Innovation for Treatments on Creutzfeldt-Jakob Disease - CSFY project

SCIENCE FAIR LOGBOOK- 2025-2026 Zimmel Nadir

July 1st, 2025

- Finalized my idea for the science fair - I want to tackle CREUTZFELDT-JAKOB DISEASE, (KROITS-felt YAH-kobe) a rare brain disorder which can lead to dementia.
- Currently there is no cure for this rare disease, as the messed up prions which are responsible for its development are difficult to handle
- I want to see if there is any way I can tackle these prions, perhaps in another body such as yeast, which can then help us move forward in tackling Creutzfeldt-Jakob Disease (CJD)

What are my goals?// Background information and research

- ☑ ~~What is this disease?~~
- ☑ ~~How does this disease occur?~~
- ☑ ~~Is it similar or different from mad cow disease?~~
- ☑ ~~What does it do to an individual? // death rates and symptoms~~
- ☑ ~~What individuals are affected?~~
- ☑ ~~Why is it so far uncured?~~
- ☑ ~~What have hospitals and scientists been doing in the meantime?~~

July 2nd, 2025

- I researched a little on how to read and write academic research. (check full document for more detail if need be)

Association, correlation, causation, and multiple regression are important vocabulary words in order to understand what your reading is true.

- Being able to read something and not just automatically assuming it's true but taking the time to analyse; is this by random chance? Does A cause B? Does B cause A? Or does something else cause both? Can be helpful in furthering research and double checking to ensure you're on the right path.
- Association - a connection between two variables
- Correlation - a connection between two variables, but more specific

- Causation - something inferred based on the connections and relationships found through associations and correlations
- Multiple regression - that a relationship is true, even when compared to other factors.
- GOOGLE SCHOLAR and WEB OF SCIENCE - good places to find reliable papers
- Make sure you double check to really see if what your reading is all fine and dandy
- And remember; you don't need to understand every little bit!
- **Know three things; if you care about the topic, what the charts show and if you should believe it (which is where all those words come in, because statistics are finicky) and why that's important.**

Writing Research - Helpful for a script

- **Title** - what is it called?
- **Abstract** - summary of the article, what you will find
- **Introduction** - Describe the problem, background information, and other similar studies used (which are also helpful resources)
- **Literature review** - Review other studies that have given knowledge, and a summary of said research, and also areas of incomplete data and remaining questions
- **Research Question** - Explain the HYPOTHESIS- question to be answered with their study (IF, THEN, BECAUSE…should be something new)
- **Materials and Methods**- details of the experiment- how it was conducted, techniques, subjects (human, animals, cells), How many subjects (the more subjects the more valid), the type of study
- It's important to dictate the sample size of the study
- **Results -** the study and its findings, which most often includes graphs and tables
- It's important to look for the MEAN (average value, what you found basically), STANDARD DEVIATION (which is how certain variables change throughout the study; a larger sample size means for deviation or change from the mean. What is different from the mean, is what is being asked) P-VALUE (as discussed, a measurement of how reliable the evidence is) and that goes into how its STATISTICALLY SIGNIFICANT (if the P value is very low, like 0.05, then its a 95% confidence interval that the study was because of what was being changed, not due to external factors)

P-Value (important for an experiment)

-P-VALUE IS NUMBERS BETWEEN 0 and 1 AND SHOWS HOW CONFIDENT WE ARE THAT AN EXPERIMENT IS EFFECTIVE. The CLOSER it is to ZERO, the more confident we are our experiment is effective and legit

-If a p-value is 0.05, only 5% of experiments are messed up (if it is higher than 0.05, it's not legit)

-The P-Value helps to determine if your null hypothesis should be rejected

-Also note; just because a statistic is super close together, it does not mean that the P values are similar to that. You can have data one percentage apart, but the P value can still be 0.02, or low enough to be considered legit.

BACKGROUND RESEARCH

July 3rd, 2025

What is Creutzfeldt-Jakob Disease?

Creutzfeldt-Jakob disease - Symptoms & causes - Mayo Clinic

- A rare brain disorder *(any condition which impairs the brain's abilities)* which leads to dementia *(a general term to describe memory loss, which affects the daily lives of an individual)*
- Belongs to a group known as **PRION DISORDERS***
- Similar to alzeimers, but it moves faster and is fatal (typically within a year a person diagnosed with CJD will pass away) This is often due to the issues which come from the disease, such as trouble eating, heart and lung failure, pneumonia, and other infections which can develop
- SYMPTOMS INCLUDE; changes in personality, loss of memory, blurry vision, insomnia, trouble talking and coordinating oneself. Dizziness, slurred speech, hallucinations, depression, withdrawal, anxiety, irritability.
- In the final stage the patient will be bedridden, the complete loss of speech, and an inevitable death.
- There is nothing which can be done at this stage in the disease (however advancements in end of life care, which focus on incurable diseases, mean the patients go out peacefully)
- A change in mental ability may be noticeable in the early stages, and later on dementia can develop

Creutzfeldt-Jakob Disease | National Institute of Neurological Disorders and Stroke

- As we know CJD and prion diseases alike so far have no known cure for these types of diseases. (prion diseases are also called transmissible spongiform encephalopathies)
- SPONGIFORM refers to how the brain looks like a sponge when affected with a prion disease, because of all the holes
- Like prion diseases, CJD creates issues around memory and coordination, often leading to dementia and, inevitably, death
- 70% of individuals will die within the first year of contracting the disease

Types of CJD -
Creutzfeldt-Jakob disease - NHS

1) SPORADIC CJD
    - Most common
    - Cause is unclear and seemingly spontaneous , but is suspected to be linked to, again, a brain protein folding which turns into a PRION*
    - Ages range from 45-75

2) VARIANT CJD
    - Suspected to be caused by consuming meat from a cow which has bovine spongiform encephalopathy (BSE, or mad cow disease) It is a similar prion disease
    - To prevent it, there have been strict controls on meat and its protection from diseases such as BSE
    - Can also occur through blood transfusion
    - The time it takes for the disease to develop after initial contact with the infected meat, is again unclear

3) FAMILIAL / INHERITED
    - A rare genetic condition where an individual will inherit a mutated prion protein from their parent, causing prion formation in adulthood, and the potential for CJD
    - The symptoms typically develop in adults in their early 50s.
    - Genetic mutation

4) IATROGENIC CJD
    - The infection is spread accidentally from someone with CJD, through medical/surgical treatments
    - Iatrogenic CJD had been spread in the past through pituitary growth hormones extracted from people with this disease (it is now synthetically made, so no there is no risk)
    - Can also occur if surgical instruments aren't properly cleaned after being used on an individual with CJD, and then had been used on someone else
    - Increased awareness has reduced this type of CJD however

IMPORTANT VOCABULARY

prion/ prion disease- A certain misshapen protein in the brain which seems to be the cause of CJD // a prion is a misshapen and misfolded protein which causes other proteins to misfold, and thus creating clumps of prions which results in brain damage
Sporadic- the most common type of CJD (85%) , and develops suddenly
Variant- A type of CJD which results in digesting cattle infected with mad cow disease, another smilat prion disease
Familial- a rare genetic mutation which results in the transfer of mutated proteins from a parent, which result then in symptoms of CJD
Iatrogenic- a type of CJD in which the disease is spread accidentally from someone with it, through a medical procedure
genetic CJD- a type of CJD where the genes mutate, thus resulting in messed up proteins, which then in turn result in prions.

July 4th and 5th, 2025

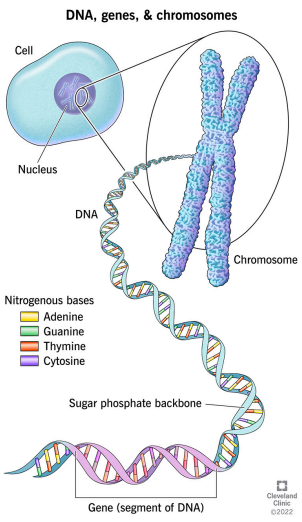
How does CJD occur? // What is a Prion Disease, and how does it occur?

[Prion Diseases | Johns Hopkins Medicine]
[Creutzfeldt-Jakob disease - Causes - NHS]
[Creutzfeldt-Jakob disease - Symptoms & causes - Mayo Clinic]
[DNA vs Genes vs Chromosomes: An Overview]

- CJD is caused by infections proteins called PRIONS in the brain
- Proteins are molecules of amino acids which help cells function. They begin as a string of said amino acids, and fold over in order to perform their functions.

The Genetics *(specifically for genetic CJD)*

- Chromosome 20 (as we know we have 46 chromosomes in total, and 23 pairs), where the prior protein is, and all genetic prion disease result from mutations in this gene
- The gene on chromosome 20 is called PRNP, and encodes for a prion protein
- RNA (translated from DNA) will communicate to the genes inside a cell's nucleus on what proteins it should make (proteins make the structure and functions of the human body)
- The nucleotides on RNA and DNA (the rungs on the ladder) make up the alphabet of our genetic code.



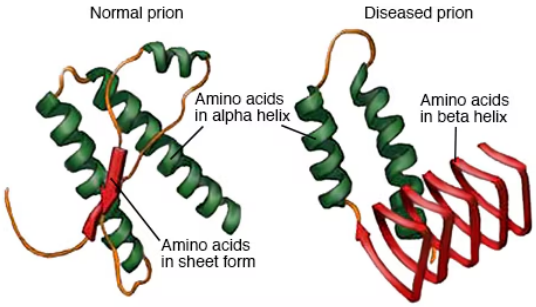
- Read in three letter pairs, which in turn make an amino acid, which in turn make a protein
- As we know, chromosomes contain DNA which contain genetic information. In order to build who you are, these three things work together.
- The GENES hold specific parts of your DNA. That DNA will send messages by RNA (mRNA), to create PROTEINS.
- If there is a genetic mutation then it can result in wonky and folded proteins or harmful PRIONS.

How do proteins and prions fold?

- We start with a normal protein, which attains a molten globule state (like partially folded), and continues to fold until it reaches its normal end stage.
- But during the folding process errors can occur (that genetic mutation) and those proteins become misshapen
- But not to worry, these proteins are sent for repair, and gets corrected so it can become normal
- But if it does not, it goes to proteases to wear down, and get recycled into the body.
- BUT, if the misfolded protein can since changed into a PRION, it resists the proteases and can not be broken down.
- This is due to the structure of said prion. A regular prion protein will have 43% alpha helices and 03% beta sheets. But a prion will have 40% alpha helices and 43% beta sheets. This difference results in that resistant (protease resistant)
- These undegraded proteins are then called PRIONS
- And then these prions can go and affect other prion proteins to misfold as well.

The Deal With Prions

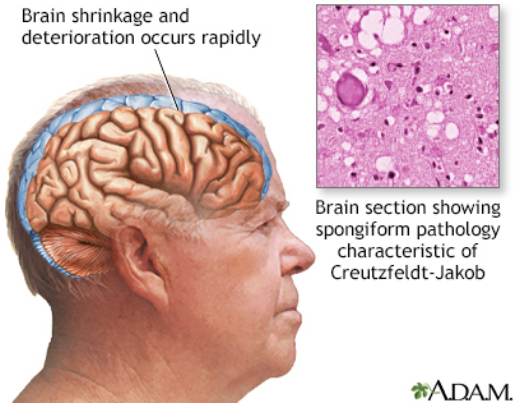
- There are normal and harmless prions, which are technically just folded proteins, and they are found in all parts of the body, especially the brain. Their cause is still unclear, but it is speculated to be responsible for transporting messages in the brain.



- However, proteins can sometimes misfold, which in turn leads to harmful and infectious prions.
- If they are not recycled back into the body and continue to misshapen and grow diseased, they can build up in the brain.
- They can also cause other proteins to misfold and clump together.
- That is a Prion Disease, and CJD is actually the most commonly acquired prion disease (even if it is rare)
- This clumping in turn causes brain damage, and as discussed many other symptoms such as memory loss and personality changes. (and it is often fatal, which is an issue as scientists don't know a lot about prion diseases)
- Prions also have no DNA, because proteins do not have DNA. They are created from messages sent by DNA.
- They duplicate and replicate by infecting other proteins

How do prions specifically cause CJD?

- As mentioned, the prions cause other proteins to misfold as well
- Brain cells will die, and then more prions are created, which attack more brain cells
- When big clusters of brain cells are killed, big clumps of prions called plaques will develop in the brain (and thus further that chain reaction)
- Holes are also created in the brain, making the brain look spongy, which in turn lead to all the symptoms associated with CJD and eventually death.



Causes for each type of CJD

1) Sporadic CJD
    - A protein spontaneously changing into a prion,
2) Variant CJD
    - CJD which is acquired from eating meat infected with BSE or mad cow disease
3) Familial CJD
    - A mutated gene which results in said abnormal prion

4) Iatrogenic CJD - iCJD
    - The spread of CJD through medical instruments
    - Due to regulations, iCJD isn't nearly as common as it once was.
5) Genetic
    - By genetic mutations which mess up the creation of proteins

Important vocabulary

DNA - exists in every cell of your body, and holds your genetic code. The body's instruction manual. There are four chemicals, (adenine) A, (thymine) T, (Guanine) G and (Cytosine) C. These chemicals (nucleotides) write the instructions.

RNA- DNA is super important and it makes up all the cells, and therefore can not leave the nucleus. So, RNA is its messenger, going in and out to make things like proteins for the body.

Genes- building blocks, and a segment of DNA. Some genes code instructions for the making of proteins, some for instructions for RNA. You get one gene from your mom, and the other from your dad.

Chromosomes- these are thread like structures living inside the nucleus of a cell. They contain the DNA, and we have 46 of them, which make 23 pairs *in each cell* The chromosome carries the DNA in the nucleus, which is responsible for building who you are. Further down, genes are segments of DNA which define specific characteristics

Genetic mutation- occurs when cells divide and multiply. They are copy and pasting your code, so if something goes wrong and a piece of the code is missing, it could potentially mean a change in how your body functions

Amino Acid - Molecules which form to make proteins

Protein - an important structure in the human body which provides structure, allows for certain functions, and transports materials. If a protein is mutated, it no longer works, or becomes a prion.

PrP^c - is to dictate a prion protein, which are present on neurons and are normal(which are mostly in the brain)

PRNP - The gene on chromosome 20, which encodes for the prion protein. The prion protein gene.

