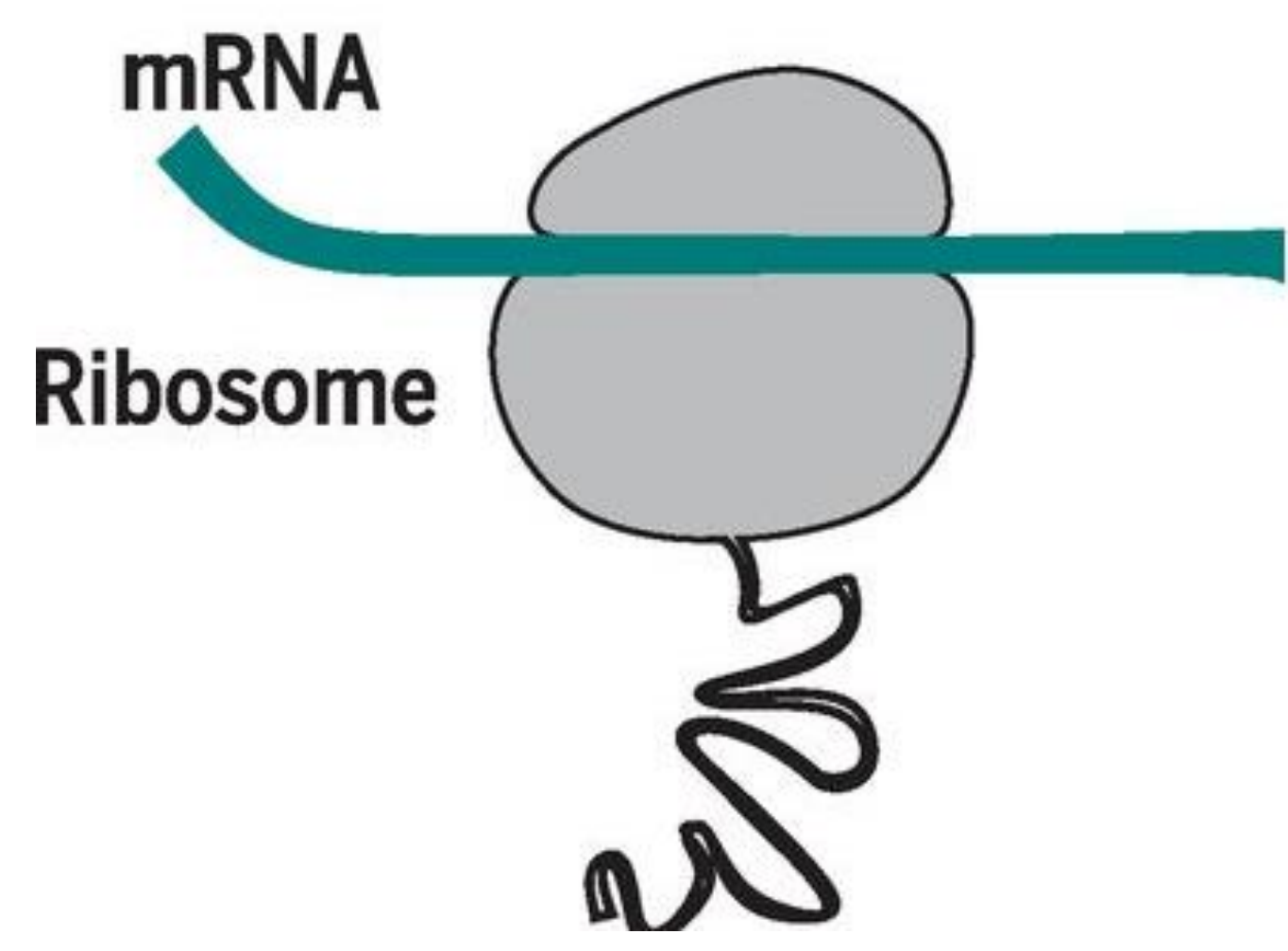
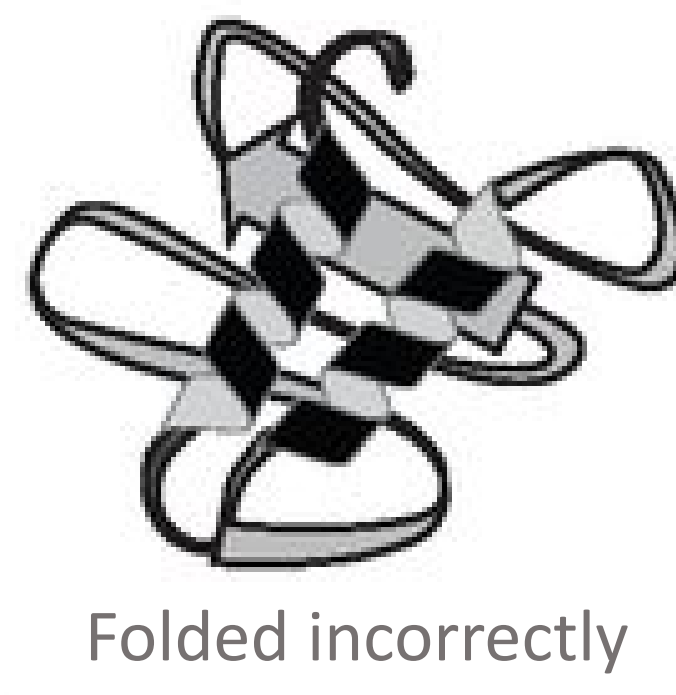
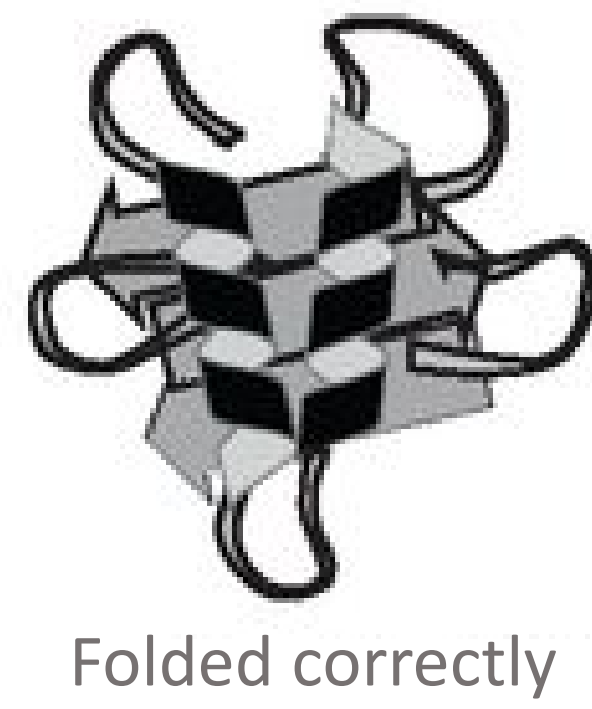


