Taiwan Society for Neuroscience

2022跨領域神經科學國際研討會

Interdisciplinary Neuroscience Congress

Linkou Chang Gang Memorial Hospital
Research Building

Sep. 2-4, 2022

ALS Satellite Meeting

Neuroscience Program of Academia Sinica
中央研究院神經科學研究計畫

621 全球漸凍人日

中華民國運動神經元疾病病友協會
Taiwan Motor Neuron Disease Association
漸凍人協會

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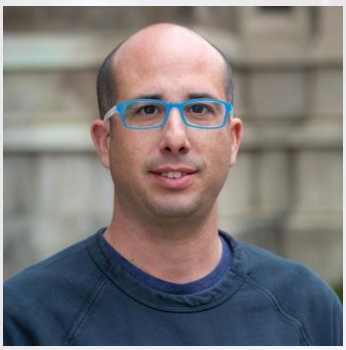

Aaron D. Gitler

The Stanford Medicine Basic Science Professor
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Expanding mechanisms and therapeutic targets for ALS

My lab is focusing on the ALS disease protein TDP-43. We have used these yeast models to perform high-throughput genomewide modifier screens to discover suppressors and enhancers of toxicity. We have extended our findings into animal models and even recently into human patients. For example, we discovered mutations in ataxin 2, one of the human homologs of a hit from our yeast TDP-43 modifier screen in ALS patients. We continue to study ataxin 2 function and to identify ways to inhibit its function as a therapeutic strategy for ALS. We are also exploring the normal function of TDP-43 and have recently discovered novel splicing targets that are dysregulated in ALS. One of these is *UNC13A*. SNPs in *UNC13A* are among the strongest hits associated with FTD and ALS in human genome-wide association studies, but how those variants increase risk for disease is unknown. We found that TDP-43 represses a cryptic exon-splicing event in *UNC13A*. Loss of TDP-43 from the nucleus in human brain, neuronal cell lines and motor neurons resulted in the inclusion of a cryptic exon in *UNC13A* mRNA and reduced UNC13A protein expression. The top variants associated with FTD or ALS risk in humans are located in the intron harboring the cryptic exon, and we show that they increase UNC13A cryptic exon splicing in the face of TDP-43 dysfunction. Together, our data provide a direct functional link between one of the strongest genetic risk factors for FTD and ALS (UNC13A genetic variants), and loss of TDP-43 function.

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Shinsuke Ishigaki
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Alteration of Tau metabolism through FUS in FTLD-spectrum disorders including ALS

The frontotemporal lobar degeneration (FTLD) spectrum includes FTLD, amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP), and cortico-basal degeneration (CBD). TDP-43 and FUS are causative for ALS and FTLD, which collectively comprise a continuous disease spectrum of multisystem proteinopathies. On the other hand, 4-repeat (4R)-tau predominant aggregations are associated with PSP and CBD, while 3-repeat (3R)-tau accumulates in Pick disease (PiD). Using a mouse model, we reported that FUS regulates alternative splicing of tau proteins in coordination with Splicing factor, proline- and glutamine-rich (SFPQ). Under normal conditions, the two proteins form a high-molecular-weight complex in the nucleus. Disease-associated mutations in FUS gene, however, disrupt formation of the complex resulting in unregulated alternative splicing of tau, a disproportional increase in the 4R-tau/3R-tau ratio, and eventually neurodegeneration. In addition, neuropathological study revealed spatial dissociation of SFPQ and FUS in the neuronal nuclei of ALS/FTLD-FUS, ALS/FTLD-TDP, PSP, and CBD. Furthermore, the ratio of 4R/3R-tau was elevated in cases with ALS/FTLD-TDP and PSP, but was largely unaffected in cases with AD. Thus, impaired interactions between FUS and SFPQ and subsequent imbalanced tau isoform ratio constitute a common pathogenic mechanism across FTLD spectrum disease. Based on these findings, we are developing therapeutics using antisense oligonucleotide to modify conformation of FUS and SFPQ as well as biomarkers which can visualize behavioral alterations in FTLD spectrum including ALS.

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Clinical features and genetic spectrum of ALS in Taiwan

From 2010 to 2020, we recruited a cohort consisting of 494 unrelated Taiwanese patients with ALS, which provided us an opportunity to understand ALS in Taiwan. In this cohort, the mean age of disease onset was 54.9 ± 12.3 years, male to female ratio was 1.4, 10.5% of the patients had familial ALS (FALS), and 19.8% had bulbar-onset disease. Among the 183 patients who received regularly ALS functional rating scale-revised version (ALSFRS-R) evaluation per six months, the mean ALSFRS-R score at first evaluation, six months and 1 year later were 36.1 ± 8.2, 28.5 ± 9.8, and 24.4 ± 11.5, respectively. The mean diagnostic delay was 12.7 ± 7.9 months. The 1st year mean ALSFRS-R score decline rate after evaluation was approximately 1 point per month. Extensive genetic analyses revealed 86 (17.4%) of the 494 patients carried an ALS-related mutation, including 41 (79%; 41/52) with FALS and 45 (10%; 45/442) with apparently sporadic ALS. The most commonly mutated disease genes were *SOD1* (4.5 %; 22/494), followed by *C9ORF72* (4.3%), *TARDBP* (3.2%), and *FUS* (1.8%). Patients with *SOD1* mutations rarely had frontotemporal dementia (FTD) and bulbar-onset disease, patients with the *C9ORF72* mutation more frequently had bulbar-onset disease and FTD. *FUS* mutations are associated with earlier disease onset.