Prion (PrP^sc) - misfolded prion protein (mutated PrP^c)

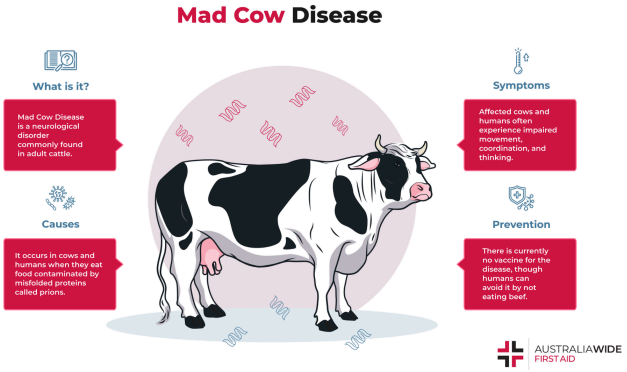
July 5th, 2025

Is it similar or different from mad cow disease?

CREUTZFELDT – JAKOB DISEASE (CJD) AND MAD COW DISEASE

Mad Cow Disease (Bovine Spongiform Encephalopathy) | Johns Hopkins Medicine

- Mad cow disease is another prion disease, however it is different from CJD
- BSE or Bovine Spongiform Encephalopathy (Mad cow disease) is typically found in cattle, and makes them act strange ie, the inability to walk normally
- BSE is actually not able to be contracted by humans, and only affects animals. However of course, we have a similar prion disease called vCJD or variant CJD, which as we know humans can acquire by consuming meat infected with BSE
- Both of these diseases come from prions, and result in death



July 6th, 2025

What does it do to an individual? *// death rates and symptoms*

Creutzfeldt-Jakob disease - Symptoms - NHS

Prion Diseases | Johns Hopkins Medicine

Symptoms

The types of symptoms can vary and change depending on the type of CJD

1) Sporadic
    - Affecting the nervous system (neurological symptoms)
    - These symptoms will rapidly worsen with time
2) Variant
    - First psychological symptoms (emotions and behaviour) will develop
    - Then will follow neurological symptoms which will rapidly worsen with time
3) Familial

- The same pattern as sporadic CJD, however the symptoms will take much longer to process
- Typically years rather than months

4) Iatrogenic
    - Unpredictable and depends on how the person came into contact with the prion which caused the disease

Neurological symptoms - initial

- Difficulty walking due to problems with balance and coordination
- Speech is often slurred
- A pins and needles feeling
- Feeling dizzy
- Trouble seeing or witnessing hallucinations

Psychological symptoms - initial

- Feeling depressed
- Withdrawal from loved ones
- Feeling anxiety or irritable
- Insomnia or troubles sleeping

Neurological symptoms - advanced

- Ataxia (complete loss of control over a person's body and coordination)
- Muscles twitch and spasm
- Loss of bladder/bowel control
- Becoming blind
- Difficulty to swallow
- inability / loss of speech

Psychological symptoms - advanced

- Severe memory loss
- Concentration issues / feeling confused
- Feeling agitated / aggressive behaviour
- Loss of appetite (leading to weight loss)
- Feeling paranoia / unusual emotional responses

The final stage

- As the disease persists and reaches the final stage, most typically everyone with any version of CJD will become bedridden, and require care at all times
- They are unable to communicate
- Death will soon follow, usually from infections or organ failure
- Nothing can be done at this point to help a patient

Death Rates In Canada

Creutzfeldt-Jakob disease surveillance system (CJDSS) report

- As reported by the government of Canada, the suspected number of people to have contracted any sort of CJD virus from 1998 to today, is around 2,900, so about 3000 people in total.
- The definitive number of people from this time period to have contracted sporadic CJD is 1381, Iatrogenic six, genetic 99, and variant only two.

Creutzfeldt-Jakob disease mortality in Canada, 1998 to 2013 - PubMed

- An investigation was conducted by Canadian health professionals and investigators associated with the central CJD surveillance registry (run by the Public Health Agency of Canada), in order to determine cases and mortality rates from CJ
- Said investigation was done through family histories, clinical profiles, and other laboratory investigations. This study was then reported by the National Library of Medicine, and reports the following information following CJD cases from 1998 to 2013. -
- They found 613 cases of sporadic, 43 genetic, 4 iatrogenic, and two variant. Since it is an older study, it makes sense that the numbers don't line up. However, the pattern of sporadic being the most common whilst variant being the least common stays consistent.
- Overall they reported 662 deaths, and reported a 95% confidence interval for their statistics

CJD FACT SHEET

- However, discussing in a more global sense, according to the CJD foundation 1 to 2 per million per year, which in turn translates to around 500 new cases per year.
- There is one CJD death per every 6000- 10,000 people
- Showing that this disease, while 100% fatal, is very rare

What does it do to the brain?

- As discussed the prions will infect the brain, creating holes and killing brain cells
- As time goes on this will worsen, and therefore symptoms and conditions will worsen as well
- Eventually leading to advanced symptoms, and eventually death

Mentioned above…

- *Prions cause other proteins to misfold as well*
- *Brain cells will die, and then more prions are created, which attack more brain cells*
- *When big clusters of brain cells are killed, big clumps of prions called plaques will develop in the brain (and thus further that chain reaction)*
- *Holes are also created in the brain, making the brain look spongy, which in turn lead to all the symptoms associated with CJD and eventually death.*

IMPORTANT VOCABULARY

Psychological - to do with the mind / brain - an emotional state of being
Neurological- to do with the nervous system
Nervous System - a network of nerves and fibres which sends messages from the body to the brain and vice versa.

July 7th, 2025

What individuals are affected?

Prion Diseases | Johns Hopkins Medicine
Creutzfeldt-Jakob disease - NHS.
About Prion Diseases.

- There may be a risk of contracting CJD if an individual has family history with prion diseases, has eaten meat infected with BSE, or came into contact with medical equipment infected by CJD
- Most often seniors are affected by CJD, typically between the ages of 45 and 75.

- Most often CJD is diagnosed as sporadic (85%), so the reasoning is often unclear as to why the disease developed (why prions had developed.) But it is speculated that this prion disease is more common amongst older people because they are more likely to have their proteins spontaneously fold as compared to younger individuals.
- However it is important to keep in mind that the disease is still very rare, even if it is more common amongst an older population
- And variant, genetic, and iatrogenic versions of CJD are still possibilities, however even more so unlikely

July 8th, 2025

Why is it so far uncured?

The Latest in Medicine: The Problem of Prions Disease — Minds Underground.

Prion diseases and the immune system - PubMed

- Prion diseases are irreversible, unable to be overcome by the immune system
- As prions are seen by the body as proteins, and does not recognize it as a foreign body like a bacteria. Therefore allowing said disease to develop further (in its spontaneous, quickly clumping, and deadly nature. This clumping is known as FIBRILS)
- And on top of that, there is no medication or drugs for the treatment of prion disease. This is speculated to be the case due to the fact that there isn't enough attention or research done on the disease, because it is so rare.
- Prions, unlike bacteria and viruses, have no nucleic acid genetic element (DNA or RNA), and therefore can not be destroyed by ultraviolet irradiation (exposing to radiation) as that is what would kill said nucleic acid.
- They also resist protease, an enzyme which degrades proteins. Making prevention even more difficult
- Due to an unclear understanding of what prion proteins do for the brain, it is unclear how to handle treatment because there is a risk of disturbing something important (these prion proteins are in the brain after all, one of the most crucial organs)

Important vocabulary

Fibrils - insoluble clumps of prions in the brain

July 9th, 2025

What have hospitals and scientists been doing in the meantime? *// diagnoses, treatment, prevention*

Prion Diseases | Johns Hopkins Medicine
CJD Foundation
Creutzfeldt-Jakob Disease | National Institute of Neurological Disorders and Stroke
Creutzfeldt-Jakob disease - Diagnosis & treatment - Mayo Clinic

How is CJD (and prion diseases) diagnosed?

Prion diseases are confirmed by taking a sample of the brain during a biopsy. (or after the death of a patient) However, a biopsy is risky, as it's taking the tissue of the brain out of someone who is living. So health care professionals instead run many other tests to detect a prion disease. These include…

- MRI (magnetic resonance imaging) scans of the brain. By taking pictures of the brain with radio waves, a doctor is able to see that spongy texture of the brain which often results from CJD. (MRI's result in high quality and clear images, and are often used for these kinds of purposes)
- Spinal Tap (lumbar puncture) is when you take samples of fluid from the spinal cord or around your brain. When such a fluid is extracted, it can help eliminate other diseases that have similar symptoms to CJD and helps to see the levels of proteins, which can then point to the possibility of a prion disease.
- Cerebrospinal Fluid (CSF) Tests is a branch of tests with spinal taps fall under. The test looks for elevated markings of proteins which dictate rapid brain cell death, which is a common factor of CJD. There is a newer test based in CSF called RT-QuIC which can actually detect certain prions which cause CJD.
- Electroencephalogram (EEG) which is a test done to look at brain waves with the use of electrodes. This is a method which measures the brain's electrical activity. If an individual has CJD, it will show an abnormal pattern.
- Blood tests
- Visual and Neurological exams to check for symptoms (nerve damage, vision loss)
- Genetic tests for the potential a prion disease is hereditary

How are Prion Diseases Treated?

- Currently, there is no cure for prion diseases. Health care professionals try to make sure that a patient with prion disease is safe and comfortable even in their final moments
- Researches have however been searching for drugs that could control CJD, and other treatments *(which I'll research when I want to see what I can do)*
- There is the CJD foundation, which is an entire organization based around providing support in the form of funds, awareness, and healthcare for families and individuals affected with CJD. They also allow for research to be submitted, in order to progress knowledge on CJD and prion disease as a whole.

Can it be prevented?

- Ensuring healthcare professionals properly clean equipment that comes into contact with the disease
- If you have the disease, it's a good idea not to donate organs or tissue
- Government regulations have ensured that cattle are raised well, and therefore there is no risk of humans of contracting vCJD

What can I do? // *Updates, current projects and initiatives, existing treatments, how proteins are dealt with, genes and DNA,*

This is the part of the project where I research what has been done about CJD, and prion disease a whole. Certain updates, initiatives, studies, experiments, and existing treatments that I can apply to my own research in developing some sort of solution and experiment to deal with prion disease and CJD. I also want to do my own background research on proteins in the brain, the folding of prions, and genetic mutations to see if there is anything there I can work with as well.
The national institution of health has given the opportunity to get involved with clinical research to deal with prion disease. This could be very helpful in the near future. Keep it in mind.
If You Have a Question | National Institutes of Health (NIH)

What are my research goals?

- ☑ ~~Updates on CJD~~

- ☑ ~~Current studies and experiments for CJD~~
- ☑ ~~Protein Synthesis~~
- ☑ ~~Genetic mutations and CJD~~

Hopefully by the end of all this research, I will develop some sort of idea.
Then, we work on that!

July 21st, 2025

Creutzfeldt-Jakob Disease | National Institute of Neurological Disorders and Stroke

Updates on CJD

- NINDS, which is part of the National Institute of Health (NIH), is actually the leading funder for research on neurological disorders. Supporting new studies and research in order to better assess CJD.
- This includes understandings, treatments, and diagnoses (other NIH institutes also partake in said research)
- They are EXAMINING and CHARACTERIZING the prions which lead to CJD (as well as other prion diseases in both humans and animals)
- They are looking to better understand the disease in hopes **of discovering how PRIONS affect nearby brain cells, how it is passed along from person to person, and how that disorder damages the brain.**
- They are also looking to see how **CELLULAR MECHANISMS take part in prion formation and build up**
- There are other projects which look to see how abnormal prions cross a blood barrier of the brain, and how it spreads.
- They are improving tests to improve measures of prion activity. These findings could result in new therapeutic targets to treat prion disease.
- **CEREBRAL ORGANOIDS** have organization, structure, and electrical signaling systems similar to human brain tissue. Being able to survive in a controlled environment for a long time can allow for studying these diseases, and have been used for other diseases such as Alzheimer's and Down Syndrome

- They are also **exploring regulations of the PRION PROTEIN GENE**, to control it and change the course of it and maybe even slow and stop it.

What are "therapeutic targets?"

- If we lower how much normal PrPC is made, then it limits the creation of harmful prions
- Spreading up PrPC breakdowns can reduce misfoldings
- If we change the direction where PrPC moves, then it can protect brain cells from getting damaged
- Certain Chemical can keep PrPC in its normal shape, and less likely to turn into PrPSc
- Disrupting interaction between harmful and harmless prions can reduce infections
-

But there are some considerations to be made…

- Prion disease is rare and acts fast, which makes finding solutions in clinical settings difficult
- There are varying symptoms, which can spur confusion
- Treatments can have trouble actually entering the bran
- Harmless prion proteins are still important…will these treatments harm them?

Important vocabulary

Cellular Mechanism - How cells carry out their functions; communicate, move, grow, etc.
The Brains Blood Barrier (BBB) - it serves as a shield in the brain, to shield it from unwanted or harmful substances from the blood, provides the brain nutrients, and will filter harmful material in the brain's blood into the bloodstream
Cerebral organoids- 3D cultures which mimic the human brain

July 22nd, 2025

Transmissible Spongiform Encephalopathies | National Institute of Neurological Disorders and Stroke

Updates on prion disease (transmissible spongiform encephalopathies) in general

- Reducing the EXPRESSION natural prion protein to reduce the chances of that protein becoming harmful (misfolds and clumps)

- There is a tool called CHARM (Coupled Histone tail for Autoinhibition Release of Methyltransferase) it **silences a prion protein through the process of EPIGENTIC EDITING**
- This tool could be used for treatment of prion diseases. Typically gene editing involves just changing the genes of an organism, **but this specific gene editing takes the GENE EXPRESSION and turns it OFF and a GENETIC TAG which then prevents genes from translating into proteins.** This is a certain strategy lead to the development of tools which **can then take harmful genes and silence them, such as the one which creates the prion protein**
- This will then result in a reduction of TSE's from being created without altering DNA.

NOTE- FOR THE ABOVE TWO POINTS, THE NIH RePORTER CAN ALLOW ACCESS FOR MORE INFORMATION.