Our work: Protein aggregation in mental illness

Proteins are produced, based on genes, as long chains of peptides



These chains must then be folded to form the final proteins. Sometimes, proteins get folded wrongly.



These incorrect proteins are normally destroyed by the cell



If the cell fails to do this, then clusters of unfolded or misfolded proteins, called aggregates, can accumulate in the cell



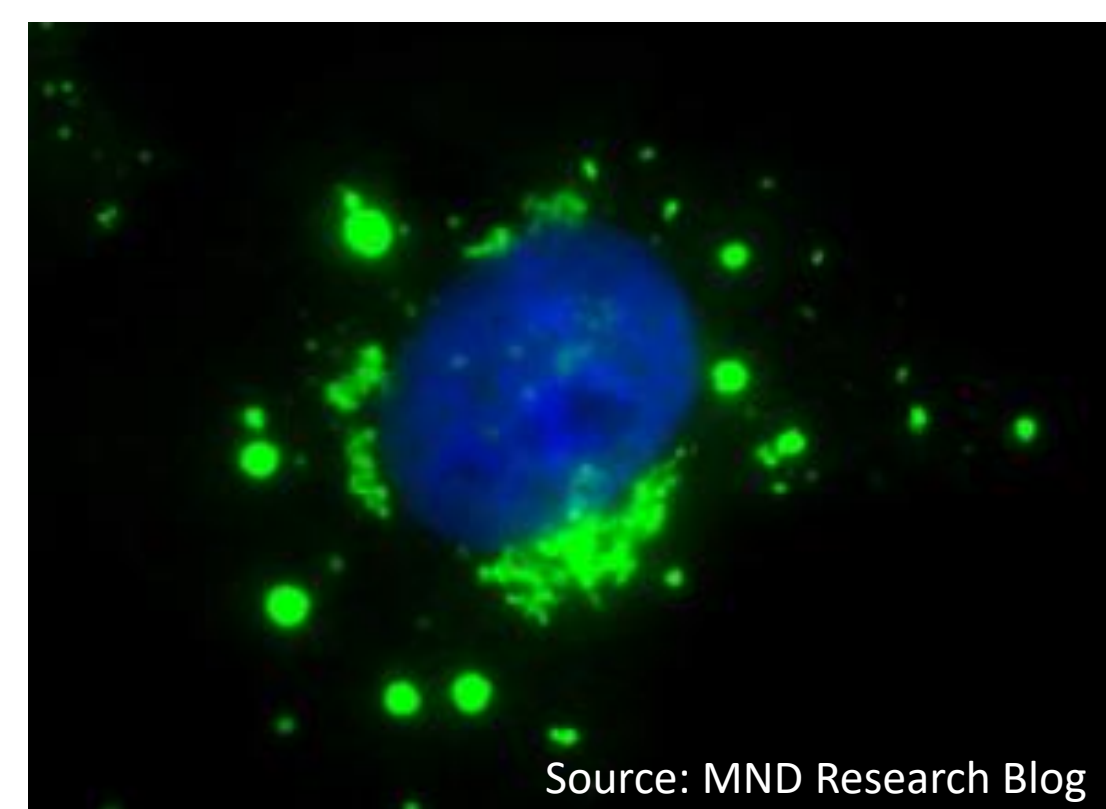
Aggregate

Figure adapted from Balchin et al (2016)

