's brain

Tau | alpha-synuclein | TDP-43





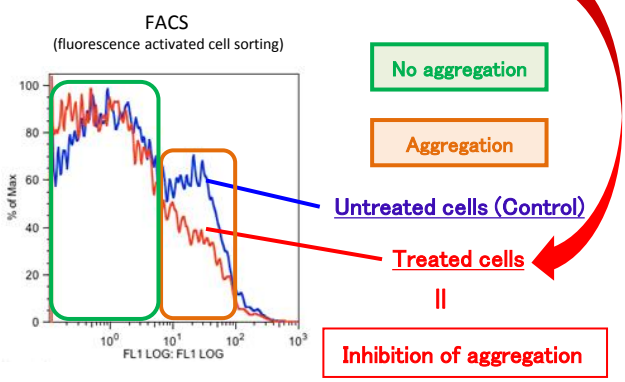
No aggregation

(Nonaka et al., J Biol Chem. 2010)

Aggregation, Phosphorylation, Ubiquitination

◆ Ex. Search for drug candidate

Selection of compound suppressing TDP-43 aggregation from Prestwick Chemical Library



We found several candidate compounds that inhibit aggregation of abnormal TDP-43

1. Seed-dependent cellular models show the pathology of accumulation of abnormal protein, such as tau, alpha-synuclein, and TDP-43.
2. These models are useful for the evaluation of medicine that inhibit the progression of AD, DLB, PD, ALS, etc.

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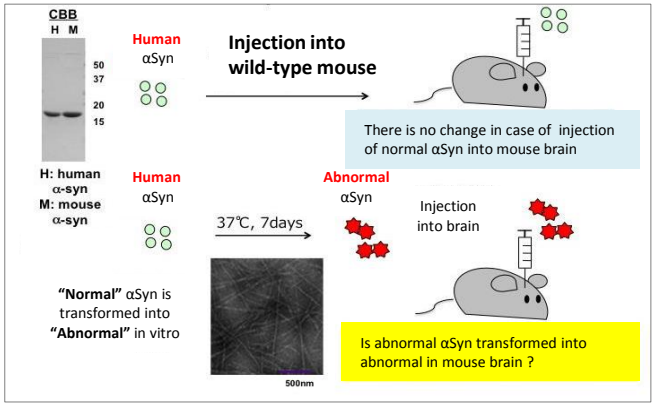
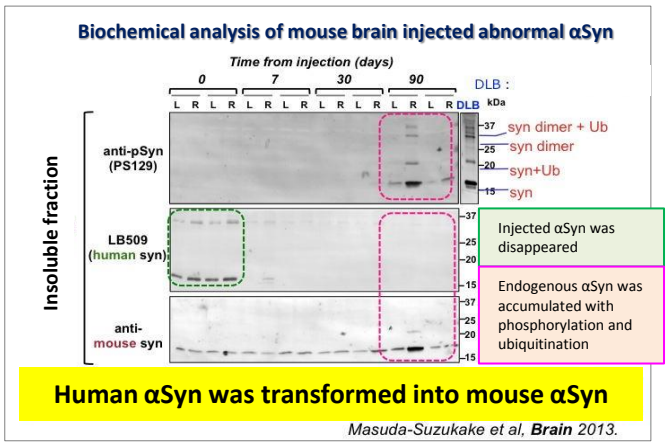
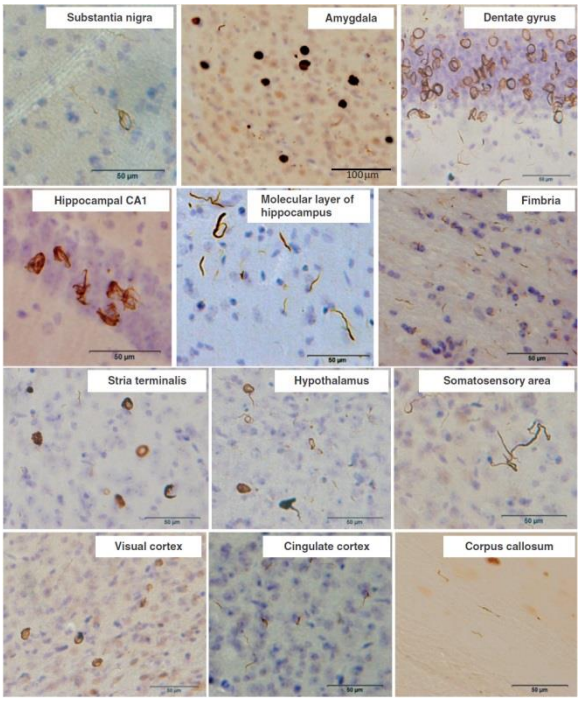
◆ Animal models