Important TOPICS

Protein Synthesis - lets talk about eyes for a bit. Your DNA has the code for the colour of your eyes. But in order for that colour to be seen, you have GENES (portions of DNA which code for PROTEINS, which in turn make that pigment in the eye. But how? Through protein synthesis! Proteins are very very important, and do all kinds of things. They transport materials, provide structure, protect the body, etc… But back to DNA. All cells have DNA which is in your cells, which is in the NUCLEUS (eukaryotes). But how is the DNA going to leave the nucleus and encode for proteins? Through RNA! There are two major steps involved in that. TRANS**C**RIPTION and then TRANS**L**ATION. Transcription happens in the nucleus, and there is an enzyme called RNA polymerase and will connect complementary bases or nucleotides to the DNA. This creates an mRNA, or a messenger. It is a message based on DNA, and made by RNA. And after some crucial editing done to the mRNA. And these guys get to leave the nucleus! And swimming in the cytoplasm they meet ribosomes, which make these proteins. And ensues the next step called TRANSLATION. In a cytoplasm you have tRNA or transfer RNA, and carry amino acids (building blocks for proteins) and when you get those amino acids together, you can get a protein! The tRNA does just that; bringing the amino acids together to form a protein. And the mRNA communicates which one. Then the tRNA will connect to complementary bases on the mRNA, and drop their amino acids. They do this in sets of

three (a CODON) Different arrangements of codons, representing different amino acids. And they are connected through a peptide bond.The protein may need to be folded or moved outside the cell, but it differs based on its function.

Gene expression and Gene regulation- The process by which the information within (or encoded) a gene, turns into a function (such as a protein, which is created by the genes information through mRNA) To say its “turned on” means its actively encoding for a function. “Volume control” is measuring how much of it is being created. You can actually measure how much a gene is expressed by a) measuring the functional activity of a gene (if a gene encodes for a protein, and that protein is well active, we can THEN see how active that gene is being expressed) or b) observing phenotypes with that gene.

Yes, again, genes have expression by performing functions often through protein synthesis. But not EVERY single gene. That is GENE REGULATION. There may be a cell in your eye with the gene to code for stomach acid. But why would it express that? It's wasteful and unhelpful. PROKARYOTIC and EUKARYOTIC express genes differently. As prokaryotic cells don't have a nucleus, the dna is just in its cystoplasm so transcription and translation just happen in their at the same time (unlike a eukaryotic) Prokaryotic cells usually have regulations during transcription. There are actually transcription factors which are proteins which can stop or encourage the transcription process. Regressor can block RNA polymerase, and then that gene will not be expressed. Helpful for when they don't need to. And if they do need that gene expressed, well then that regressor has to move out of the way. This regressor is either moved or stuck by LACTOSE. If lactose is not present, the regressor will stay and then the gene cant be expressed. However, if that lactose is there, it will move the regressor out of the way and then the mRNA can be created, and the gene expressed. (as one example) And eukaryotes have a whole bunch of these regulations. There is one POST transcription, but before translation. Let's say an mRNA is made in transcription. And during the editing process, some parts of that mRNA can be removed. This is called an INTRON. And therefore, are not expressed. During translation, you have the mRNA, the ribosome, and tRNA. There is a protein called EIF-2, which helps translation get started. However, this protein can also be regulated, through being phosporalated. This means a phosphate group was added to it. The shape changes, and can't initiate anything. Without that, there is no translation. And therefore, the gene isn't expressed. There's also regulation after translation.

Sometimes chemical groups can be added to proteins, which change function and location. As we know, certain environmental factors (like UV light or lack of nutrients) can also affect the expression. And ubiquitin, which signals a protein to be degraded.

Phenotypes - An observable trait of an organism, which is tied back to certain genes. By seeing those certain traits, you can also then see a gene's expression. (by observing where that phenotype is, when a phenotype is created, and the volume of said phenotype can all provide insight into that gene's expression.

July 24th, 2025

Developing treatments for prion diseases | National Institutes of Health (NIH) - *very interesting // understanding this seems to be important for our own project and initiative*

- Quick recap of prion disease; prion disease can either be spontaneous or as a result from mutated genes. The misfolded prion proteins will infect each other, causing more folding, and they will clump and kill brain cells. This leads to cognitive decline, dementia or Alzheimer's, and worsening symptoms until death. CJD is one of the prion diseases which affect humans.
- There are treatments for prion disease. However, it is known that the prion protein is not essential for survival.
- Studies show that mice were able to live without this protein, and then because of that, avoided the risk of them folding. And even reducing the prion protein after an infection, can slow down some of the symptoms associated with prion disease, and has little to no side effects.
- This shows that reducing prion proteins could potentially be a method of treating prion diseases.
- This could be done through the aforementioned EPIGENTIC EDITING (to affect how DNA is used, without affecting the genetic sequence)
- There was a tool designed for turning genes off called CRISPRoff. This takes the protein Ca9 with the CRISPR editing technology, to target a gene with an enzyme that methylates DNA. But it is not yet suited for therapeutic use, as its too big to fit into a harmless virus known as adeeno- associated virus, which delivers gene therapy

- And also, too much methylates can be toxic to cells, so CHARM was created (again as mentioned before)
- This tool activates existing methylating enzymes in cells, instead of bringing it in themselves.
- In mice, this showed to turn off the prion protein gene and reduce prion proteins by 80%. This however seemed to be too much, so they programmed CHARM to shut off itself after the prion protein gene would be turned off.
- Thai could be the beginning of further treatments for prion diseases.
- “CHARMs are an elegant solution to the problem of silencing disease genes,” Weissman says, “and they have the potential to have an important position in the future of genetic medicines.”

IMPORTANT VOCABULARY

Enzyme- proteins which help to speed up your metabolism, or biochemical reactions faster to ensure they are useful.
Methylated- a chemical reaction between a small group of molecules called methyl and DNA/proteins to change how they act. (such as altering gene expression)
Therapeutic use- to ensure a procedure actually helps heal and rejuvenate a patient's health. (preventing, diagnosing, curing, etc) If they are not for therapeutic use, it can not be said whether or not a procedure can be used for preventing, diagnosing, curing, etc.
Adeeno - associated virus- a virus which can be used and engineered to deliver DNA to target cells. This means to take certain genes within the DNA to other cells to change their function when treating disease.
Genome - an organism's complete set of DNA
Epigenome - certain markings or changes which change the way a genome acts

IMPORTANT TOPICS

Gene regulation and the OPERON - all your cells have the same DNA, but depending on which genes are expressed from that DNA, will change the functions. This is called genetic expression, where your DNA gives instructions and your genes then do all the things to do that function (often through protein synthesis) but it's important to regulate that so that nothing is wasted and the body works efficiently. What genes will be on and

which ones will be off. There are positive and negative transcription factors which are able to either encourage turn ON the expression (positive), or decrease it which can lead it to turn OFF (negative). And there is a certain fancy way to do it called the OPERON. There are some key players in an OPERON, such as RNA polymerase (an enzyme which starts transcription, by creating mRNA) But this enzyme needs something to bind too in order to work, so a PROMOTER or a section of DNA allows that to happen. Sometimes however, the RNA polymerase comes across an operator on the DNA strand, where a regressor can bind too. If the RNA Polymarese comes across it, it can not go across and will not make an mRNA. So the gene will not be expressed. Talking more about genes, after the operator there are three segments of genes which code for enzymes which break down lactose, or sugar. If there is lactose, bacteria want said enzymes to be made so they can eat the lactose. And then they can metabolize it. (the gene lacI codes for the repressor) If there were no enzymes, why make the enzymes that eat it? It's a waste. But if lactose IS present, it will bind to the repressor, remove it, and then RNA polymerase can go ahead and do what it needs to do.

Epigenetics say there's two twins, who have the exact same DNA. If they have the same DNA, why might one get a disease, and not the other. This has to do with the study of epigenetics, where DNA interacts with other molecules to activate and deactivate certain genes. DNA and genes are expressed when they're transcribed into RNA, which then turns into proteins by ribosomes. Those proteins determine a cell's characteristics and function. Epigenetics can boost or interfere with the transcription of certain genes. This can be done by certain chemical tags being attached to the proteins or DNA such as a methyl group, which limit gene expression. (by tying the DNA tighter around a protein for example)
And these epigenetic changes can be carried when cells divide, so a person can have them all throughout their life. And this is a constant throughout a person's life. An embryo will have one genome, which will divide. Some genes in those divided cells will be activated, while others deactivated. So all cells have their genomes, and special epigenomes
The certain chemical tags that turn gene expression on and off can be affected by environmental factors. An experiment with rats saw that when moths neglected their babies, their stress regulator genes were methylated and turned off, and this could appear to be hereditary, and affect upcoming generations. Which could be the same for humans! And when we understand how it affects us, we could go ahead and affect it.

CRISPR - a gene editing tool which can help tackle genetic based diseases. CRISPR has actually been a naturally occurring process, and it is a bacterial immune system. It defends cells from bacteria, with two main processes. Short repeating segments of DNA (called CRISPR) and CAS or crispr associated proteins, which chop DNA like molecular scissors. When a virus comes into a bacteria CAS will snip it, and put it into the CRISPR space. This takes a screenshot of the virus, and will create RNA, which connects to a protein called CAS9. so if that virus appears again, that protein will recognize and destroy it.
This process can be engineered to edit genes. RNA is made to match a segment of DNA they want to match and is put onto CAS9 which is led then to the targeted gene. The protein cuts off a segment. The cell will try to repair the DNA, but the repair process known as nonhomologous end joining will often have mistakes, and will often turn the gene off. But with some help, if the cells use homology directed repair, it will serve as a blueprint to rebuild the gene by repairing the defective gene or inserting a new one.
This can lead to all sorts of potential cures and treatments for genetic diseases.

July 27th, 2025

Environmental Factors and Prion Disease

Prions mutate and adapt to host environment | ScienceDaily

- Apparently, prions are able to adapt and therefore survive in new host environments.
- They lack RNA and DNA, and can not be destroyed through UV light. And the body does not realize they are infectious, like a virus.
- Despite this, they do share qualities of viruses.
- Charles Weissmann found that when one prion strain was transferred to a different cell line (some kind of cell grown in a lab) it actually changed and adapted, rather than staying the same. This could be through certain cell interaction and affect on those cells.
- It has adapted, and is different from the original prion strain and therefore a variant prion strain. It has changed to thrive better in that new environment. If they move again, they adapt again. If they move back to where they originally were, they change back again.

- It is also seen that prison calls follow Darwinian evolution, and can change over time. This included drug resistance, such as is the case with viruses.
- Therefore it seems most logical to deal with the prion protein before it mutates.
- And it seems that prions can also demonstrate survival of the fittest. That when a prion strain is moved to a new host, some variants of the prion (those changed ones) may duplicate faster and lead to a dominant strain . This is an evolutionary advantage in order to spread more efficiently.
- This means they can ADAPT, CHANGE OVER TIME, and RESPOND TO THEIR ENVIRONMENT like a virus, despite not having any nucleic acid (DNA or RNA)
- They sort of behave like QUASI- SPECIES, which are basically genetically diverse viruses, in a single host, which mutate through replication.
- This can be compared to prions, which can be diverse through variants (certain misfoldings which can mean different things for a prion) and mutate through replication
- However, it is important to realize that because there are similarities, it doesn't mean they are the same thing.

August 1st, 2025

Preventing misfolding of the prion protein by trimethylamine N-oxide - PubMed

- This is a study reported by the national institute of health, which discusses ways to prevent the actual formation of PrPC into a PrPSC
- Initially they discovered that chemical chaperones such as trimethylamine N-oxide (TMAO) prevents this formation in scrapie infected mice
- They decided to take this study further, and through simulations, discovered that the addition of this chaperone was able to slow gyration rates, and increase the hydrogen bonds.
- But rather than extending the structure of the infected prion, it causes the N-terminus to form an omega loop, which breaks the formation of PrP^C to PrP^Sc
- Understanding this process further could lead to developments in therapeutic treatments for patients affected with TSEs aka Prion Disease (CJD)

IMPORTANT VOCABULARY

N-terminus- The beginning of a protein structure, where the amino acid is not part of the peptide bond. A protein is linked by these peptide bonds, and the amino acid sequence itself is called a polypeptide chain. The N-terminus is the end of a peptide bond where the compound -NH2 becomes free. Meaning it is there, but does not connect with another amino acid in a peptide bond. This interesting structure can allow for special functions to be performed for the protein. (the c-terminus is at the end, and uses -COOH).

TMAO- a certain molecule made in the body when gut bacteria metabolize certain compounds in food. Meaning they break down those compounds into something your body can use. It can stabilize protein through direction interaction, or affecting its surroundings.
Gyration- just fast spinning in a circular motion.
Chemical chaperone - small molecules that stabilize proteins
Omega loop- non regular form of a protein, and characterized by a loop polypeptide chain

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July 28th, 2025
Since my research in exploring already done experiments and studies for developing treatments and understanding prion disease and CJD, I have uncovered a few interesting ideas. I wrote them down in my notebook, but I will restate them here.

My goal with this project is not to completely cure or abolish prion disease/CJD. My goal is to uncover something new about prions, the main factor which leads to CJD. Some sort of technique or method I create which actively helps in navigating these mutated proteins. Hopefully this will make progress in the field of this rare and understudied disease, and lead to better and more effective treatments in the future.

Apparently humans don't actually need the prion protein for survival. Which is why most studies explore ways to silence the prion protein gene or the prion protein to prevent the possibility of a misfolding. Hence the ideas of genetic expression, regulations, and the efforts to see how prions affect the brain and the cells. I was then thinking, if there was a day to analyse prion proteins to see if they turn infectious, and then get rid of them before they mutate would be an applicable solution to these issues. However, CJD is

spontaneous; there is no way to know for sure when it will occur. And for genetic/familial genetic disease those experiments of gene regulation/expression have already been done.

So then what can I do? My next idea was then to tackle the misfolded prions themselves. Because if we're looking for ways to progress in TREATMENTS, it would make sense to tackle the disease once it has been contracted. Oftentimes prion disease is spontaneous and people contract the disease for seemingly unknown reasons. A doctor can diagnose them based on certain risk factors like family history, methods of diagnoses (mentioned above), and exposure. But there is no way to predict, and then deal with it accordingly. The matter then is, ***how can we tackle prion disease once it has been diagnosed within a patient?***

I hope to answer that question by creating or discovering a new method or way of dealing with prions. And I have two ideas. *One is to actually work on unfolding the prions.* This is logical enough; if the problem is being created from the misfolding of prions, would unfolding them back into their regular shape solve the issue? This I suppose would be done by disrupting or breaking the bond of the fold, but I am unsure. There have been experiments and studies done on trying to figure out how to unfold prions, but I'd be lying if I said they weren't confusing. But they are very valuable and meaningful studies, and I will take the time to decode and understand them.

My second idea was to *work more with the idea that prions can adapt and react to their environment, and change over time.* I might need to do more research on this topic to understand it better, how I can use it, and what it actually means for the prion; and then what that means for the future.