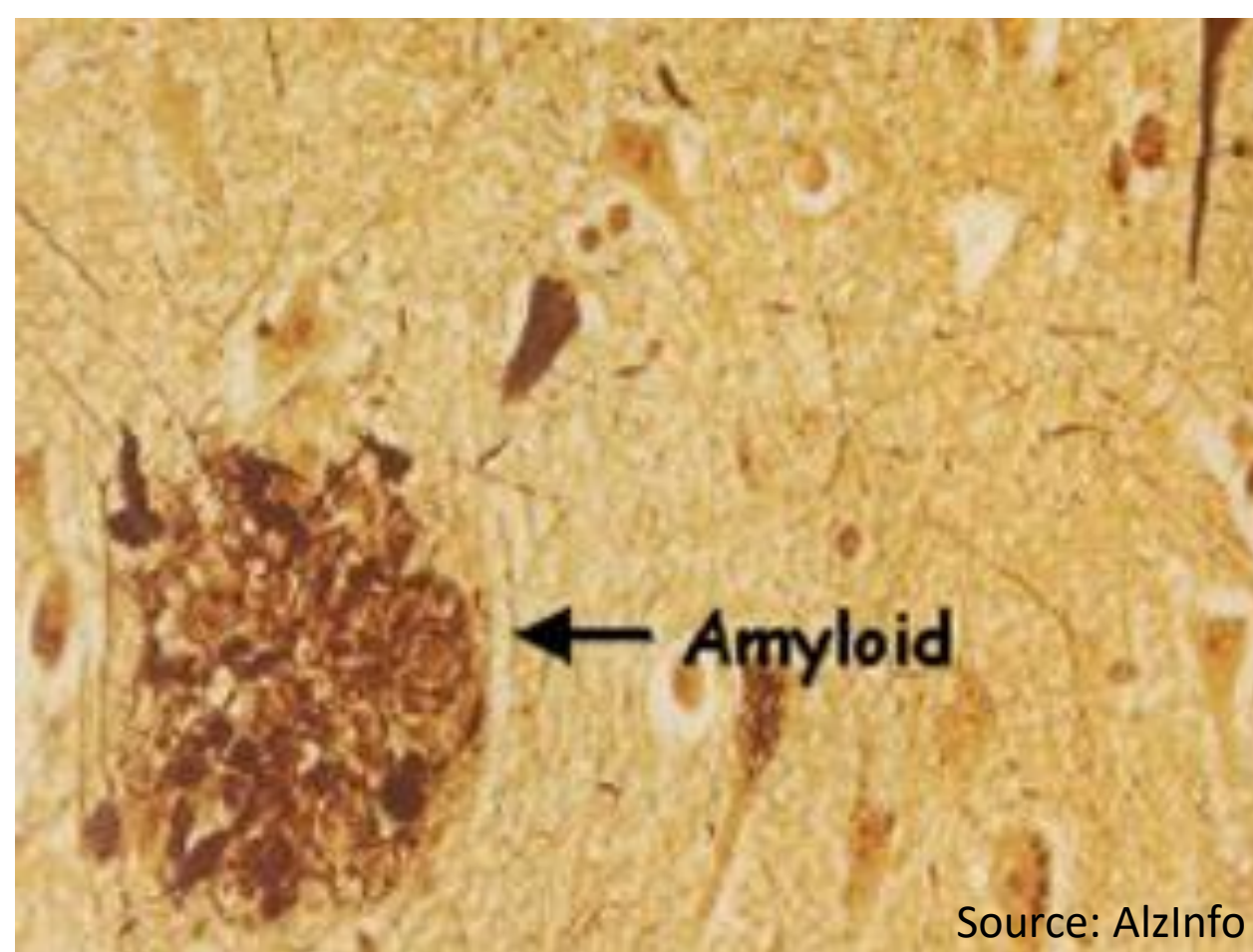
Protein aggregation in disease

Protein aggregates are found in many major brain diseases, including:

- Alzheimer's disease
- Parkinson's disease
- Huntington's disease
- Amyotrophic lateral sclerosis (ALS)



Aggregated FUS in a cell model of amyotrophic lateral sclerosis



"Plaques" of aggregated Aβ peptide in the brain of an Alzheimer's disease patient

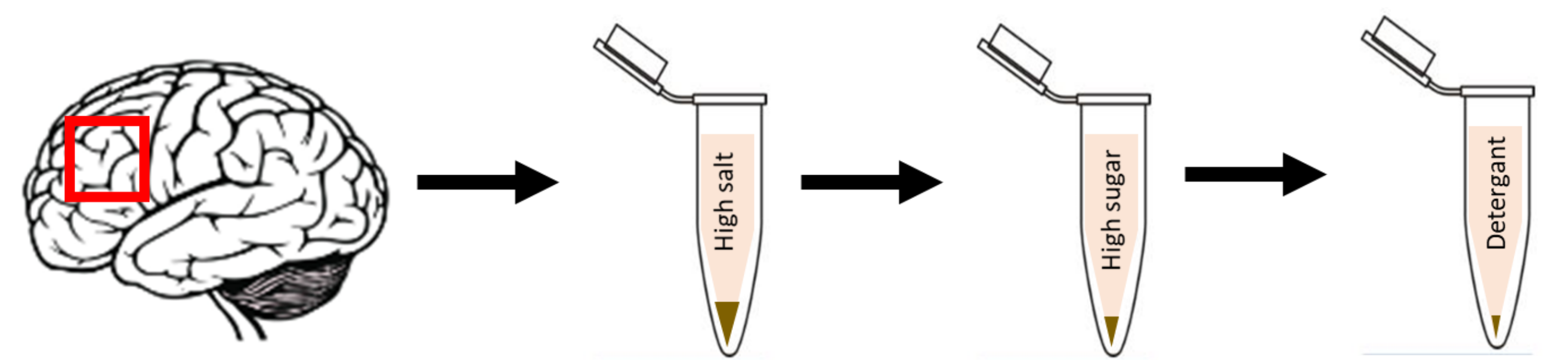
Like these diseases, schizophrenia and other mental illnesses are often chronic.

