Study uncovers protein interactions as a potential path for ALS cure

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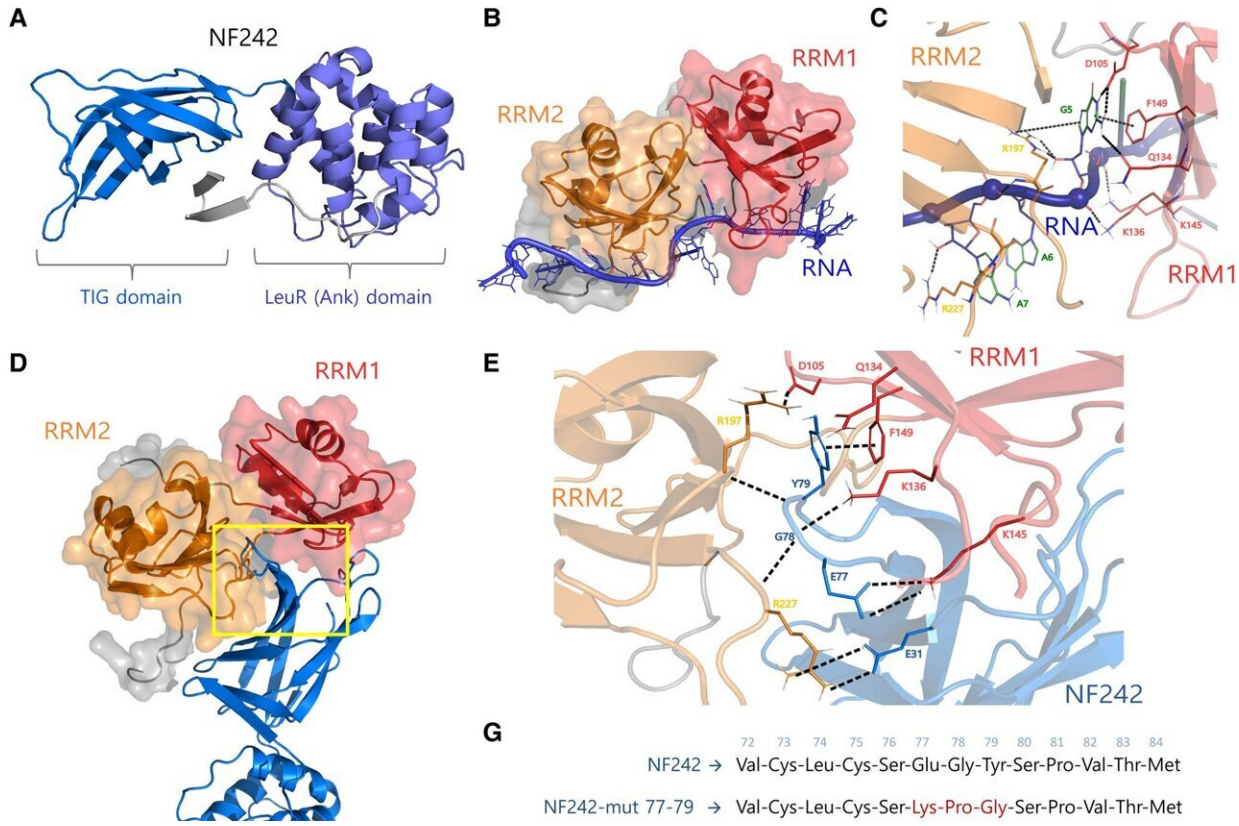

Modelling of TDP-43-NF242 interaction. Credit: *Brain* (2024). DOI: 10.1093/brain/awae078

In a Canadian discovery powered by philanthropy, a team of Western University researchers led by Dr. Michael Strong has uncovered a

potential path toward a cure for amyotrophic lateral sclerosis (ALS).

The research, which illustrates how protein interactions can preserve or prevent the nerve cell death that is a hallmark of ALS, is the culmination of decades of Western research backed by the Temerty Foundation.