And I plan to use yeast as my test subject. But really, all I know about it is that it contains prions. I'm going to have to do some extensive research on this as well and how I'm going to use it as a subject for the experiment, or if anything else will be better suited.

What Are My Research Goals?

The Unfolding of Prions

- ☑ ~~Previous studies and experiments~~
- ☑ ~~What it means and what it does~~
- ☑ ~~How is it possible / what can I do?~~

The Adaptability and Responses Prions Have to Their Environment, and How They Change Over Time

- ☑ ~~What does this mean for prions?~~
- ☑ ~~What does/can this look like?~~
- ☑ ~~What does this result in?~~

July 29th, 2025

THE UNFOLDING OF PRIONS

Previous Studies and Experiments

Mechanism of Unfolding of Human Prion Protein - PubMed

IMPORTANT VOCABULARY

Free energy- a quantity of thermodynamics. This represents how much WORK a SYSTEM can perform. This is then combined with its ENTROPY. This helps to predict whether a process will occur spontaneously (or randomly)

Free Energy Surfaces- This is a representation between free energy and its MOLECULAR CONFIGURATIONS through graphs. This helps see how energy changes in say, a protein and its shape!

Native State- The correctly folded shape of a protein which helps it perform its necessary functions in the body.

Global Minimum- The lowest point of a free energy landscape. This is the most stable state of the system. When talking about a protein, it is the shape with the lowest energy.

Conformational Free Energy Landscape- A representation of all different shapes (CONFORMATIONS) of a protein, along with their energies.

β-sheet - Strands of amino acids linked by hydrogen bonds; primary structural element of proteins

Metastability- relatively stable, but not so much so. This form can persist, however may exist in a form where outside changes can affect it (such as different conformation)

Helices/Helical Segments- another structural part of a protein. It is when the amino acids twist into a spiral shape (alpha helix). Segments are just the regions of the protein that look like this.

Tertiary contacts - Interactions between a proteins structure which help to maintains its shape (hydrogen bonds, ionic interactions, etc)

Solvation Forces - Interactions between Solute molecules (proteins) and Solvent molecules (water) these are factors which in turn affect the stability/ folding of that protein, since it influences how it reacts with its environment

Perturbations- Changes or some disturbance in a system which affects its stability/state. This includes temperature, pH, etc.

Intrinsically- Fundamental to a system.

Work- Energy transferred from one object to another through displacement

Energy- the ability to do work

Displacement- a vector quantity (directional) of an objects position

Entropy- a system's unavailability; the randomness of a system.

System- something which a scientist studies

Molecular Configurations- the permanent and specific shape of atoms in a molecule (including spaces, either single/double/triple bonds, and angles)

Oligomerization- this is the process in which an oligomer is formed from a monomer. A monomer is a singular molecule. Oligomers are made of monomers, but they are not very big. (unlike polymers, which are also made of monomers, however can grow quite large)

- The National Institute of Health strikes again with more interesting information on how to unfold prions.
- Prions are the result of many neurodegenerative disorders, including CJD. Therefore the idea of prions has sparked much interest within the scientific community. And thus brings the idea to unfold said mutated protein back into its stable PrP^c form, before it **oligomerizes** into the scrapie or infectious form, PrP^sc.
- They analyzed ways to unfold the human prion protein (huPrP) **through multiple microsecond-long metadynamics simulations.**
- Through these processes, several possible unfolding pathways or changes have been discovered.
- The unfolded state seemingly has lower free energy than its native state, meaning it appeared more stable (hence its global minimum on the landscape)
- But it did not involve increased Beta sheets, which was assumed to be integral to the structure of PrP^Sc
- And analysing the metastability (stable, but not the most stable form) on the helices, they randomly coil.
- The prion proteins are weakly stabilized by tertiary/ solvation forces. This means that perhaps small changes in the environment can lead to its unfolding. (LITERALLY WHAT I WAS THINKING)

IMPORTANT TOPICS

metadynamics simulations- a method involving computers which takes the three sciences (biology, chemistry, and physics) and is used to estimate free energy and other functions or systems which would have been possible due to energy barriers. It explores that free energy landscape and allows the study of rare events and explores all possible states.

July 30th, 2025

I've developed some new ideas on dealing with prions and prion disease. As a reminder, I want to perhaps create some new technique or discovery revolving around prion disease

once a patient has contracted it. This will hopefully help with treatments revolving around these kinds of neurodegenerative diseases, like CJD.

The above study confirmed my idea that the environment a prion protein is in could perhaps lead it to be unfolded. (which i'm very excited about) However, the above study was not physical, but rather a computerized simulation as to what COULD happen. I feel testing it in real life with yeast could serve some purpose.

And in addition to that, I've been thinking more about the structure of a protein and a prion protein (normal and scrapie versions) And it got me thinking; if somehow in some way, would it be possible to take a normal prion protein, and use it to fix a misfolded protein? Some sort of bond, or structural element that the PrPC has and the PrPSc doesn't have that could help mend it? It's interesting to think about, but I'm going to need to dive especially deep into the structural aspects of these proteins. But regardless, I did find this other study published by NIH, and I think it may help me in developing some of my ideas.

Temperature-Induced Misfolding in Prion Protein: Evidence of Multiple Partially Disordered States Stabilized by Non-Native Hydrogen Bonds - PubMed

- This study also talks about using free energy landscapes and simulations to see the stability/ energy of the prions they are working with at different temperatures.
- The main focus here *is* temperature and things like thermal deregulation; where a protein loses structure due to heat.
- And many things were uncovered regarding the structure of the prion proteins and how the temperature affects them
- They used a temperature dependent free energy surface. This means that due to temperature changes, the energy of the proteins changes as well, which in turn affects their conformation. The free energy surface provides insight into the stability and shapes of proteins.
- It uncovered that proteins may misfold when they are in a metastable state. At this point, the prion protein is in many metastable states which means it could really form in any sort of way if given the correct conditions.

- And when a protein misfold, it may be due to the fact that in that metastable state, that protein bonded with non-native contacts, or bonds that don't usually connect with each other in a healthy prion protein (such as a non-native hydrogen bond)
- This can then lead to the misfolding of the prion protein.

- Some metastable prion proteins have about 30-40% beta sheet content, and low alpha content of around 10-20%. These prion proteins may be the precursors or lead to the final PrPSC during oligomerization
- These conformations or shapes also saw an unstructured N-terminal domain. Because it is unstructured, its flexibility may lead to non-native contacts
- And yet another thing was uncovered; that despite being folded, the proteins were still very compact, suggesting they are still interacting with various contacts
- It was also found that the structure of the molecules deviate from their original or native forms when temperature increases. And despite losing some contacts, the overall structure doesn't fall apart completely suggesting that even when misfolded, the prion still has some structure to it (perhaps from the non-native bonds)
- This study agrees with what they thought earlier; that the C-terminus (second and third helices) are crucial for the stability of a prion, and without them it could lead to their misfolding. Hence why it's called the achilles heel or prion stability. (the weak point)

What it means and how it works.

August 1st, 2025

Prion protein misfolding - PubMed

- Transmissible spongiform encephalopathies (TSEs, also known as prion disease) results from the shape of the normal prion protein PrP^C, into a fibril forming PrP^Sc isoform (the mutated prion protein)
- The conformational change from the Alpha-helix rich to the mainly beta sheet form starts something called an *autocatalytic reaction (which means to create your own chemical reaction)*

- This results in fibrils and neurodegeneration
- The exact molecular mechanisms/process are still unknown, as we remain unsure how a polypeptide chain can be two different forms
- The review aims to tackle certain structures of the protein which lead to this conformational change
- There have been ideas to compare other proteins who can have fibrillar states to these prions, to understand them better.

August 2nd, 2025

Molecular Mechanism of the Misfolding and Oligomerization of the Prion Protein:

- TSE's or prion disease results from the misfolding/aggravation of the prion protein (PrP)
- Not many things are well known about this disease. It is not understood HOW exactly the folding of a prion leads to neurodegeneration, however it is mostly accepted that the formation of PrP^Sc is the triggering event for the disease and the main part of the process responsible for the transmission of the disease
- In addition to this information being elusive, the exact structure of PrP^Sc is also unknown
- But recent studies suggest that misfolded oligomers in the PrP may result in that toxicity/ infectious behaviour found in PrP^Sc
- This is why understanding the molecular mechanisms of the formation of misfolded oligomers in PrP is crucial for understanding prion disease and develop therapeutic treatments

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What can I do? - Final thoughts

In the past few days I have been diving into several studies and experiments reported by the National Institute of Health on how prion proteins could unfold. Typically what is done is the team will run computerized metadynamic simulations on the human prions with free energy landscapes. This helps to actually see the conformations of PrP^c And PrP^Sc, and how their structure and energies change, and therefore their stability **(an example is temperature, as changing the temperature of prions surrounding affects its energy, and therefore its stability)** This is important because the free energy dynamics of the simulations help scientists to understand the molecular mechanisms of

these prions protein, and why they misfold, which a typical molecular dynamic could not do, due to energy barriers.

1. They discovered that small environmental changes may lead to their unfolding since tertiary and solvation forces are weak.
2. They discover that when a prion protein is in a metastable state, it may be more prone to misfolding.
3. They may create non-native bonds, which furthers their misfolding.
4. PrP^Sc is still very compact, despite folding (suggesting structure from said non-native bonds)
5. Temperature can affect the stability of prion protein (such as thermal deregulation) however the entire structure does not fall apart completely (due to the contacts between non-native bonds)
6. They restated their belief that the C-terminus of a protein is crucial for its stability. So much so, they call it “the achilles heel of prion stability.

Another thing I noticed is that the structure of the PrP^C and the PrP^Sc is also very crucial in understanding the processes and mechanisms of prion disease. However, these mechanisms and structures are still unknown when it comes to this disease. I think it is important to dive into these structures. The role they play, how they interact, how they differ, etc. That will help us understand what to tackle when it comes to our experiment. But what crucial information have I learned do I think I could use?

- The fact that tertiary contacts and solvation forces are weak, so small environmental changes could affect them. (such as temperature)
- Yet due to non-native contacts and unforeseen stable structure, it may not unfold completely.
- The metastable state is when it seems best to act on it.
- The C-terminus is a place to target, being the ‘achilles heel’

My ideas that I mentioned above earlier regarding environmental factors and somehow allowing PrP^c to help mend PrP^Sc is something I’m looking into. I think diving into the STRUCTURE of these proteins will help a lot with a final declaration.

THE ADAPTABILITY AND RESPONSES PRIONS HAVE TO THEIR ENVIRONMENT; HOW THEY CHANGE OVER TIME

August 4th, 2025
What does this mean for prions?
Environmental and host factors that contribute to prion strain evolution - PMC.

IMPORTANT VOCABULARY
Prion strain- While PrP^Sc is the leading cause of prion disease, Prion strains are a bit different. Prion strains are different versions of PrP^Sc that cause different characteristics of the disease they produce. They differ in things like **conformation** (shape), **incubation** (amount of time for disease symptoms to appear) **Neuropathology** (different patterns of brain damage // lesions) **Cell tropism** (different effects on certain cells) and finally **host range** (some hosts may be more likely to contract certain strains)

Self templating- when a structure uses itself to replicate - hence, using itself as a template
Etiology- the causes of a disease
Novel pathogens- a microorganism which can cause disease
Repertoire- full supply of what you can do
Prevalence - how common
Subset- a part of a larger group

- The pubmed abstract describes how certain environmental and host factors can in fact affect prion strains
- Environmental factors include how strains may stick to certain surfaces differently than others, which may affect their transmission
- They may be resistant to certain environmental changes, increasing chances of survival
- Host factors include amino acids in PrP^c, which then affects the strain and how strong its ability is to infect a host
- The amount of PrP^C may mean some strains thrive
- Certain changes can also affect strains in a favourable manner
- And sometimes strains affect themselves. If there is competition between two, one may come out as the dominant strain

Reflection

Recalling my reading of an earlier study, I gathered that prions are able to react, adapt, and change over time based on their environment and other factors. They also touched on prion strains, and mentioned that when said prion strain was moved, it was able to do just that in order to survive in its new host. These are factors which help a prion strain thrive. Becoming immune to certain vaccines and drugs, and adapting when it is moved to a new host, are all evolutionary benefits a prion strain has so it will survive.

We see how in the study above, certain environmental and host factors also affect prion strains and their survivability. It seems all these factors play in the prions favour. That is important to remember in regards to an experiment.

Speaking of experiments, since I am using yeast, perhaps I can bake something with that yeast. Somehow if I do something with the prions inside, when I actually use it for say a bread loaf, I will get different results which then tell me something about the prions inside the yeast. Interesting idea, but of course, we have to figure out all the things with yeast, and prion protein structures.

August 5th, 2025

What does this look like?

- When discussing the topic of adaptation, a prion does not necessarily adapt like a living organism would.
- They change structure/shape, to change their properties/characteristics; such as stability and their ability to infect cells.
- And these behaviours will differ based on the environments a prion finds itself in.
- As discussed earlier, a prion strain can change when transferred to a new host, and back again if it goes back to its original host
- Certain host factors and environmental factors will cause prions to bind with the soil, or finding itself in wats, sticking/contaminating it, and then transmitting.
- Or perhaps it is able to withstand certain conditions, increasing its chances of survival

What does this result in? - final thoughts
These changes prions are seen to make all come down to its need to survive and thrive. The way it adapts to different environments by changing its shape is so the prion proteins are able to survive, like any other organism would. As I stated in my reflection; *Becoming immune to certain vaccines and drugs, and adapting when it is moved to a new host, are all evolutionary benefits a prion strain has so it will survive. We see how in the study above, certain environmental and host factors also affect prion strains and their survivability. It seems all these factors play in the prions favour. That is important to remember in regards to an experiment.*

Perhaps there is some way to flip this on its head. Have these certain environmental factors lead to the unfolding or destruction, rather than the survival rates of the prion protein. Or perhaps somehow affect the ability of these prion strains to prosper. But I am unsure what that could be. I will have to look more into that idea in the future.

August 6th, 2025

DEVELOPING AN EXPERIMENT- what have I learned, and what can I do?
So we see that prion disease is of course very complex and difficult to treat. Due to the way prions adapt to new environments, the way they are structured, are immune to protease, have no DNA, and the way the disease is contracted spontaneously, all contribute to the difficulty surrounding these types of disease. And while this disease is very rare, that contributes to a lack of research which in turn contributes to a lack of knowledge and understanding.