There are also many common symptoms between major mental illnesses and the early stages of protein aggregation disorders.

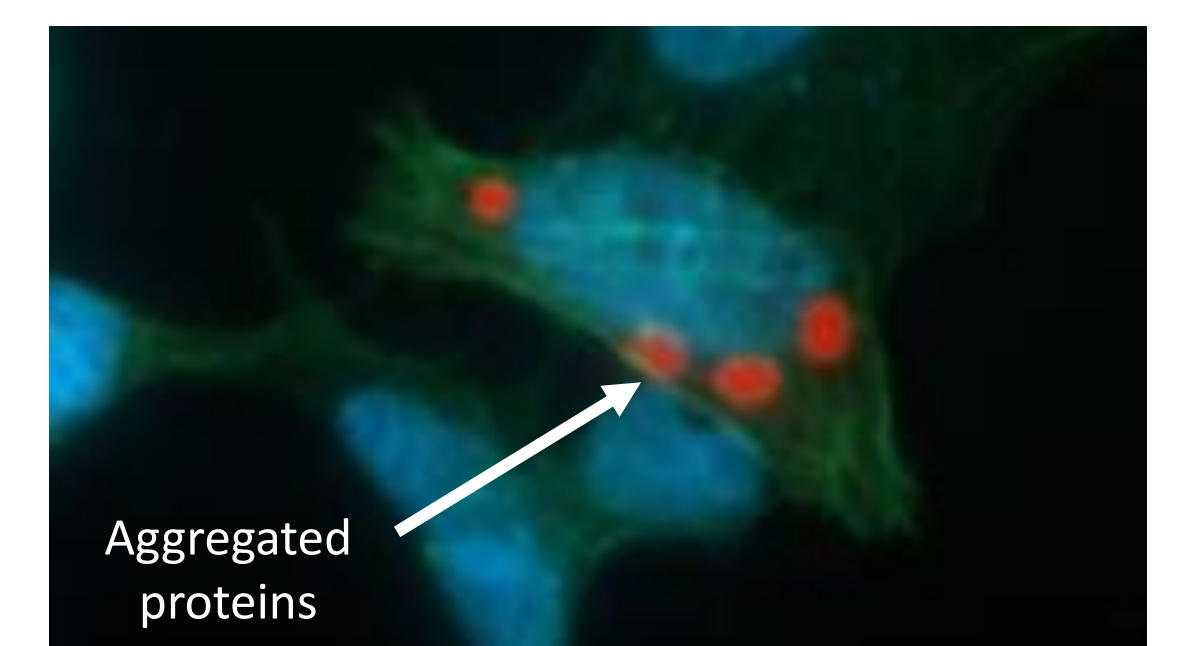
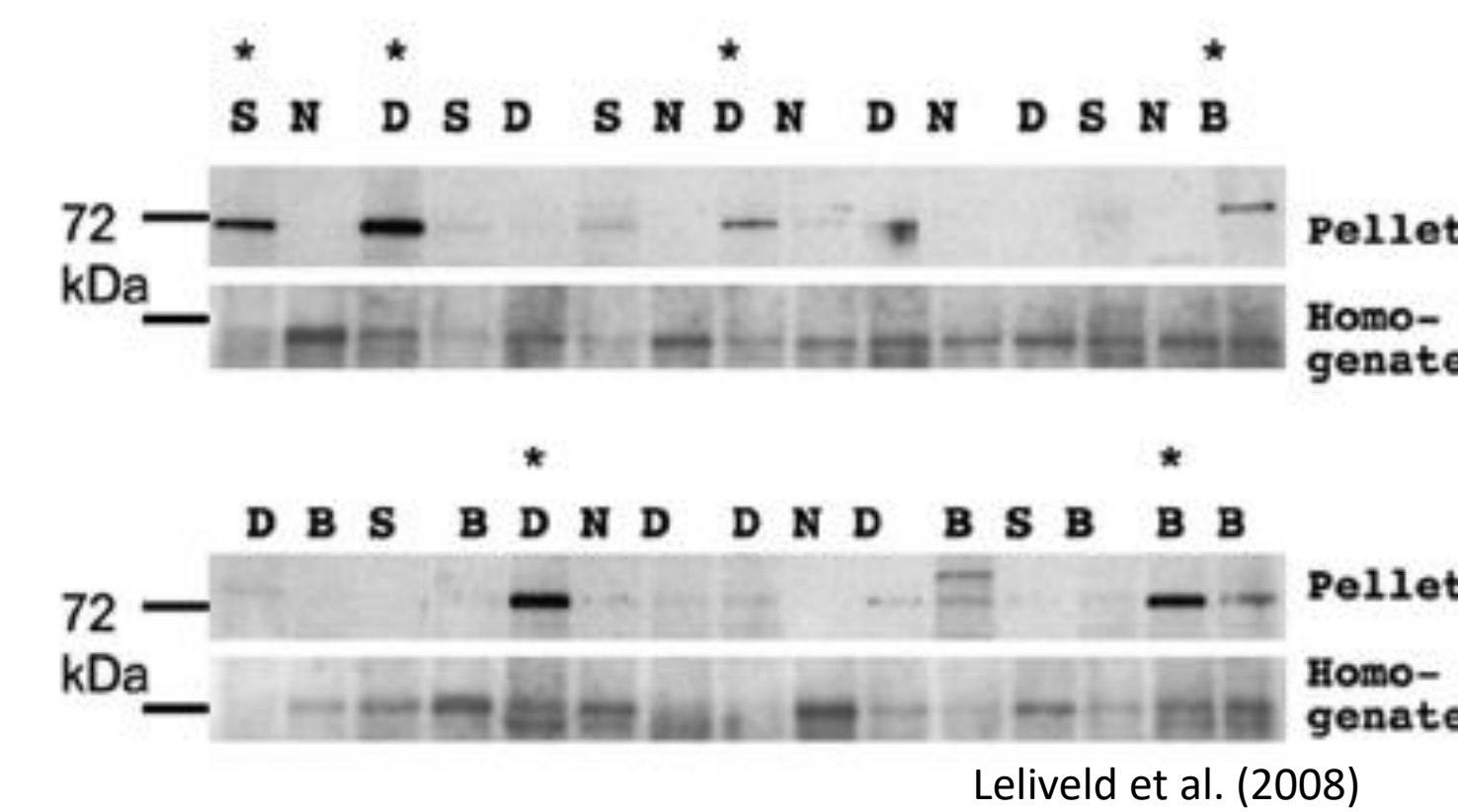
Could similar aggregates exist in the brains of patients with chronic mental illness?