"As a doctor, it's been so important for me to be able to sit down with a patient or their family and say to them, 'we're trying to stop this disease,'" said Strong, a clinician-scientist who has devoted his career to finding a cure for ALS. "It's been 30 years of work to get here; 30 years of looking after families and patients and their loved ones, when all we had was hope. This gives us reason to believe we've discovered a path to treatment."

ALS, also known as Lou Gehrig's disease, is a debilitating neurodegenerative condition that progressively impairs nerve cells responsible for muscle control, leading to muscle wastage, paralysis and, ultimately, death. The average life expectancy of an ALS patient post-diagnosis is a mere two to five years.

In a study published in the journal *Brain*, Strong's team found that targeting an interaction between two proteins present in ALS-impacted nerve cells can halt or reverse the disease's progression. The team also identified a mechanism to make this possible.

"Importantly, this interaction could be key to unlocking a treatment not just for ALS but also for other related neurological conditions, like frontotemporal dementia," said Strong, who holds the Arthur J. Hudson Chair in ALS Research at Western's Schulich School of Medicine & Dentistry. "It is a gamechanger."

In virtually all ALS patients, a protein called TDP-43 is responsible for forming abnormal clumps within cells, which causes cell death. In recent

years, Strong's team discovered a second protein, called RGNEF, with functions that are opposite to TDP-43.

The team's latest breakthrough identifies a specific fragment of that RGNEF protein, named NF242, that can mitigate the toxic effects of the ALS-causing protein. The researchers discovered that when the two proteins interact with each other, the toxicity of the ALS-causing protein is removed, significantly reducing damage to the nerve cell and preventing its death.

Dr. Michael Strong, Arthur J. Hudson Chair in ALS Research at Western's Schulich School of Medicine & Dentistry, has discovered a protein that could lead to a treatment for ALS. Credit: Allan Lewis/Schulich School of Medicine & Dentistry

In fruit flies, the approach notably extended lifespan, improved motor functions and protected nerve cells from degeneration. Similarly, in mouse models, the approach led to enhanced lifespan and mobility, along with a reduction in neuroinflammation markers.

The team's path to discovery was paved by the Temerty family's long-standing investment in ALS research at Western—support Strong calls "truly transformational."

Now Strong and his team have set a goal to bring their potential treatment to human clinical trials in five years, a mission that is fueled by a new gift from the Temerty Foundation.

The foundation, established by James Temerty, founder of Northland Power Inc., and Louise Arcand Temerty, is investing $10 million over five years to power the next steps to bring this treatment to ALS patients.

"Finding an effective treatment for ALS would mean so much to people living with this terrible disease and to their loved ones," said James Temerty. "Western is pushing the frontiers of ALS knowledge, and we are excited for the opportunity to contribute to the next phase of this groundbreaking research."

The new gift by the Temerty Foundation brings the family's total investment in neurodegenerative disease research at Western to $18 million.

"Dr. Strong's relentless dedication to his field is matched only by the Temerty family's deep desire to make a difference for the thousands of people around the world diagnosed with this devastating disease," said Western President Alan Shepard. "The investment—and foresight—of the Temerty Foundation has accelerated progress in finding an effective treatment for ALS. We are grateful for the Temerty family's

commitment to life-changing research."

"This is a pivotal moment in ALS research that could truly transform patient lives," said Dr. John Yoo, dean at Schulich Medicine & Dentistry.

"With Dr. Strong's leadership, our continued investment in the best tools and technology and the visionary support of the Temerty Foundation, we are thrilled to be heralding in a new era of hope for patients with ALS."

More information: Cristian A Droppelmann et al, Mitigation of TDP-43 toxic phenotype by an RGNEF fragment in amyotrophic lateral sclerosis models, *Brain* (2024). DOI: 10.1093/brain/awae078

Provided by University of Western Ontario