Most studies focus on handling the prion protein or PrP^c before it misfolds into the actual PrP^Sc form. This is done through things like gene regulation/expression, epigenetics, genetic editing (CHARM, CRISPR, etc) This is a plausible and understandable solution, as when the prion protein actually misfolds, there isn't a lot you can necessarily do to treat the disease since unfolding it within the brain is risky and difficult. However, since CJD (the most common prion disease in humans and the one I

am tackling) most often is sporadic (80%), meaning it is contracted spontaneously. So there often is no way to know if a person will contract CJD; how will you then treat it early on?

Therefore I want to ask the question; **How can creutzfeldt-jakob disease be treated once already contracted within a patient?** The prions are misfolded, the patient has been diagnosed. What can we do? As I mentioned earlier in this document;
My goal with this project is not to completely cure or abolish prion disease/CJD. My goal is to uncover something new about prions, the main factor which leads to CJD. Some sort of technique or method I create which actively helps in navigating these mutated proteins. Hopefully this will make progress in the field of this rare and understudied disease, and lead to better and more effective treatments in the future.

Naturally, I am inclined to tackle the prions themselves. Logically thinking, if a misfolded prion protein or PrP^Sc is causing the issue; wouldn't unfolding it solve it? I thought about this the very beginning of my research, and now I have dived deep into it. Studies have been reported on unfolding prions through metadynamic simulations. I will relay my earlier findings.

- ***They discovered that small environmental changes may lead to their unfolding since tertiary and solvation forces are weak.***
- ***They discover that when a prion protein is in a metastable state, it may be more prone to misfolding.***
- ***They may create non-native bonds, which furthers their misfolding.***
- ***PrP^Sc is still very compact, despite folding (suggesting structure from said non-native bonds)***
- ***Temperature can affect the stability of prion protein (such as thermal deregulation) however the entire structure does not fall apart completely (due to the contacts between non-native bonds)***
- ***They restated their belief that the C-terminus of a protein is crucial for its stability. So much so, they call it "the achilles heel of prion stability.***

And in addition to that research, there has been more found on the adaptability of prions to new environments.

These changes prions are seen to make all come down to its need to survive and thrive. The way it adapts to different environments by changing its shape is so the prion proteins are able to survive, like any other organism would. As I stated in my reflection; Becoming immune to certain vaccines and drugs, and adapting when it is moved to a new host, are all evolutionary benefits a prion strain has so it will survive. We see how in the study above, certain environmental and host factors also affect prion strains and their survivability. It seems all these factors play in the prions favour. That is important to remember in regards to an experiment.

With all this new information, I have developed three ideas which could be developed into an experiment.

1. Test how different environmental changes affect the prions. (disrupting the folding process, breaking a bond, etc)
2. Dwell on the structure; study, analyze, and see if any part of it can be manipulated to break it down (such as the C-terminus, or the achilles heel of prion structure)
3. Slightly more complicated idea…taking a unfolded/healthy prion protein, and using its structure to somehow help a misfolded protein

These are my three main ideas in order. I must decide which one I want to do. And with that, comes two more topics to study. Prions in YEAST, and the structure of PrP^c and PrP^Sc. I plan for yeast to be my test subject (because obviously I can't use human prions…) So I must understand how they work in order for my experiment to go well. And as well, understanding to a tea the structure of PrP^c and PrP^Sc could also help a lot in understanding what mechanism I am manipulating.

What are my research goals?

Prions in Yeast

- ☑ ~~What even are prions in yeast? The roles they play, how they fold, etc…~~
- ☑ ~~How is this the same from human prions? How is it different?~~
- ☑ ~~What experiments have been done with yeast?~~
- ☑ ~~How can I actually USE it?~~

PRIONS IN YEAST

August 9th, 2025
Fungal prions: structure, function and propagation - PubMed.

IMPORTANT VOCABULARY

Self propagating- induce and cause other proteins to change shape
Alternative confirmations- the different shapes a protein can take; important due to the different functions different conformations can entail.
Primary sequence- the chain/order of amino acids. Yeast and human prions are different in their structure
Yeast Saccharomyces Cerevisiae- commonly known as bakers/brewers yeast.

- Prions are not only found in animals, where they can cause extremely harmful neurodegenerative diseases; they can also be found in fungi such as yeast **(Saccharomyces cerevisiae)**
- Like human prions, these fungal prions are also able to change their conformation on their own terms. Adopting multiple shapes/conformations, and causing other proteins to do the same. (they are able to exist in one or more self-propagating alternative conformations)
- However, continuing this comparison, they share a little primary sequence relationship with human/mammal prion proteins.
- Fungal prions hold a great diversity of proteins, which do participate in key cellular mechanism (such as transcription and translation)
- “Upon switching to their prion form, these proteins can generate stable, sometimes beneficial, changes in the host cell phenotype.”
- This direct quote from Pubmed means that when a protein is stable, it can maintain its shape for a good while (allowing self propagation, or the transfer of changes to other cells)
- However, unlike in mammals, these misfolded prions can provide unforeseen benefits to the host, such as how it grows and adapts (the phenotypes)

August 10th, 2025

Amyloid Prions in Fungi - PubMed.

IMPORTANT VOCABULARY

Fungal protein- protein specific to fungi, such as yeast. Causing changes to an organism phenotype through their misfolding.

Fibrillary - describing something made of fibrils

B-sheet- a structure found in proteins, which are amino acids connected through hydrogen bonds, and appearing in a sheet structure

Protein Aggregates- clusters of proteins

Amyloids- specific kind of protein aggregate, characterized by their fibrillary structure, high B-sheet content, and a resistance to degradation

non-Mendelian genetic elements - the genetic material is found in the cytoplasm of a cell, rather than the nucleus. This does not follow the typical medallion genetic pattern as it does not pass traits directly through genes.

Propagation- reproducing/spreading

Chaperone- proteins which assist in protein folding // in the context of prions, it helps protein aggregates.

Brief note of clarification

As we know, the term fibril is to describe a slender fibre type material (like thread, and are typically very small). How does this relate to prion disease? Well, when the PrP^C misfold into its PrP^SC form, it has the tendency to aggregate (clump). Therefore, said PrP^Sc will clump together to form FIBRILS, which are insoluble. And said fibrils are classified as amyloid fibrils. (a type of protein aggregate, classified by fibrils, and a high b-sheet content)

- Prions which are found in fungus behave like cytoplasmic non-Mendelian genetic elements
- This means that the genetic material is found in the cytoplasm of a cell, rather than the nucleus. This does not follow the typical medallion genetic pattern
- But prions do not have genetic material; the article is referring to the fact that these fungal prions can act like a heritable trait, by passing down their traits to induce misfolding.

- It ensues a chain sequence of misfolded prion proteins. This is considered cytoplasmic non-Mendelian genetics BECAUSE that trait is being passed down without any transfer of genetics.
- Fungal prions correspond, or most often match with AMYLOIDS (rich in B-sheets, a fibrillary structure, and a type of protein aggregate)
- The article goes on to discuss how fungal proteins have been used widely to understand mammalian prions, as they are easy to manipulate and experiment with
- They helped discover how prions have no DNA or RNA but misfold all on their own (protein-only nature), the basics of protein strains, and the role that chaperones have in the propagation of prions.
- And yet they do have their differences, like how the fungal prion misfoldings help the organism rather than harm it.

August 11th, 2025

Amyloids and yeast prion biology - PubMed

- The prions in Saccharomyces cerevisiae (bakers yeast) act as genes. They copy their formations from one to another, like how DNA would send messages to make certain things happen.
- As we know, most times the prions in yeast are amyloids, and single sequence of protein can also have variants (protein strains)
- This is comparable to DNA and the different possible alleles.
- An ALLELE is defined as the differences you get from the same genes (from your biological mother and father) these slight differences (variants) can affect observable traits on a person (their phenotypes)
- But an issue which has developed is the structure of this templating process. Many people believe that the B-sheet structure found in these infection fungal prions, may be the reason for said templating.
- Another thing known is that while most often the prions are disease causing, some, specifically Podospora anserina may be beneficial to the structure
- To conclude, fungal proteins are very useful in helping understand human amyloid disease, especially as new information arises.

August 12th, 2025

Amyloid Fragmentation and Disaggregation in Yeast and Animals - PubMed

Hsp104, Hsp70, and Hsp40: A Novel Chaperone System that Rescues Previously Aggregated Proteins - ScienceDirect

IMPORTANT VOCABULARY

Fragmentation- the process of being broken down into smaller parts

Disaggregation- The opposite of aggregate; to break into smaller parts, and then analyzing those individual components of the original aggregate

Exogenous- relating to external factors; something which comes into an organism from the outside

Important topic-chaperones

Hsp104 is a chaperone (which is defined as a protein which helps the other proteins) specifically to fungi such as yeast. This chaperone is interesting, because rather than preventing the misfolding of proteins like chaperones Hsp40, 70, and 110, by working together, sharing information, etc, it takes the already aggregated proteins due to stress such as heat, toxins, etc, and helps it to unfold and keep the fungi safe.

- As we know, amyloids are a certain type of protein aggregate characterized by its high beta sheet content, and fibral like structure. These types of amyloid aggregates are found in animals, they are similar to the prions found in yeast and fungi as well.
- The propagation, or reproduction/spreading, of said fungal prion amyloids can be done through the chaperone Hsp104
- Now this chaperone usually works to unfold infected prions, if it does so too small it may actually lead to the prions misfolding even more as more normal proteins become infected
- Animals such as humans do not have this certain chaperone, but we do have others such as Hsp 40, 70, and 110 which all help with the disaggregation of prions by stopping them from misfolding in the first place
- If Hsp104 is introduced (exogenous Hsp104) from another source, it may be able to team up with these chaperones and promote disaggregation in humans and therefore help with treating diseases associated with amyloids
- But there is still doubt that this would work at all, as scientists worry that Hsp104 alone may not be enough. These limitations may mean that other treatments will have to be used alongside this introduction of a fungal chaperone.
- The study was to show and explain findings on how certain chaperones in fungi and humans can work together, and then perhaps lead to certain therapeutic

treatments for certain diseases associated with them (amyloid diseases, such as CJD)

August 13th, 2025

Prion diseases of yeast: amyloid structure and biology - PubMed

- As a reminder, prion strains (or variants) are prions that have an identical prion sequence (amino acid chains) but show different characteristics. This includes incubation (how long it takes for symptoms to appear after being in contact with prions), the shape, and the brain/nervous system damage they cause (neuropathology)
- We see that in fungal prions, including prion strains such as [PSI+], [URE3] and [PIN+] have a specific structure of beta sheets
- Discussing specifically the structure, the B-sheets in amyloids seems to be the reason as to why a prion can be self templating (why the shape of the prion can be transferred to another prion, creating a chain reaction of misfolds)
- Hence, explaining how these prions act as genes in yeast.
- But how is the idea of prion strains and the non-mendelian behaviour of fungal prions connected? Well, as we know these different strains have different characteristics. These differences impact the way it transmits and spreads itself, and therefore impact certain trains of other proteins. This is all done through the beta-sheet structure (which ensured stability and also effective self-templating). And this ability to self-template (the ability of different prions to pass along their different traits to other proteins) reinforces the idea of these prions acting as genes.

More on prion strains in bakers yeast (Saccharomyces cerevisiae)

[PSI+]- related to a protein called SUP35. This protein plays a role in translation termination. PSI leads to something called nonsense suppression- which leads to incomplete proteins

[URE3]- associated with a protein called Ure2, which regulates nitrogen utilization. When this prion is present, it disrupts this utilization, which means that different nitrogen sources must be used.

[PIN+]- links to a protein of the name Rnq1. this prion enhances the reproduction of other prions (the propagation)
They all follow non-mendelian behaviours, making them interesting to a fungi protein structure.

August 14th, 2025
Yeast and Fungal Prions: Amyloid-Handling Systems, Amyloid Structure, and Prion Biology - PubMed

IMPORTANT VOCABULARY

Self propagating- a system which can continue its existence, without needing external energy/ influence to sustain it.
Biological properties- a characteristic of features of a living organism, relating to its structure/function/behaviour etc.
Chaperone imbalances- an imbalance within the normal levels of chaperones (assistants) within a cell/ organism

CLARIFICATIONS

Self propagating vs. Self Templating-
A misfolded protein in a system can self-template, meaning it can use itself as a guide to let other proteins misfold in the same way. This at the same time is self propagation, because the misfolded proteins are able to sustain themselves by themselves using self templating
Chaperone imbalances
As we know, chaperones are helpers. They can assist either proteins OR prions. When there is an imbalance among the chaperones can lead to a variety of issues such as misfolding/aggregation.

RECAP

- Yeast prions have become important models for human prion and amyloid diseases.
- A prion protein can misfold into many different amyloid forms. These different forms have different characteristics and are called protein VARIANTS or STRAINS.
- These prions are self propagating and have different biological properties.

- The beta sheet structure within yeast prions is suggested to be the reason prion variants can pass along their information (self templating)

- As we know, chaperones exist to help both the proper folding of proteins, but can also help prions thrive
- Because of this, said yeast prions can propagate with these chaperones
- If there is an IMBALANCE, then it may stop the spreading of yeast prions and cure it
- *Btn2/Cur1 can help heal the prion strain URE3. These two proteins recognise misfolded prions, and target them to prevent their accumulation, and therefore their spread.* ***They do this through DEGRADING the protein, or INHIBIT THE PROPAGATION.***
- The article mentions two prion strains found in fungus- PSI+ and URE3
- PSI+ is a variant which affects the translation of proteins, which can lead to non-functional proteins
- While it can be lethal if in large amounts, however it is often mild and can allow the yeast to handle stressful conditions.
- The other strain URE3 is related to nitrogen metabolism, and like PSI+, depending on the quantity it can either be lethal of helpful
- The study suggests that because these variants are rare, they could have severe detriments (such as toxicity or decrease in reproduction) to yeast despite their beneficiary properties.
- However, in a surprising twist, the protein variant [Het-s] is beneficial to the host.
- It participates in something called **heterokaryon incompatibility** which can help an organism distinguish its cells from different ones with a different genetic background, preventing the spread of harmful genetic elements in that organism
- This difference highlights the complexity of the fungal protein structure.

August 15th, 2025

WHAT CAN I DO? - FINAL THOUGHTS

The GOAL

What I am trying to accomplish with my experiment is to deal with PrPSC once a patient has already contracted it. The protein is already misfolded, and the patient has been diagnosed. ***Is there a way to unfold this prison? To stop it from spreading/propagating?*** What can be done? I summarized everything in my notebook, and here are some key points I found interesting.