Aggregating proteins in mental illness?

To find out which proteins form aggregates in a sample of brain, we can purify from it only the proteins that are insoluble (do not dissolve)



We can then test these insoluble protein "pellets" to see if specific proteins are found only in the brains of patients



Bradshaw et al. (2017)

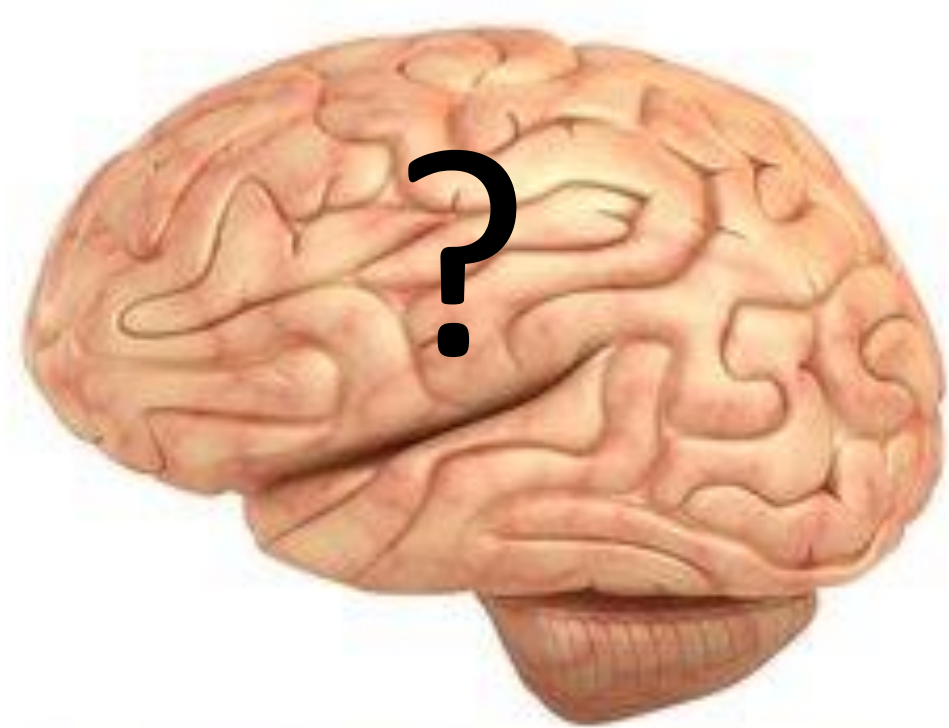
These proteins can then be put into cell culture, to test if they aggregate and what effect they have.

So far, five proteins have been found that might aggregate in schizophrenia and/or the affective disorders

