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Combined genetic lesion and toxin exposure model for motor neuron disease

Craig Leslie Bennett
Duke University, USA

Amyotrophic lateral sclerosis (ALS) is a degenerative disease with progressive loss of motor neurons (MNs) in the brain and spinal cord leading to muscle atrophy, spasticity and death usually within 3-5 years of onset. About 5-10% of ALS cases are familial, with the reminder of unknown cause. Just four genes with the highest disease causing frequency account for 50% of ALS cases. Yet taken together they account for only 2-5% of all ALS cases. Mouse models based upon single gene mutations alone do not effectively recapitulate human ALS. The toxin BMAA, produced by blue-green algae is a key environmental risk factor for ALS. Focus on BMAA began 50 years ago due to the 100x increased ALS incidence on the island of Guam. New evidence suggests BMAA underwent bio-magnification on the island, and it has also been shown to enter the conserved protein synthesis pathway. Several pieces of evidence suggest that ALS onset may represent a multi-step process, like cancer. Thus, we are developing a next generation ALS mouse model based upon combined genetic and environmental triggers. TDP-43 is important as its nuclear clearance and cytosolic aggregation are accepted hallmarks of ALS pathology. BMAA is a pervasive environmental toxin. For up to 18-months duration, we will expose the hTDP-43A315T-Ki pre-disease mouse, to chronic BMAA exposure, with and without sensitizing low protein diet. We anticipate that this model may develop true ALS motor phenotypes, allowing for new drug development.

Biography

Craig Leslie Bennett has completed his PhD at University of Sydney and Postdoctoral studies in Human Genetics at University of Washington in Seattle. He has been an active Researcher in the fields of Charcot-Marie-Tooth disease and motor neuron disease for more than 18 years. He has published 40 peer reviewed papers and has been serving as a regular grant Reviewer for the Australian National Health & Medical Research Council (NHMRC) since 2012.

craig.l.bennett@duke.edu

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