KEY POINTS (I found important)

- They can be beneficial towards certain stressors yeast can face (such as temperature) which can trigger misfolding-while that is detrimental that folding can actually be a way for the yeast to survive.
- Similar to amyloid structures, which have helped in *developments* for human amyloid disease (such as CJD)
- They can also also have variants and chaperones

- These prions self template and self propagate (non-mendelian)
- This self templating is done through the B-Sheet structure of said prion.
- They have *certain prion strains* which do damage, but also systems which fight against that (*Btn2/Cur1 can help heal the prion strain URE3)*
- HET-S acts on **heterokaryon incompatibility**
- Certain stressors lead to its misfolding

August 16th, 2025

MY IDEA - ***(this idea is not final. It may change or be tweaked- be aware of potential changes that could be made as research continues)***

Im coming back to my old idea of taking some part of the fungal protein which actively fights against and prevents the fungal prions from misfolding.

Things like Btn2/Cur1 which work towards fighting against the URE3 protein strain. They recognize the misfolded protein, target them, and work to either DEGRADE or INHIBIT THE PROPAGATION of said prion.

If we take these proteins, and insert them exogenously within a system of yeast that has been ridden with misfolded proteins, would the introduction of these proteins fight against that propagation and degrade the protein, therefore ceasing its reproduction? If the prions stop reproducing, then they are unable to form protein aggregates, quelling the disease. (I may have to somehow remove the *Btn2/Cur1* from the test on yeast, to see if it will work. Perhaps removing that protein will be a more honest replica of human prion protein systems, leading to a better connection)

The concept of introducing something from outside its system has been thought of with the chaperone HSP104, in order to have mammalian chaperones work together and perhaps fight the prion misfolding. Could it not be done with other structural elements of the fungal system? And if this method of exogenously inserting these proteins works, that same logic could be applied to the human brain. Backing off again the idea with the HSP104 chaperone, it was thought to insert that within a mammal in order for it to work with their mammalian chaperones. Could the protein *Btn2/Cur1* be used the same way?

I will have to dig deep into these structural elements, and see what they're all about.

The Next Step - Understanding Btn2/Cur1 and Prion Strains in Yeast

Before I start dwelling on an experiment, I have to understand the parts of the puzzle I'm actually dealing with. What is Btn2/Cur1? What roles does it play? Do they differ between systems? What really are these yeast prion strains? *Understanding these pieces will allow for a smoother time in the final experiment.* I will begin tomorrow.

August 20th, 2025

Understanding Yeast Prion Structure -

What are they? What do they do for yeast AND humans? What do we know/don't know? Etc…

Antiprion systems in yeast cooperate to cure or prevent the generation of nearly all [PSI+] and [URE3] prions | PNAS

IMPORTANT VOCABULARY

Filamentous polymers- simply describing the structure of which is a long, thread like material which can be made up of things like proteins, carbohydrates, etc. These are different from amyloid structures, as amyloids are a specific type of filamentous polymer, and are further characterized by their high beta sheet content and a resistance to degradation.

Antiprion system- These are cellular mechanisms in yeast that help to fight against prion formation/propagation. Say for example you have the prion URE3, which is infecting other yeast proteins and causing an amyloid structure. The antiprions job is to either STOP them from spreading, forming, or simply eliminate the prion all together. Chaperones like Hsp104 help the already misfolded protein. Btn2 and Cur1 isolate and eliminate the prion, and other systems all serve in this means of ANTIPRION.

Sup36p / Ure2- these are proteins found in bakers yeast, which can turn into prions such as URE3

Pathogenesis- the process by which disease develops.

What is the difference between amyloids and prions?

Prions are a special type of amyloid. This is because they self-perpetuate (or continue) after aggregation

- There are two infection prion strains we know already- PSI+ and URE3.
- These are described as amyloids (filamentous polymers) of Sup35p and Ure2
- In a system, most times antiprion systems will defeat prions. Inhibiting the creation of prions, limit pathogenesis, and block the infection.
- If a system LACKS an antiprion system, the PSI+ protein strain will develop 5000- folds when compared to a normal strain
- The proteins Btn2 and Cur1 can fight against URE3, HOWEVER instead will promote the generation and propagation of PSI+
- Said Btn2 is known to isolate the URE3 amyloid.

Anti-prion systems in yeast - PMC

- As we know yeast systems are one of the ways we as humans can solve for amyloid related diseases, being similar to the amyloid structure of humans,
- We also know that the yeast prions (most of them anyway, unlike Hsp104) are pathogenic, meaning they are able to carry disease

- Antiprion systems are able to defeat these prions; it is said to be possible that humans also have them, which could mean progress in the human ability to fight the disease (relating to that of things which are humoral immune, meaning protection against a virus)

Prion Amyloid Polymorphs – The Tag Might Change It All

- As we know, Sup35 is a protein within bakers yeast (Saccharomyces cerevisiae) This protein can actually reproduce like in a prion type manner, which turns it into insoluble fibrils. Basically, they become prions.
- Sup35 is a large protein, and shows three domains (or main parts). This is the N domain (beginning), M domain (middle), and the extended globular domain (end part, which is involved in the function) The C terminus is the very end.
- Discussing previous studies, they looked at different parts of the Sup35 protein. Specifically which were tagged (attached to proteins) by Poly-histidine at the N-terminus. The poly-histidine is a chain of amino acids, which help with identification. This was at the front of this protein (hence N-terminus)
- They also untagged the middles and beginnings (NM), but tagged one which was tagged at the very end (the C terminus). They studied both of these proteins.
- And using a method called **SOLID-STATE NMR**, they studied the structures of said proteins (their folding)
-
- What did they find? Well, they found little to no difference between the tagged and untagged NM. **However the tagged C-terminus showed drastic changes in the NM structure**
- The study then concludes that the C-terminus/globular domain (the end of the protein) influences the structure, which is quite substantial. This shows an unexpected twist in fibril behaviour which could be used for other prions such as PSI+

***Why should we care?* - It has realized that the small changes in prions are important, and experimenting with tags and this factor of fibrils, may lead to further developments in medicine and treatments for prion and amyloid disease.**

September 8th, 2025

So I've been a bit swamped with school and new assignments and tests, however all my classes have introduced me to new ideas and opportunities. In biology we learned about

this concept called hydrolysis, which is at its basics, taking a polymer (such as a protein) and by chemically adding water, you break that bond into its monomer units (amino acids). SO…I've been thinking. If we have a prion, a misfolded protein, and perform hydrolysis on it to break the bond, wouldn't that mean that prion doesn't exist anymore, and then the disease is quelled? And if that is done, since prions cause other prions to misfold, that wouldn't happen to the extent that it does because the prions are, in theory, no longer able to do that since that bond was broken. Right?

THE NEW IDEA

Using hydrolysis (or catabolism), we can take a polymer (such as a protein) and break the bond into its monomer units (amino acids). Prions have the same amino acid structures as their healthy protein counterparts, it is simply the shape which causes them to become infectious. If we have a prion and perform hydrolysis on it to break the bond, it would be assumed that only the prion would be destroyed. Since these prions cause other healthy proteins to misfold, causing a large sum of brain cells to die, breaking down those prions early in the process may stop the disease from spreading.

October 22nd, 2025

Four links about hydrolysis and catabolism I will research and read over in the following week. I hope to come up with an idea for an experiment after I read them all

October 27th, 2025

Today I talked to Ms.Fan about the science fair and my idea, only to come across a problem I had not predicted would come up. I expected to perform my experiment in a lab setting, as I understand that dealing with prions at home would be dangerous. However, I did not take into consideration the challenge of actually finding that place of research. Apparently, the overall process to actually get set up (especially as a grade 11 student) is very time consuming, meaning that participating in the actual science fair would not be a possibility as of this year. But before that, actually finding a willing professor, and I suppose a place to conduct the experiment, is an entire issue on its own. Very much a harsh blow to the original plan.

At this point I am unsure what to do. Ms.Fan suggested I take a theoretical approach to the topic, however I am completely unsure as to how to create one that is actually meaningful and well put together. On top of that, I really wanted to actually perform an experiment :-(However, Ms.Fan is very smart and knows a lot, and so do other teachers. This coming Thursday we will have our first meeting, and next week I hope to actually talk with her on what to do moving forward (because quite frankly, I have no idea. It seems what I can do is very far away from what may happen, which is a downer). I hope I am able to talk to Mr.Andrews as well, and maybe Mr.Dawe and Ms.Dawe on the topic. I also hope to talk to Mr.Mackay on the subject, as he has done his own lab work, so perhaps he has some insight.

Overall, the new information has left me less than excited for the future of the project. It's not great to be unsure and confused.

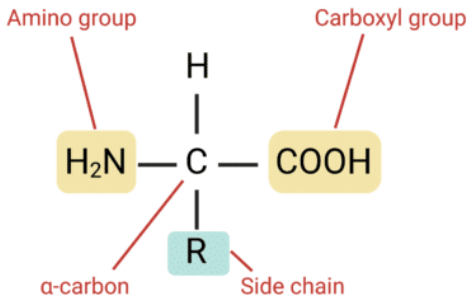
(continued)

BACKGROUND RESEARCH

October 29th, 2025

[Structure of an Amino Acid - Rapid Novor]

AMINO ACIDS are organic materials which make up proteins. Different amino acid sequences will make up different proteins, giving proteins different 3-D structures.



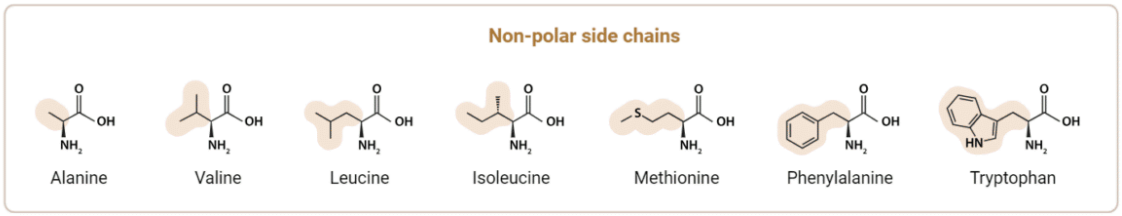
The structure of a protein is also important to keep in mind. A protein has an amino group (NH2), a carboxyl group (COOH) , and an R group (all attached to the central carbon atom). The R group will change based on what amino acid you're dealing with. In this enzymatic hydrolysis, the proteases/enzymes will break down the peptides to free those amino acids.
There are different structures (stereoisomers, meaning a change of structure based on space) called L-forms and D-forms. L forms have the amino group on the left, and are most commonly found in nature (for reasons unknown. D-groups have that amino acid on the right instead.

TYPES OF AMINO ACIDS

There are many types of amino acids which impact how they react with other molecules, and also impact the structure of the amino acid.

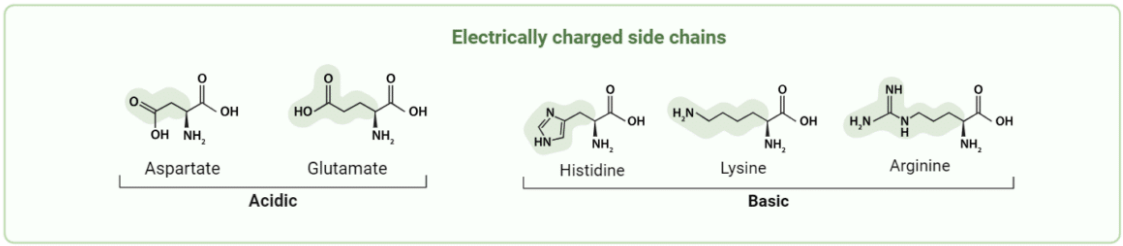
Non-Polar Amino Acids

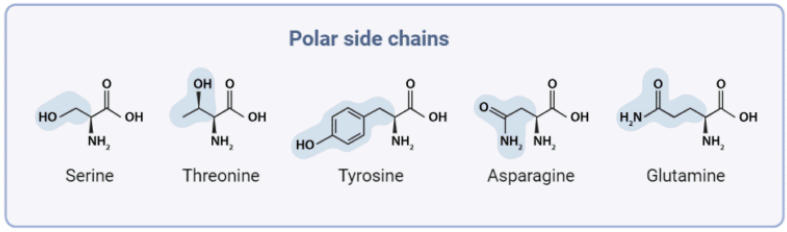
- A hydrophobic side chain (r-group)
- Interiors of proteins (whilst polar amino acids would be found on the surface because of their hydrophilic properties)



Polar/ electrically charged

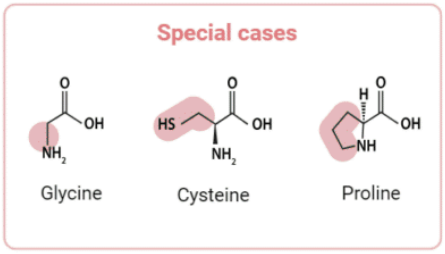
- At a physiological PH (a tight range of Ph for bodily functions), five amino acids can actually have an electrical charge
- This plays a role in stabilizing tertiary protein structures, and can perform electrostatic attractions (pulling things together)

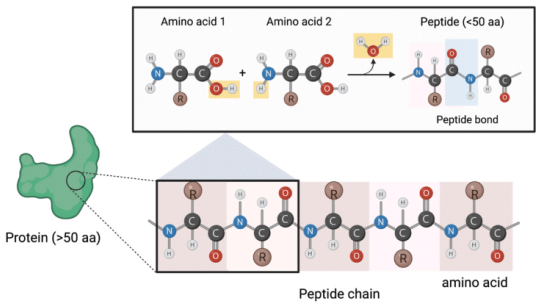




Special amino acids

- Glycine is very simple and has hydrogen in its R-group, giving it a lot of flexibility to fit into different parts of proteins.
- Cysteine can form a disulfide bond with itself, as its side chain contains sulfur. This happens through oxidation (losing electrons)
- Proline can cause kinks in a protein chain because its side chain can form a ring with its backbone. This makes this amino acids rigid and limits its shaping ability





PEPTIDE BONDS

Amino acids are joined by these peptide bonds

In two amino acids, one will lose a hydroxyl from its carboxyl group, the other a hydrogen from its amino group.

A water molecule will be made, and the bond will be created between the two amino acids. This is called dehydration synthesis

Peptides (usually less than 50 amino acids) can perform many biological functions. Neuropeptides can act as transmitters as an example. A polypeptide is when more than 50 amino acids are present in a structure. A protein, finally, are these polypeptides attached together.