Selected 5 recent publications:

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Jun-An Chen (陳俊安)

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Exploiting ncRNA as new therapeutic avenues in ALS

Progressive degeneration of motor neurons (MNs) is the hallmark of amyotrophic lateral sclerosis (ALS). Limb-innervating lateral motor column MNs (LMC-MNs) seem to be particularly vulnerable and are among the first MNs affected in ALS. Here, we report association of this differential susceptibility with reduced expression of the *mir-17~92* cluster in LMC-MNs prior to disease onset. Reduced *mir-17~92* is accompanied by elevated nuclear PTEN in spinal MNs of presymptomatic $SOD1^{G93A}$ mice. Selective dysregulation of the *mir-17~92*/nuclear PTEN axis in degenerating $SOD1^{G93A}$ LMC-MNs was confirmed in a double-transgenic embryonic stem cell system and recapitulated in human $SOD1^{+/L144F}$-induced pluripotent stem cell (iPSC)-derived MNs. We further show that overexpression of *mir-17~92* significantly rescues human $SOD1^{+/L144F}$ MNs, and intrathecal delivery of adeno-associated virus (AAV)9-*mir-17~92* improves motor deficits and survival in $SOD1^{G93A}$ mice. Thus, *mir-17~92* may have value as a prognostic marker of MN degeneration and is a candidate therapeutic target in *SOD1*-linked ALS.

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Love, Courage, Gratitude: Taiwan MND Association

Kiki Qu, Executive Director of Taiwan MND Association

Kiki Qu 屈穎女士
Executive Director
Chair of PR and Marketing Committee
Taiwan MND Association
2014-2020 Board member, the International Alliance of ALS/MND Associations

Kiki Qu, born in Xi'an, China, moved to Taipei in 2009 with her husband, Tom Chen, Ph.D., the first president living with ALS, Taiwan MND Association from 2016-2018. Kiki is an active ALS advocate both in the local and international ALS community. She served as the board member for two terms in the International Alliance of ALS/MND Associations. Under her effort, the first and second Asia Pacific Regional ALS Conference was held in 2015 and 2017, respectively in Taipei and Beijing, and three local ALS/MND organizations joined the International Alliance.

In Taiwan, Kiki not only has served on the board of the Taiwan MND Association for more than ten years, but also initiated and promoted many important projects and programs, such as developing the enhanced eye-gaze system, BCI communication system, voice banking and speech generating systems. She also led the PR and Marketing team launched successful fundraising campaigns and press conferences. In 2018, in order to raise the public awareness on young caregivers in the ALS family, Kiki worked with a young talented illustrator, Stephish Liu, to publish a picture book *The Melody of Dreams* (夢想的音符), which is the only picture book on ALS in Taiwan up to date.

Kiki and her husband, Tom, co-authored *You Are My Breath* (你是我的呼吸) in 2012. Their new book *From Chang'an to Taipei* (追光之歌) just published in June 2022.

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ALS給我不同的人生

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學歷

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臺灣腦庫介紹

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「腦庫」在臺灣是新的概念，但是病友「捐腦建庫」的呼籲與期待卻是很早。二十多年前開始，罹患神經退化疾病的病友，雖然承受苦難，卻勇於提出往生後捐腦神經組織，期待可以作為研發治療藥物的起點。這樣大愛的呼聲一直沒有停歇，感動了社會各界的熱心人士，包括專業團體(醫師、律師)與病友團體，大家共同努力，把病友的大愛，落實為「臺灣腦庫」的建置。

緣起：大愛的延伸，成為藥物研發的契機

從 2017 年至今，臺灣腦庫的推動，可以分成幾個階段：準備期、規劃期、建置期，這是一個由民間努力、結合政府支持，非常成功的案例。建立臺灣腦庫，是臺灣從未有過的經驗，特別是相關法令，都是在有腦庫的概念之前所訂立。腦庫是在捐腦病友往生之後，才能取得腦神經組織；為了避免蛋白質、基因分子的破壞，需要往生之後，在最短時間取得腦神經組織，因此需要相當多的溝通，以及法令的行政解釋，才能達成最短時間取得達到研究標準的腦神經組織，這是一段非常漫長的努力過程。

因此國衛院「論壇」在2018 年選定「腦庫」作為主題，探討、規劃在臺灣建立腦庫的可行性。在臺大醫學院和臺灣神經罕見疾病學會的合作下，組成「腦庫工作小組」來研議可行性、規劃腦庫的建置。這段努力的過程，得到公益團體與媒體的關注與協助推動，經過兩年多的密集會議與討論，並得衛生福利部的支持與指導，以行政解釋，提供建置腦庫的法源依據。

臺灣腦庫的現況

在病友與各界的殷切期盼下，由臺大醫學院和臺大醫院提供場地與建設經費，設立、建置臺灣腦神經組織庫（簡稱臺灣腦庫）:並在中央研究院陳建仁院士的倡議下，並同步發起成立相對應的民間公益團體，以「臺灣腦庫協會」來推動，腦庫的硬體工程已經完成，現在正申請衛生福利部的生物資料庫審核，一旦正式成立，將可以滿足所有病友與正常捐腦者的熱切期盼，這也會成為所有捐腦者的「家」，有系統地收集捐腦者的腦神經組織，成為研發藥物的基礎。

腦疾病的研究除了病友的腦組織，並需要正常人的參與，作為比較的基準。在臺灣腦庫成立的初期，除了罕見疾病及神經退化疾病，並鼓勵正常人簽署同意書捐腦。在腦庫萌芽與發展過程中，也與推動「大體老師」、「器官捐贈」的民間團體密切合作：因為不同捐贈，有不同的條件要求，三個團體協調合作，當捐贈者不符合某一種條件時，可以鼓勵以另一形式轉捐，滿足捐贈者的大愛遺願。

本文引用自NHRI論壇，國立臺灣大學醫學院謝松蒼副院長”臺灣腦庫：現況與展望”(https://forum.nhri.edu.tw/r75/)