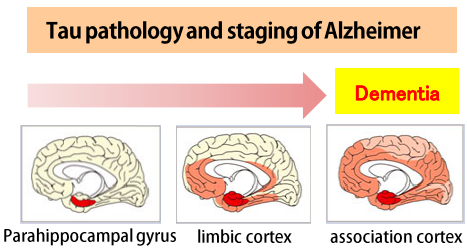
"Propagation" of abnormal protein as seen in patient's brain

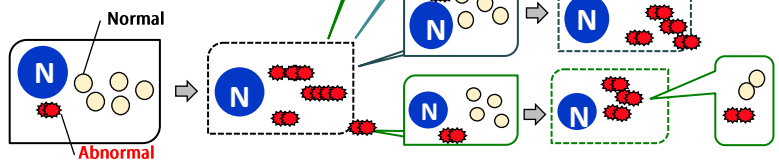
Tau | alpha-synuclein











◆ Lab's web site

Tokyo metro. Inst. Med. Sci. Dementia project
URL: http://www.igakuken.or.jp/dementia/

◆ Papers

・Masuda-Suzukake M, Nonaka T, Hosokawa M, Kubo M, Shimozawa A, Akiyama H, Hasegawa M. Pathological alpha-synuclein propagates through neural networks. *Acta Neuropathol Commun*. 2014 Aug 6;2:88.
・Masuda-Suzukake M, Nonaka T, Hosokawa M, Oikawa T, Arai T, Akiyama H, Mann DM, Hasegawa M. Prion-like spreading of pathological α-synuclein in brain. *Brain*. 2013 Apr;136(Pt 4):1128-38.
・Nonaka T, Watanabe ST, Iwatsubo T, Hasegawa M. Seeded aggregation and toxicity of α-synuclein and tau: cellular models of neurodegenerative diseases. *J Biol Chem*. 2010 Nov 5;285(45):34885-98.
・Nonaka T, Arai T, Buratti E, Baralle FE, Akiyama H, Hasegawa M. Phosphorylated and ubiquitinated TDP-43 pathological inclusions in ALS and FTLD-U are recapitulated in SH-SY5Y cells. *FEBS Lett*. 2009 Jan 22;583(2):394-400.
・Nonaka T, Kametani F, Arai T, Akiyama H, Hasegawa M. Truncation and pathogenic mutations facilitate the formation of intracellular aggregates of TDP-43. *Hum Mol Genet*. 2009 Sep 15;18(18):3353-64.

◆ Patents

- Tdp-43-storing cell model, **JP 5667872, US 8715643, 9128081, EP 2272955 DE,FR,GB**
- Protein which can serve as nucleus for polymerization of protein polymer, cell having the polymer introduced therein, and process for production of the cell, **JP 5665258, EP 1964918 DE,FR,GB**
- The screening method of the neurodegenerative disease therapeutics, **JP 4948845**
- Antibody binding specifically to tdp-43 aggregate, **JP 5439176, US 8940872, EP 2189526 BE,DE,FR,GB,NL**
- Method for producing insoluble aggregate of neurodegenerative-disease-related protein, **CN 201280044001.5**

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