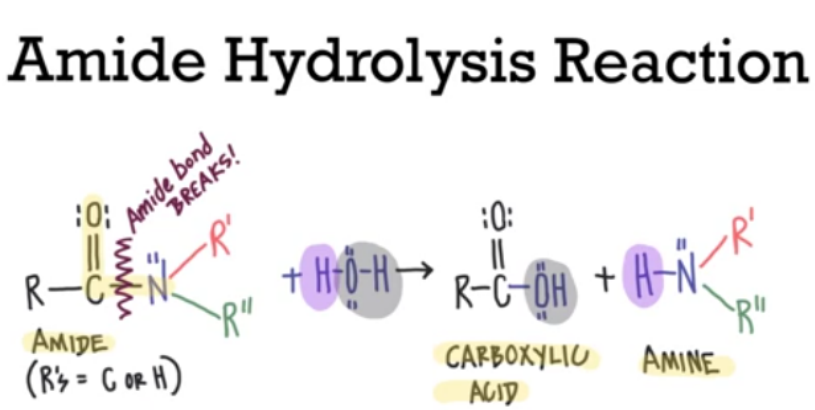
Amino acid sequences can be difficult to determine, however it is important to understand their function and shape. Some methods include **Amino-Acid sequencing** and **De Novo amino acid sequencing.**

PROTEIN HYDROLYSIS

[396 BCH3023 Hydrolysis Reactions of Proteins Yielding Amino Acids] - not done

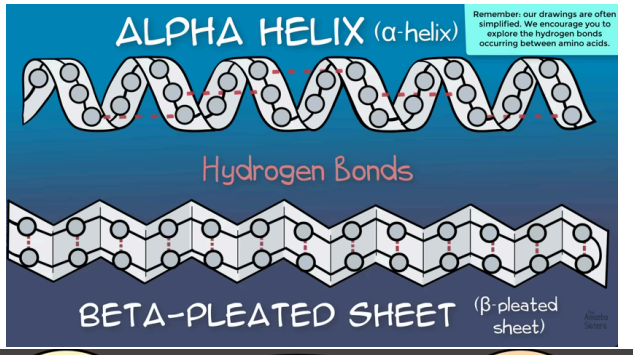
- Water is a reactant, which breaks down the bonds between individual amino acids (breaking the amino acids)
- We have a tertiary or quaternary structure of a protein.

- Through the stomach's acidity, that structure will simply become a chain. This readily prepares these proteins to be broken down into simpler peptides until they become amino acids. They will then reassemble into what your body needs.
- This takes many chemical reactions within the body.

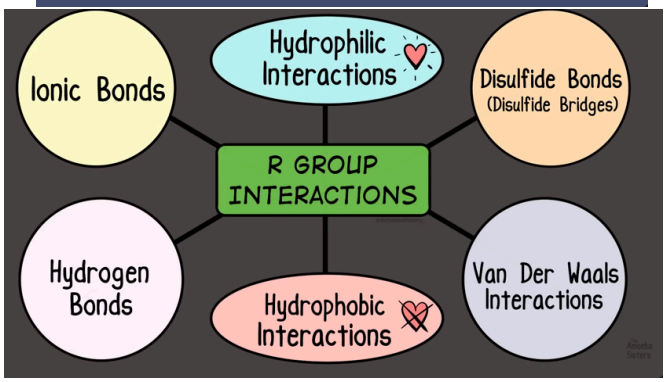


This diagram shows how the amide group (a compound containing a carbonyl group bonded to a nitrogen atom) was broken down by water (as catalyzed by an enzyme) into two different amino acids.

[Protein Structure and Folding]



Proteins have amino acid structures based on DNA, and can have either alpha helix structures or beta-pleated structures as a secondary structure. This is done through hydrogen bonds, typically of the carboxyl and amino groups.



R-groups (side chains) will allow for different tertiary structures of a protein, which can be affected by all kinds of interactions (depending on the R-group itself)

October 26th, 2025

Hydrolysis - an overview | ScienceDirect Topics

- A chemical reaction where a compound is broken down by water
- One molecule gains a hydrogen ion, the other a hydroxide ion
- The reverse of dehydration synthesis
- Hydrolysis can happen either chemically (through concentrated acids/alkali) or biochemically through enzymes.
- ENZYMATIC HYDROLYSIS is used often to prevent corrosion (and keep the protein from becoming damaged) and the expenses of the chemical methods. This method is also typically used for foods, where those food proteins are broken down so their peptides are able to be used for something else.

Enzymatic Hydrolysis - an overview | ScienceDirect Topics

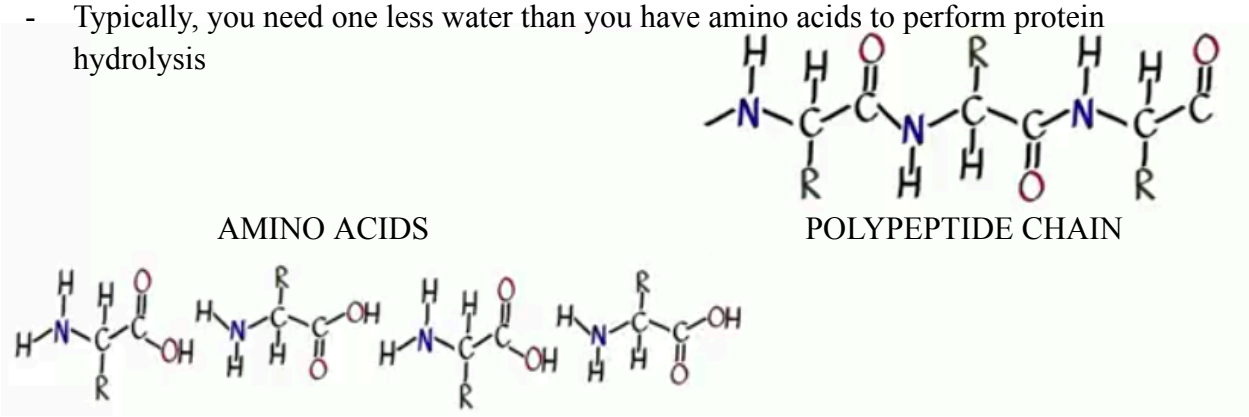
- This form of hydrolysis alters the function and biological properties of proteins, disrupting tertiary structures, reducing their molecular weight, leading to more reactions with their peptides.
- Amino acids will be released, however there will be very fast changes in PH which is why neutralizing solutions are important to maintain an optimal ph range.
- After this hydrolysis, heating the enzymes ensures they stop working, and then centrifuging (a method of separation) the mixture to get the peptides from them which are then freeze dried.
- This method of using enzymes to break down soy protein has been used to extract those peptides and then used for health purposes.

I think what I'm going to have to do is research different ways hydrolysis is performed on proteins. This will be so I see what is happening and how it is different for each one, so I can determine which one is best suited for the goal of the experiment. The process of hydrolysis can not be 'harsh', as this disease inhabits the brain. Using materials like acid does not make sense. To do this, understanding the ins and outs of proteins is also beneficial.

November 3rd, 2025

Amino Acids 12. Protein Hydrolysis.

- An alkali or nucleic acid is used to break apart a compound with the use of water
- Protein hydrolysis can be difficult! Either you REFLUX (simplified, you heat a reaction till boiled) the protein with 6moles of hydrochloric acid for 24 hours, or try and break them down with proteases at room temperature for several hours.
- It takes a long time and effort because a protein has a very complex structure- as you must break down the quaternary, tertiary, and secondary structures before you reach a polypeptide chain
- You must break all those bonds that are causing those twists and folds; van der Waal forces, electrostatic attractions, hydrogen bonds, or disulfide bonds
- Typically, you need one less water than you have amino acids to perform protein hydrolysis



November 7th, 2025

So it is certain that an experiment will not be possible for this project as it is far too risky. Therefore, it will be a theoretical/research project. I am rethinking my original idea regarding the protein hydrolysis, as if we were to apply that to the actual brain a) those proteins would be extremely difficult to distinguish between and b) actually performing hydrolysis on them would be seemingly impossible because of it. However, my original question still stands on how we can deal with this disease once it has contracted. Due to the fact that CJD is spontaneous, there is no way to detect or predict when an individual may contract it. ***So, is it possible there is a way to detect and destroy the spore of this disease, or any sort of beginning infection before the proteins continue to misfold?*** And overall, the next steps of this project involve taking my soon to be completed research and narrowing it down into something more specific. Additional experiments and future studies can be something else I look into, as well as connecting the project to the way it serves, protects, and helps people.

November 11th, 2025

We are back with some clarity and direction. I did some review over the criteria for the science fair, and know my next steps in regards to moving forward with the experiment. I'm feeling more confident knowing what lies ahead regarding this project :-)

November 12th, 2025

Problem / Testable question

Creutzfeldt Jakob disease is a very dangerous disease because it is immune to the enzyme which breaks down protein (protease) and uv violet radiation doesn't treat it due to the fact prions have no nucleic acid genetic element (DNA or RNA). On top of that, the rarity of the disease has restricted the ability to do research. Therefore, treating it has been a challenge.

The problem with treatment surrounding CJD is that it is a sporadic disease, meaning it is spontaneous and extremely difficult to predict. Therefore, dealing with the disease prior to a diagnosis is redundant, since it is a shot in the dark (such as with gene regulation) However once the disease itself is contracted, another issue arises. Since it is a neurodegenerative disease, any action performed to squash the disease must take place in the very delicate and crucial organ of the brain. That is difficult enough, but prions are hard to distinguish between the actual helpful proteins. If you destroy an actual protein, what would be the consequence? This reason supports why destroying/attempting to unfold the prions isn't necessarily an option either (at least with our current understanding).

QUESTION: Is there an inbetween stage between the contraction of CJD and the misfolding of proteins in the brain? Are there ways we can kill or weaken its effect before it infects the proteins of the brain, preventing neurodegeneration?

November 14th, 2025

In addition, I think it is important to note that this project is focused on classic CJD which is sporadic, and not variant CJD caused by the consumption of beef infected with BSE. Due to regulations, this variant of the disease is not likely as compared to classic CJD.

(continued)
Background Research

What are my research goals?

- ☑ ~~Is there an "inbetween stage" for CJD?~~
- ☑ ~~What does this stage entail for a patient?~~
- ☑ ~~What are the symptoms/signs?~~
- ☑ ~~Ways to confirm vs. symptoms which may suspect CJD~~
- ☑ ~~What actually is the entity causing this?~~

Clinical Overview of Variant Creutzfeldt-Jakob Disease | vCJD | CDC

- Yes, there is an 'inbetween stage which is *called the incubation stage* of vCJD and CJD.
- Typically this stage is measured in years, most likely meaning this stage of the proteins becoming infected can take a very long while until specific symptoms are noticed

November 19th, 2025

Prion Diseases | Memory and Aging Center

- In sporadic CJD (85% of cases), symptoms include things such as imbalance/incoordination, memory loss, and impaired thinking
- There are also psychiatric symptoms such as depression or anxiety.
- However, once symptoms do appear, CJD will progress very quickly and within a few months it will be considered fatal.

Creutzfeldt-Jakob disease (CJD): Symptoms, causes, and treatment

- The reason for this is because the incubation period of CJD is extremely long and can take decades for symptoms to appear.
- Key hallmarks of CJD include rapid progression of dimension/involuntary muscle movement. These symptoms will worsen over time, and vision as well as the ability to move and speak is lost. They may also enter a coma.
- It resembles Alzheimer's, but the difference is that symptoms take weeks not years to form

- There is also no test that can confirm CJD other than a biopsy, which is extremely dangerous when a person is alive (but they typically show a spongy texture on the brain, showing tiny holes where nerve cells have been destroyed)
- However treatments which measure and check symptoms, as well as the ruling out of dementia and showing signs ofCJD by an MRI can help

November 22nd, 2025
Creutzfeldt-Jakob Disease - StatPearls - NCBI Bookshelf

SPORADIC CJD
- In the early stages of sporadic CJD, a patient may develop mild symptoms which aren't necessarily specific to CJD.
- Things like vertigo, fevers, headaches, fatigue, and sleep disorders may fall under these issues. As well as issues with memory, being irritable, depression, and mood swings.
- As the disease progresses, a patient will endure worsening cases of confusion, disorientation, and cognitive problems.
- On top of this movement problems can develop, such as ataxia, involuntary jerky movements, myoclonus, muscle stiffness, and involuntary muscle twitching.
- Overtime patients will lose mobility, and disease like pneumonia can be fatal
- Patients are typically 55-75 years old. It is similarly presenting to dementia, however progresses much quicker

EVALUATION
- Since the disease is similar to dementia, diagnosing CJD uses similar tests used for rapidly progressive dementia (RPD) this includes…

Complete blood count, Complete metabolic panel, Blood magnesium level, Rapid plasma reagin, Erythrocyte sedimentation rate, Antinuclear antibody, C-reactive protein, Thyroid function tests, Vitamin B12 level, HIV test, Lyme disease titer. Autoimmune antibodies, Urinalysis. CSF studies, including glucose, oligoclonal bands, and cell count with differential, **CSF 14-3-3 protein** (a specific test for prion disease) Venereal disease research laboratory (VDRL) test

- MRI's, FLAIR, and DWI's can also provide more detailed information on the regions involved.
- And while CSF 14-3-3 is a specific test, a brian MRI is a more specific and sensitive test
- These tests can reveal abnormalities in the brain's gray matter such as cortical ribboning

TREATMENT/MANAGMENT

- No definitive treatment as of current day
- However **intraventricular pentosan polysulfate** can be proven effective in rodents to stop prion protein formation. In patients, survival rates increased from 37-114 months.
- However most often, end of life planning is a necessary treatment. This can be benefited by early detection of the disease
- And most often if a person is suspected to have CJD, treatments used to determine RPD can be used. In addition, if a person is suspected to have RPD, CJD must be evaluated.

PROGNOSIS

- Despite attempts in understanding CJD, most often the disease will result in death. However, contracting the disease is very rare.

November 23rd, 2025

Creutzfeldt Jakob Disease (CJD) - MD Searchlight

WHAT IS IT?

- CJD primarily infects the central nervous system or CNS, consisting of the brain and spinal cord
- The CNS contains the neuron which sends, holds, and receives information. It can not naturally regenerate, like other types of stem cells in the brain (a stem cell being a cell that can become different types of cells)
- Neurons are organized according to tasks they perform, some controlling automatic movements whilst others control voluntary ones
- Neurons connect through and communicate through structures called axons and dendrites.

