

令和5年2月17日

17th Feb. 2023

大学院学生各位  
To All Graduate Students

令和4年度

## 基盤医学特論 開講通知

Information on Special Lecture Tokuron 2022.4-2023.3

**Title: TDP-43 misregulation in neurodegeneration**

**Teaching Staff: Jemeen Sreedharan, MRCP, Ph.D.**  
Wellcome Trust Senior Research Fellow and Honorary  
Consultant Neurologist at King's College London,  
King's College Hospital

**Time and Date: 16:30-18:00, 30th March (Thu.)**

**Room : Research Institute of Environmental Medicine, South Building,  
Seminar Room 204, (Higashiyama Campus)**

**Language: English**

**Abstract : ALS is a largely sporadic motor neuron disease without cure. 97% of cases demonstrate cytoplasmic aggregation and nuclear depletion of the RNA binding protein TDP-43. Mutations in *TARDBP*, the gene encoding TDP-43, account for only ~1% of all ALS cases but offer an opportunity to understand the mechanisms underlying disease. Most TDP-43 studies have focussed on transgenic overexpression of TDP-43 to recapitulate histopathological hallmarks of disease, but these models may demonstrate artefacts of transgenesis. We have used CRISPR to generate disease models more reflective of the human condition at the genetic level. We have discovered that *Tardbp* mutation can disturb TDP-43 autoregulation in mice, causing cognitive rather than motor phenotypes. *TARDBP* mutation can also disturb autoregulation in human cells. We have been working to develop the TDP-43(Q331K) knock-in mouse as a translational tool using in vivo 9.4T MRI to guide molecular studies. Our iPSC tools are currently being used to better understand the mechanisms of TDP-43 autoregulation and to develop platforms for genetic and small-molecule regulators of TDP-43 expression. We are only scratching the surface in these preliminary studies and a more extensive characterisation of *TARDBP* mutations using knock-in approaches may be of great value.**

**References:** Sreedharan et al Science (2008), Sreedharan et al Current Biology (2015), White et al., Nature Neuroscience (2018), White et al., Acta Neuropathol Commun (2019).

Contact: Koji Yamanaka, Neuroscience and Pathobiology, RIEM. (Ext: 3867) No registration required.

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\*事前連絡は不要です。

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