Amyotrophic lateral sclerosis (ALS) is a devastating and incurable neurodegenerative disease that affects people in adulthood. It leads to the death of neurons involved in muscle control, eventually affecting almost all facets of the body, including walking, swallowing and breathing. Dr Nancy Bonini and Leanne McGurk at the University of Pennsylvania are using fruit flies, mammalian cellular systems like neurons, and in vitro protein preparations to investigate promising new molecules that could open avenues to new treatments for this devastating condition.

Risk factors are not well understood but include older age, with most people diagnosed in middle to older adulthood. A small proportion of cases are inherited and run in families, whilst most cases are apparently sporadic in nature. Although several genes have been linked to ALS, no one gene that has been discovered can account fully for the disease.

The urgent need for more research into ALS has gained awareness after high-profile campaigning by advocacy and patient groups. A very successful ‘Ice Bucket Challenge’ online campaign, firmly cemented ALS in the public consciousness in the past years and raised over $100 million to support vital research and services for the people living with the disease.

Despite increased awareness and funding, there are currently no cures for people living with ALS. Existing treatments for the condition, after decades of research, there are currently no cures for people living with ALS. Treatment options are limited and can help patients manage symptoms. As the disease advances, people living with ALS find their breathing becomes more difficult and eating becomes impossible as muscles associated with swallowing are affected. Almost all people with ALS will eventually find their ability to speak frustratingly difficult, leading some to rely on technology to communicate – with early versions of this technology perhaps best represented by Stephen Hawking’s infamous computerised voice.

The most common cause of death for people with ALS is respiratory failure as the disease interferes with patients’ ability to breathe or cough. Many people with ALS die within two to five years of their diagnosis with many still in middle age.

After decades of research, there are currently no cures for people living with ALS.

FRUIT FLIES TO MODEL ALS

Drs Nancy Bonini and Leanne McGurk have modelled ALS in fruit flies by manipulating cells in the nervous system to express human TDP-43. Flies expressing this human protein showed both the long-held hope that fruit flies might be expected, from movement to social interactions. The fact that fruit flies have a smaller genome than other laboratory animals, such as mice, means that their DNA can be studied more easily than mammals. Their shorter life spans that can be measured in days rather than months make it easier, quicker and less expensive for researchers to track disease-related changes that occur over a lifetime. A number of molecules have been tested in these tiny creatures, some have even ended up in clinical trials for a range of diseases.

PROMISING NEW HORIZONS

Dr Leanne McGurk, a postdoctoral researcher in the Bonini lab, modelled ALS in fruit flies by expressing human TDP-43. Flies expressing this human protein showed both neurodegeneration and a shortened life span, similar to features reflective of ALS. This advance was a vital milestone as it offered the team a model for efficiently studying ALS on the molecular level. Further studies with fruit flies shed light on the behaviour of TDP-43, focusing on protein clumping, TDP-43 transportation throughout the cell and the response of the protein in conditions of stress, such as that seen in the disease.

TDP-43 TARGETED THERAPIES

In exciting follow-up experiments, Bonini and McGurk’s team found that the damage caused by the human TDP-43 protein could be prevented by using a PARP inhibitor, which is known to work well in mice. This finding is promising as it suggests that PARP inhibitors may be repurposed to treat ALS in people. Further research is needed to validate these findings in larger studies and to understand the underlying mechanisms.
caused by expressing TDP-43 in the fly can be rescued. They discovered that reducing levels of an enzyme known as PARP-5 meant that the flies expressing TDP-43 stopped the early death. The researchers believe that PARP enzymes could be key to understanding why proteins accumulate in the cell cytoplasm outside of the nucleus and further, could shed light on ways to reduce the build-up of TDP-43 in this part of the cell.

When McGurk and Bonini investigated this with their collaborators in human spinal cord cells, they found that PARP—a chain of molecules tagged on to target proteins by PARP and controls the toxicity of TDP-43—were found in high levels in the nucleus of motor nerve cells. This suggested that levels of PARP activity in the human spinal cord were elevated in the presence of ALS.

Together, McGurk and Bonini have made important strides to pinpoint molecules that could help tackle some of the processes that go awry in the condition.

To test this theory further, the researchers tested a drug to reduce activity of PARP-1/2 in a rat nerve cell model of ALS expressing human TDP-43. Promisingly, the drug—originally developed as a cancer treatment—was shown to reduce neural death caused by TDP-43. The findings suggest that PARP enzymes could be a vital target for investigating new drug treatments in diseases linked to TDP-43 clumping.

**FUTURE STEPS**
There is still much to learn about PARP enzymes before they could be used to treat ALS patients, including how the subtypes of PARP enzymes work together and how they affect the transport of TDP-43 throughout the cell. However, these findings shed light on the molecular mechanisms underlying the disease and are a beacon of hope in a drug discovery landscape blighted by a drought of advances in recent years. The findings could also shed light on treatments for disorders that share some of the same molecular characteristics, including frontotemporal degeneration. Whilst there is some way to go before it can be determined whether PARP-based therapies could work for ALS, scientists such as Drs McGurk and Bonini continue to strive towards understanding ALS at the molecular level, offering hope to those living with this devastating condition.

**References**


**Personal Response**

**What steps would have to be taken before PARP enzyme-based therapies could be tested in a clinical trial?**

ALS is a heterogeneous disease, meaning that there are many different genes that when mutated give rise to the disease. We need to understand if PARP inhibitors are beneficial to all, or only some of these disease gene situations using our model systems of cells and animals. These types of studies will inform if certain patients may be better suited to these compounds, should they prove promising. Many of the developed PARP inhibitors have very specific modes of action and some are better at crossing the blood-brain-barrier than others. We need to first understand if there are differences in these PARP inhibitors in treating ALS-associated toxicity in cells and in neurons so that we can select the best compound or compounds for further testing. Traditionally, drugs are tested in rodent models of disease before they can move forward into a clinical setting. The field has made much progress in rodent models that recapitulate aspects of the disease process. Once we know which inhibitors are most promising in our settings, the next step will be to advance and test in a rodent system.

**Collaborators**

Investigators at Penn:
- Dr Virginia Van Deursen
- Dr Edward B Lee
- Dr Virginia M-Y Lee
- Dr John G. Trojanowski
- Dr James Shorter
- Dr Robert G. Keb

**In Vivo Model for Human Neurodegenerative Disease.**


**Personal Response**

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