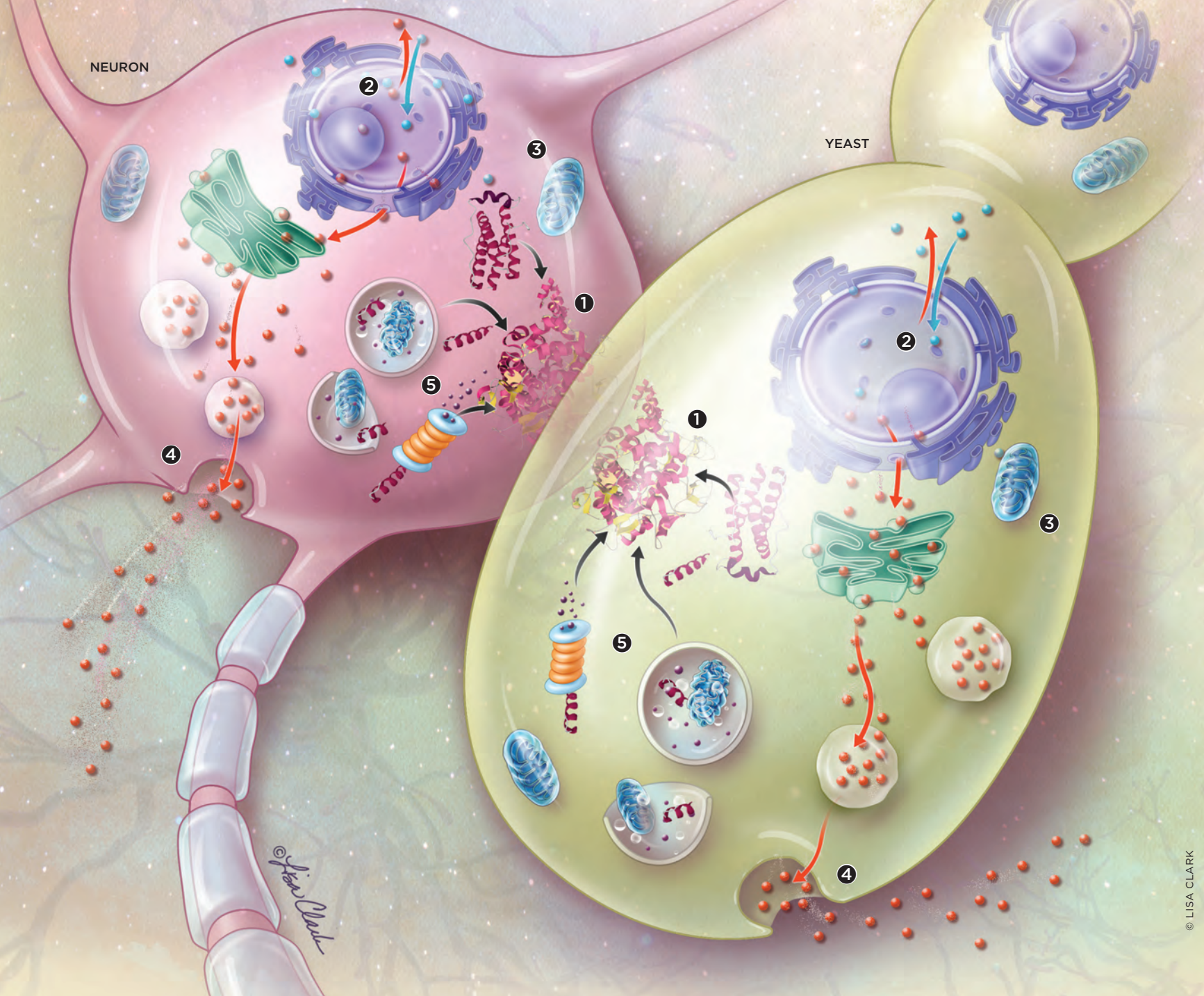
MODELING NEURODEGENERATIVE DISEASES WITH YEAST

Neurodegenerative diseases kill cells by disrupting basic biological processes shared by species as diverse as humans and yeast. The conservation of cellular structures and functions across eukaryotic life allows researchers to study the genetic and molecular underpinnings of neurodegenerative diseases in various model organisms. Yeast cells are a particularly valuable system, as the fungi grow rapidly, are inexpensive to maintain, and can be genetically modified more readily than any other eukaryote. By introducing mutations linked to certain brain diseases, researchers have made yeast models that lend an unmatched speed and scale to research on neurodegeneration. Here are some examples of disease mechanisms that researchers have begun to untangle using yeast.



❶ PROTEIN AGGREGATION

When proteins are damaged or misfolded, they often stick together, forming clumps known as protein aggregates. If not removed by the cell, protein aggregates increase in size and number, impairing a variety of cellular functions and ultimately killing cells.

Yeast research helped establish the predominant role of protein aggregation in numerous neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, ALS, dementia, and Huntington's disease. Yeast have also become an important platform for identifying and screening therapies capable of preventing or reversing protein aggregation.

❷ NUCLEOCYTOPLASMIC TRANSPORT

Cells move molecules into and out of the nucleus for many purposes, such as exporting mRNAs following transcription and importing newly-synthesized nuclear proteins.

Yeast research helped establish that nucleocytoplasmic transport is impaired in ALS and dementia. A Biogen clinical trial is testing a new drug that improves this process.

❸ MITOCHONDRIAL FUNCTION

Mitochondria generate the majority of a cell's energy and regulate its metabolism. Because neurons consume large amounts of energy, they are uniquely vulnerable to defects in mitochondrial function.

Yeast research established that the mutations that cause Friedreich's ataxia and Mohr-Tranebjarg syndrome kill cells by damaging mitochondria and that aberrant activity of several proteins, such as the ALS-linked protein SOD1, impairs mitochondrial function, pointing to new therapeutic targets for these diseases.

❹ VESICULAR TRAFFICKING

Cells shuttle membrane-bound vesicles to the plasma membrane to insert transmembrane proteins and secrete vesicular contents. This vesicular trafficking is especially critical for the health and function of neurons, which use this process to release neurotransmitters during synaptic transmission.

Yeast strains expressing human amyloid-β helped establish how the aggregation of this protein impairs vesicular trafficking and kills cells in Alzheimer's disease.

❺ PROTEIN QUALITY CONTROL PATHWAYS

Damaged and misfolded proteins are removed from the cell through the action of two protein quality control pathways, the ubiquitin-proteasome system and autophagy. Age-associated declines in the activity of both pathways cause damaged and misfolded proteins to aggregate and ultimately lead to neurodegeneration.

Many of the components and mechanisms of the ubiquitin-proteasome system and autophagy were first discovered in yeast, and yeast have helped researchers understand how mutations in many disease-linked genes cause impairments in both pathways.