The next steps: Our current research approaches

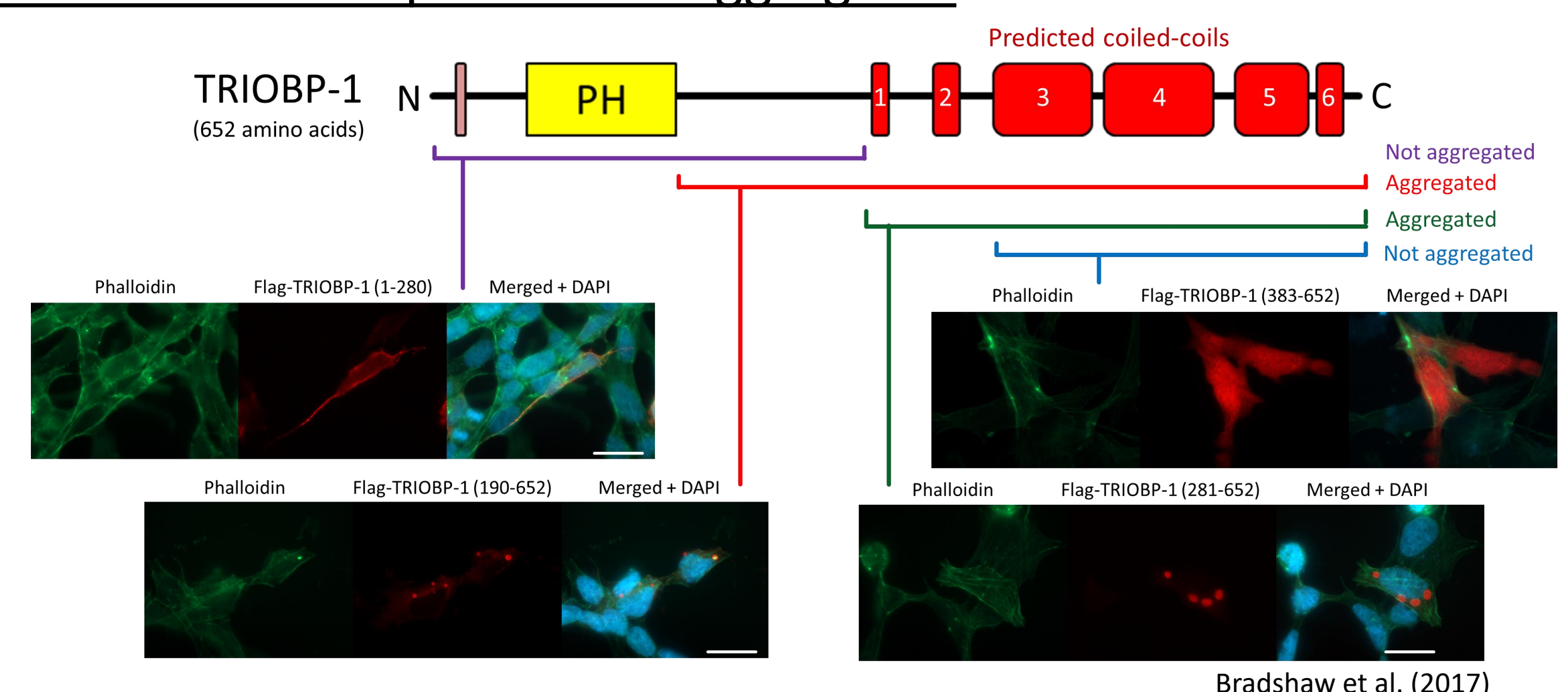
Do the proteins aggregate in clinical samples?

To be sure that a protein is relevant to mental illness, we must confirm that it aggregates in large numbers of patients.



While it is protein aggregates in the brain that may cause mental illness, detecting them in other parts of the body may help with diagnosis.

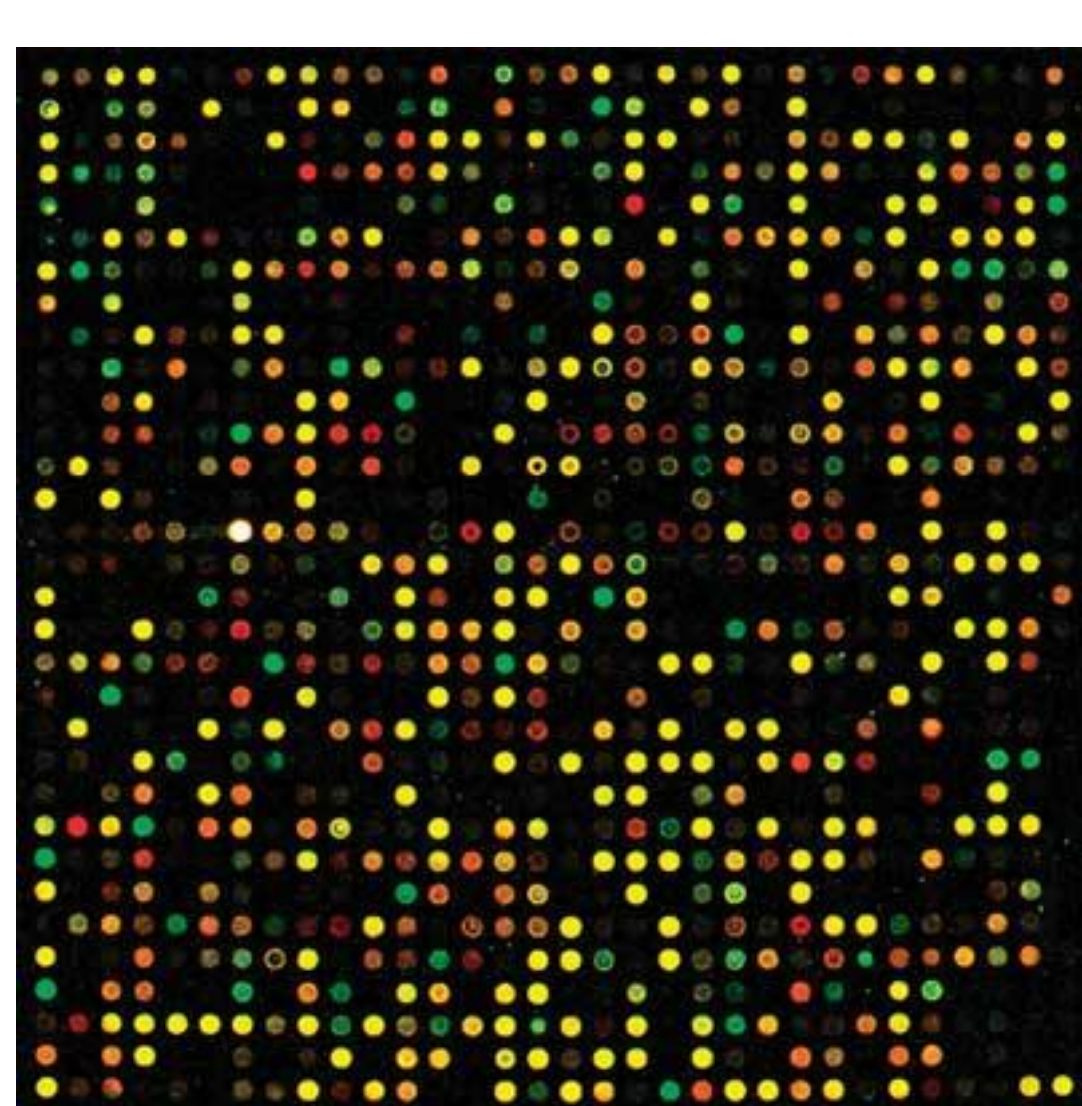
What causes these proteins to aggregate?