- Nissl bodies help in the making of proteins and neurotransmitters (chemicals the brain uses to communicate)
- Neurofilaments maintain cell shape and contribute to nerve signaling
- There are also several glial cells such as astrocytes which guard against harmful substances.
- CJD builds up inside these neurons, damaging the brain's cells.

SIGNS AND SYMPTOMS / TREATMENT

- In sporadic CJD, symptoms can relate to that of rapidly progressing dementia and problems which physical coordination (as it affect The CNS)
- Treatment can include blood and urine tests as well as other tests for Lyme disease, HIV, and other autoimmune diseases,
- However, sometimes a sample of cerebrospinal fluid (fluid surrounding the brain and spine) will also be taken to detect proteins associated with CJD. This includes the protein 14-3-3 (however it is not specific to the brain)
- CT and MRI can also be used to get a photo of the brain. MRI for example allows details about parts of the brain associated with CJD, and with EEG's you can get pretty close.
- A new method however, called "second-generation Real-Time-Quaking-Induced Conversion (RT-QuIC) is specific to CJD, recognizing the abnormal proteins in cerebrospinal fluid. Examining this fluid is especially helpful (as well as in addition to other tests such as blood tests, CT's, and MRI's) to differentiate between RDS and CJD.

FINAL THOUGHTS

The incubation period for CJD is actually extremely long and not able to be known since no symptoms are present. And once they do, it is already too late for the patient. There are ways to check for CJD and various unspecific symptoms which will be present, but again once symptoms appear the patient has nearly six months to live.

This may mean that seniors (who are most susceptible to CJD) should go under the multiple tests that doctors can provide such as urine samples, blood samples, MRI's, EEGS, etc, so that if that misfolded protein is present the family and the doctors know, and we can deal with the disease before symptoms even show. In addition to this, it could

lead to other diagnoses such as RPD, as well as other neurological complications. However this involves spreading awareness on CJD, and making it known to the public so they can protect themselves and their family members.

However, there are a few things to take note of which could help doctors diagnose CJD. This includes the protein 14-3-3, as well as intraventricular pentosan polysulfate. Combining existing knowledge on these two seemingly big causes of CJD may be something to look into.

December 29th, 2025

I recorded this information on the CSFY to-do list, and submitted my ethics sheet roughly a week ago (I do not recall the exact date). This is what I have written, and I will wait for the submitted review to be approved.

Purpose of experiment or research: Innovating ideas on how to treat the prion disease, Creutzfeldt-Jakob disease, before conditions in a patient become critical.

Description of experiment or research study: Creutzfeldt-Jakob disease is the most common prion disease found in humans, being fatal yet under-researched. Not only is it unable to be recognized by the immune system as a threat, but no existing treatments have been found to silence the disease completely. The purpose of this investigation is to innovate solutions on how to treat Creutzfeldt-Jakob disease before a patient's condition becomes critical.

December 31st, 2025

14-3-3 PROTEINS AND INTRAVENTRICULAR PENTOSAN POLYSULFATE

14-3-3 proteins: structure, function, and regulation - PubMed

- 14-3-3 proteins are a group of **conserved regulatory molecules** within **eukaryotic** cells (cells with a nucleus)
- What is special about these kinds of proteins is their ability to bind together diverse **signaling proteins**
- This includes **kinases, phosphatases, and transmembrane receptors**
- This function can allow 14-3-3 proteins to play a role in wide range of **vital regulatory processes**

- This includes **mitogenic signal transduction, apoptotic cell death,** and **cell cycle control**

IMPORTANT VOCABULARY

Conserved regulatory molecules

These are molecules which have remained unchanged throughout evolution, showing that they are extremely important for biological processes (such as gene expression, signal transduction, and cellular metabolism.

THE TYPES

Transcription Factors: These are proteins (such as histones) that help transcribe genes (copying DNA, or genes, to make messenger RNA. Then ensues translation, which takes that mRNA to make proteins)

Signal Molecules: Transmitting signals within and between cells (think hormones or neurotransmitters. An example is cAMP)

Enzymes: An organic catalyst assisting in biochemical reactions.

14-3-3 is an example of one of these guys

Signaling proteins

Messengers which coordinate activities like growth and immunity. They trigger cellular responses from signals received by hormones and neurotransmitters to transfer information within cells and between cells.

Both kinases and phosphates communicate and control a cell's behavior, hence what they are signaling proteins.

Kinases

Enzymes that help in the transfer of phosphate from ATP to a substrate (like a protein) This is called phosphorylation. It changes what a protein can do. **Phosphorylation typically activates or deactivates signaling proteins, thereby influencing various cellular processes, such as metabolism, cell growth, and apoptosis.**

Basically phosphorylation is adding a switch to change a protein's behaviour. For metabolism, turning it on can help the cell access energy. For growth, it helps the cell multiply and divide. It can also help a cell to die.

14-3-3 as a protein, are helpers in a cell. (From kinases) they can latch on to proteins with a phosphate tag which can keep the protein stable, and help control it by telling it what it needs to do and where it needs to go. (like if you think about it…) it's like a babysitter keeping a watch on them.

Phosphatases
Removes phosphates from proteins (dephosphorylation, the reverse of phosphorylation and therefore the reverse action of kinases) Therefore meaning actions done by phosphorylation can be reversed
In relation to 14-3-3, phosphates can also remove this protein, which can stop its activity on that protein.
Transmembrane receptors
Receive outside signals, control a cell
Vital regulatory processes
Important functions; allow cells to stay healthy (regulate activities like growth, metabolism, and cell survival.)
Mitogenic signal transduction
Signals for cell growth (division)
Apoptotic cell death
Programmed cell death; removes unwanted cells
Cell cycle control
Managing how a cell divides
The protein 14-3-3 can bind those specific signaling proteins together, which can assist in processes which keep organisms healthy and alive.

January 1st, 2026
The 14-3-3 Brain Protein in Cerebrospinal Fluid as a Marker for Transmissible Spongiform Encephalopathies | New England Journal of Medicine.
(What is 14-3-3 doing for CJD?)

- An antibody of a 14-3-3 protein reacted with cerebrospinal fluid (which is a clear fluid around the brain and spinal cord which serves protection) proteins 130 and 131, but not with any other proteins in the cerebrospinal fluid
- This tells us that proteins 130 and 131 are 14-3-3 proteins.

- This discovery helps us diagnose transmissible spongiform encephalopathy such as CJD.
- Patients with CJD had this 14-3-3 protein.
- Meanwhile healthy individuals or individuals with other diseases such as Alzheimer's did not have this protein.
- This helps us differentiate between these two diseases (CJD and Alzheimer's) which have very similar symptoms. Therefore, allowing proper treatment as needed in order to maximize a patient's health before symptoms arise.
- This was done through an immunoassay of 14-3-3 (a procedure for detecting or measuring specific proteins or other substances through their properties as antigens or antibodies, defined by google dictionary)

Detection of 14-3-3 protein in the cerebrospinal fluid supports the diagnosis of Creutzfeldt-Jakob disease - PubMed

The analysis of 14-3-3 protein in cerebrospinal fluid (CSF) was shown to be highly sensitive and specific for the diagnosis of Creutzfeldt-Jakob disease (CJD).
- (directly from website)

- Using a western blot (WB) technique, it showed that around 95% of patients were confirmed to have CJD while 92% were suspected to have it. Therefore, the majority of patients who had the 14-3-3 proteins also had CJD.
- However in some cases the test stated a patient did not have CJD, though they did. Showing that the test isn't necessarily fool proof. However these patients did have other conditions such as herpes simplex encephalitis, hypoxic brain damage, atypical encephalitis, intracerebral metastases of a bronchial carcinoma, metabolic encephalopathy,
- If the test was positive, it was 94% accurate. If it was negative it would be 92% accurate.
- Overall, the study concludes by saying an analysis for 14-3-3 proteins should be done if CJD is suspected in a patient.

CSF analysis for 14-3-3 protein should thus be performed in any case suspect for CJD. - ***(directly from website)***

Accuracy of diagnosis criteria in patients with suspected diagnosis of sporadic Creutzfeldt-Jakob disease and detection of 14-3-3 protein, France, 1992 to 2009

*Sporadic Creutzfeldt–Jakob disease (sCJD) is the most common form of human prion disease, a group of rapidly fatal untreatable and transmissible encephalopathies. Clinical diagnosis of sCJD has relied on criteria revised over time to incorporate the detection of 14-3-3 protein in the cerebro-spinal fluid (CSF) - **(directly from website)***

- The article brings the reliability of the 14-3-3 protein into questioning. It says relying on this detection system may lead to an overdiagnosis of CJD and a misdiagnosis of neurodegenerative diseases which are treatable.
- However, as the study concludes (done in France from 1992 to 2009) it states that this wasn't necessarily the case and that the test should be done in diagnosing suspected CJD.

In conclusion? This test is pretty good and reliable!
(Why aren't we investing in this…?)

January 2nd, 2026
Continuous intraventricular infusion of pentosan polysulfate: clinical trial against prion diseases - PubMed

- As we have established, there is no current existing treatment for CJD (or any prion disease for that matter…)
- However, Pentosan polysulfate (PPS) has shown some results in mice, prolonging the incubation periods those infected with prion diseases
- There have been human studies in European countries and Japan where PPS was prescribed to patients with prion diseases, and it was able to be tolerated by said patients
- 11 patients have been treated with PPS (three familial CJD, two iatrogenic CJD, and six sporadic CJD cases)
- Survival after treatment about 24 months (2 years), and those who died seemed to have died from diseases such as sepsis and pneumonia
- Overall, while no necessary improvements were seen in a patient's health from PPS, the medication did seem to expand the life spans of a few patients.

*Although our preliminary study of the new treatment with PPS by continuous intraventricular infusion showed no apparent improvement of clinical features in patients with prion disease, the possibility of extended survival in some patients receiving long-term PPS was suggested. - **(directly from website)***

Intraventricular infusion- The direct delivery of a drug or therapeutic agent into the fluid-filled cavities of the brain, known as the cerebral ventricles

Pentosan polysulfate sodium (oral route) - Side effects & dosage - Mayo Clinic

- Pentosan polysulfate (PPS) is a commonly used medication to treat bladder pain, relieving the symptoms of pain and discomfort that come with it.

Pentosan polysulphate prolongs survival in CJD, study indicates - PMC

- This article also says that PPS seemingly prolongs the lives of patients who take it, however does not halt the neurodegeneration done by the prions
- While usually taken in pill form for bladder pain, it in injected directly into the brain of patients with CJD
- Ian Bone is a Glasgow neurologist, who conducted a study to test this

*Of the seven patients, three had variant CJD (...) two had iatrogenic prion disease from growth hormone; and two had the hereditary form of CJD. All were aged under 35. Three of the seven died before the study's end. - **(directly from website)***

- While the study did not prove it, it did show that PPS may prolong the survival of patients who take it.

"The average survival in vCJD is generally believed to be about 13 months. All of these patients lived longer than that from the time of diagnosis."

There are apparently four possible situations

1) The estimate for the expected survival of a patient is wrong, as previous patients may have been diagnosed late in the course of their disease.
2) These patients survived longer due to aggressive treatments for other conditions (like pneumonia) *(however data suggests this isn't a likely case)*
3) It is a simple chance finding due to the very small sample
4) PPS actually works in treating CJD!

Ian Bone says the following about the study conducted

"There are some things the families can take away from this. There will now be more research, particularly animal research, because we need to measure the drug's penetration into the brain. Also, the concerns over possible dangerous side effects seem to be groundless. And there is limited evidence of prolongation of life."

However, there is the possibility that this drug may be able to prolong the life of patients contracted with CJD.

January 3rd, 2026
Postmortem findings in a case of variant Creutzfeldt-Jakob disease treated with intraventricular pentosan polysulfate | Journal of Neurology, Neurosurgery & Psychiatry

- This study details a study done on patients with CJD who had been treated with PPS.
- Out of 176 patients, 5 were treated with PPS
- 40 months is the maximum survival of patients with CJD who had not been treated with PPS. Of the five patients who were treated they survived 16 months, 45 months, 84 months, 105 months and 114 months.
- The patient who survived for 105 months underwent postmortem examination (a medical examination of a dead body), and it was found that the patient showed typical signs of CJD such as neuronal loss and extensive prion protein deposition in the brain.

Overall, this study concludes the same thing as the earlier articles. That while PPS may not heal or cure prion disease, it may be able to prolong the lives of patients who have been diagnosed.

***The article above is interesting as it says that I must pay some sort of fee for copyright purposes if I wish to use their findings. To be frank…this conundrum perplexes me… (I don't want to pay, I'm broke) And while the article restates a lot of already established information, there are some seemingly helpful charts and case studies I may want to use if I take this idea further. However, I am now unsure of the ethics of such usage. I will ask Ms.Fan about it, to get a more thoughtful opinion on the matter.**

Summary of Research

The following is a summary of all the conducted research above, what I have learned, and why it is important. It will be found in the part two of the logbook

Hypothesis / Thesis

Based on the conducted research I will be able to create a hypothesis or thesis (depending on whichever fits better) for innovating ideas on how to treat the prion disease, Creutzfeldt-Jakob disease, before conditions in a patient become critical. This will then ensue the next part of the project which involves my own reflections and thoughts on the matter. (I don't wish for this project to simply be me info-dumping all of the information I have learned. I wish to add something to it, that being my own (hopefully original) ideas) It will be found in the part two of the logbook

It is important to keep in mind the "scientific principle"criteria of research projects.
Make sure you understand and explain the underlying scientific principles of the subject/problem you are studying. Often a small demonstration of the underlying scientific principle or "Law" is valuable; you should also be able to explain the conditions for known departures from the scientific principles in question.

As well as DATA, which involved charts and tables which reflect and (hopefully) support the hypothesis

(this can be explaining translation (DNA to RNA) and transcription (RNA to amino acids) and the complicated topics like you are teaching a class that knows nothing of what you are talking about. In addition, having models can help to allow that understanding)

My goal is that by the end of January, I should have my hypothesis/thesis solidified and be decently into the research for it (ideally about half way, perhaps realistically ⅓ of the way?)

***NOTE -** *as this project advances in its complexity, the titles and other written pieces of displayed information within the project may change and become more specific as I actually get a firm grip on what this project is tackling (because right now it is still relatively vague) And I may start a new document for the other research because this one really is a lot of me actually*

learning what prion disease is. With a more specific goal now in mind, I think starting a new document is suitable (after I write my hypothesis)

Transmissible Spongiform Encephalopathies Affecting Humans - G. B. - 2013 - International Scholarly Research Notices - Contains image used for project