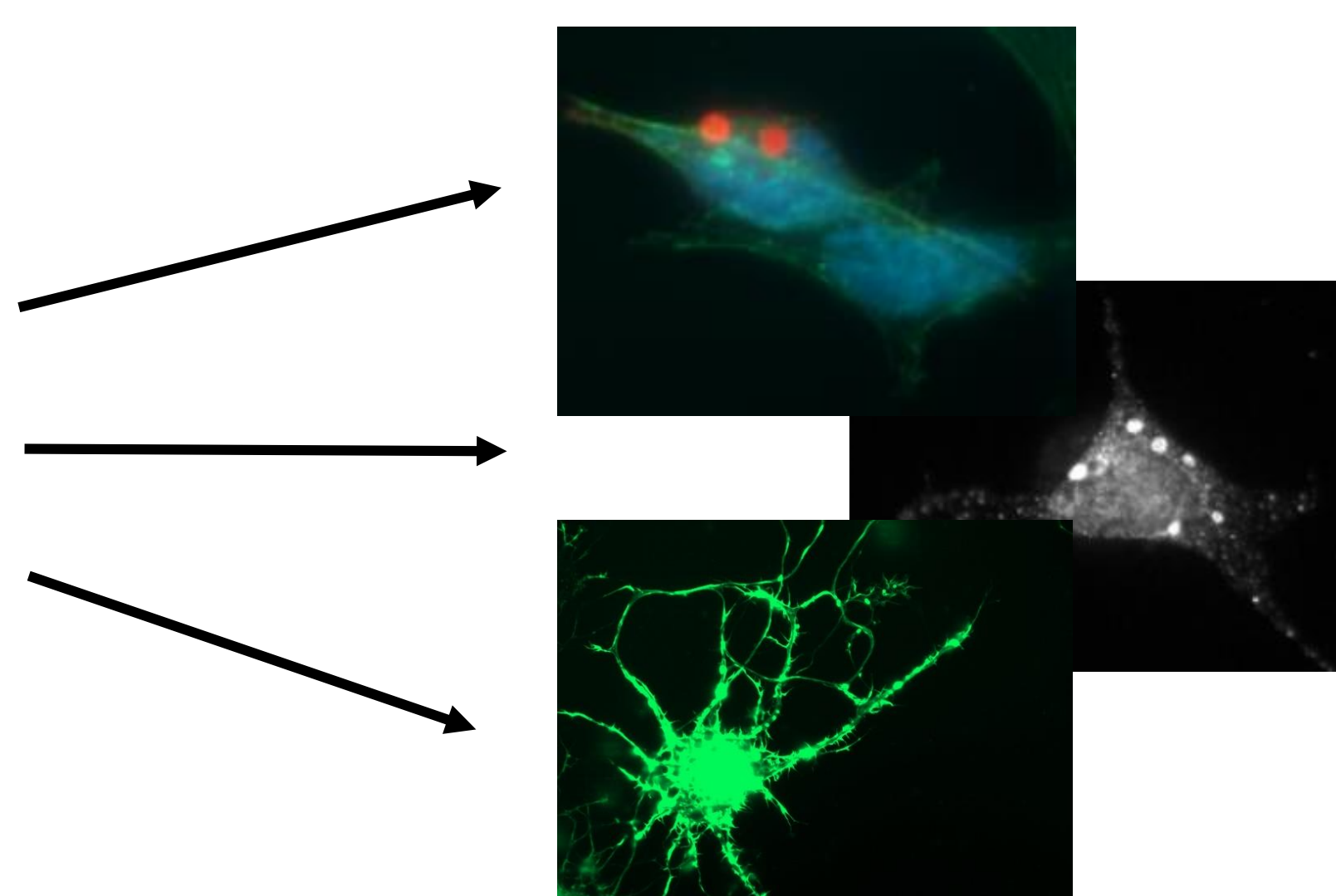
Bradshaw et al. (2017)

By determining which parts of a protein cause it to aggregate, we can begin to understand how aggregation occurs – and maybe how it can be stopped?

Which other proteins may aggregate in mental illness?



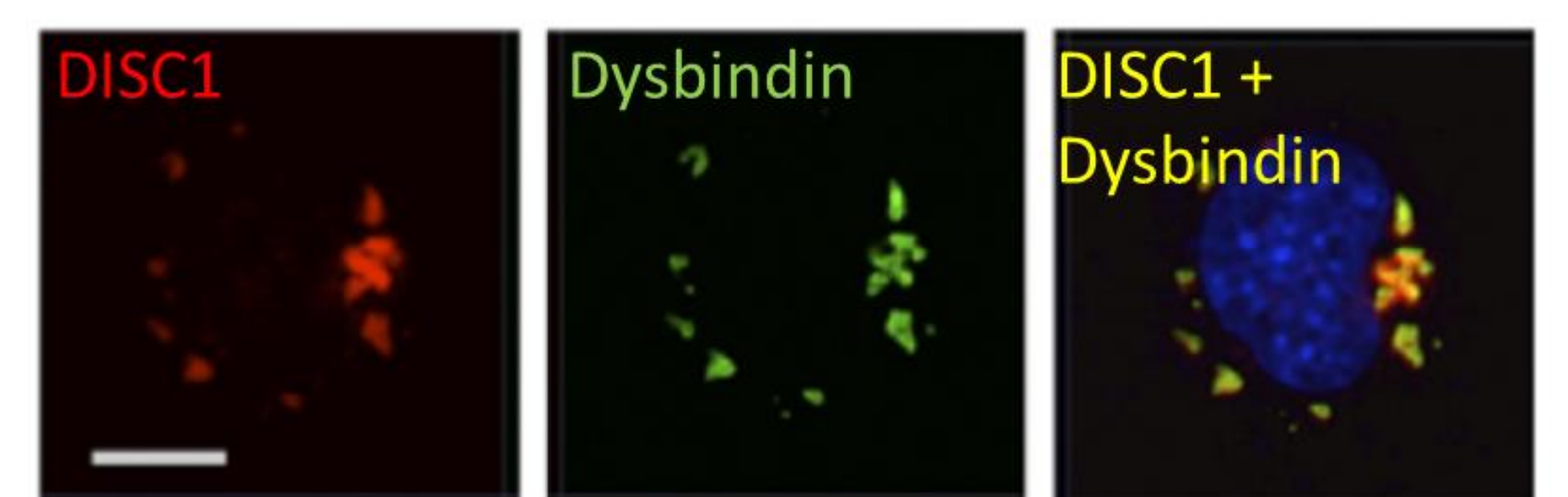
Source: Promega



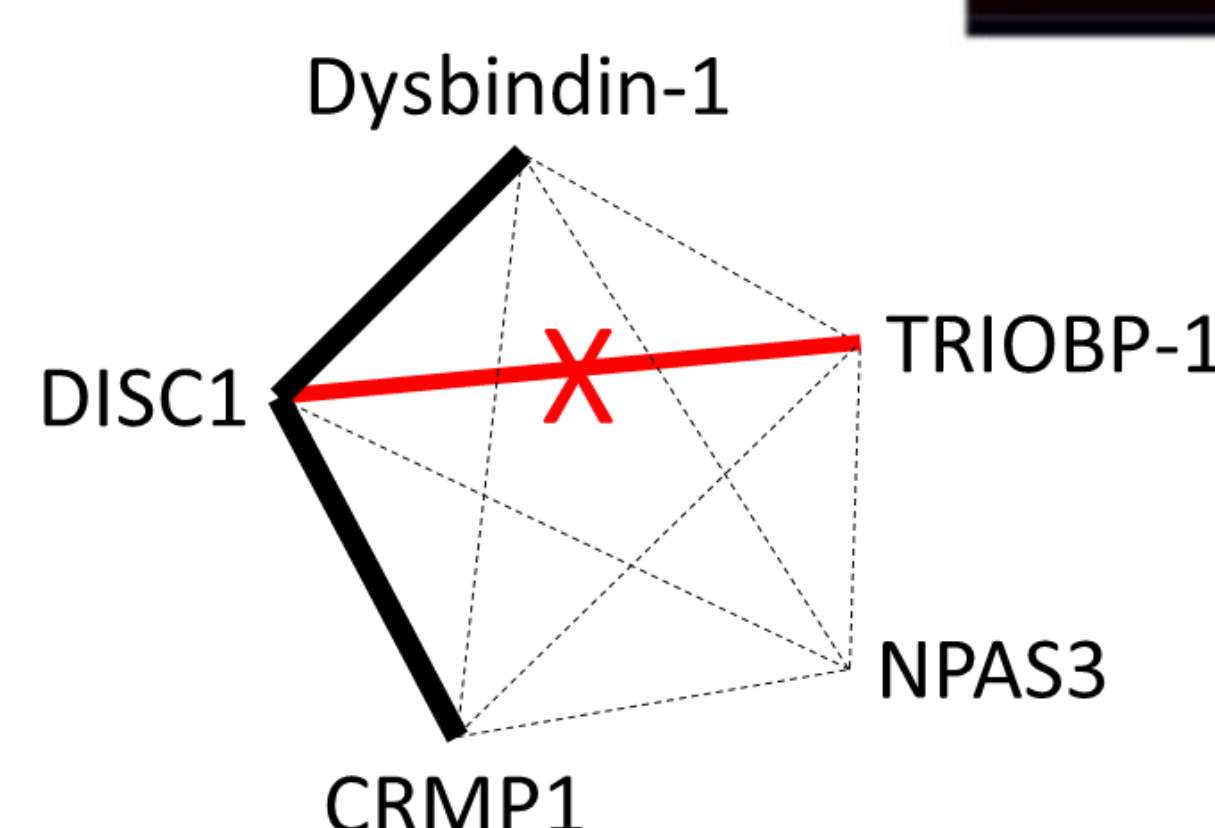
With the help of collaborators in Germany, we are testing new proteins which also may aggregate in schizophrenia and depression

Do these proteins aggregate together?

Some of these proteins aggregate together in cells, making each other worse.



Ottis et al. (2011)



We are trying to understand how these proteins work together, and with other proteins, to form aggregates.

Ultimately, we want to understand what the effect of these aggregates is on neurons, and thus how they may effect mental illness.