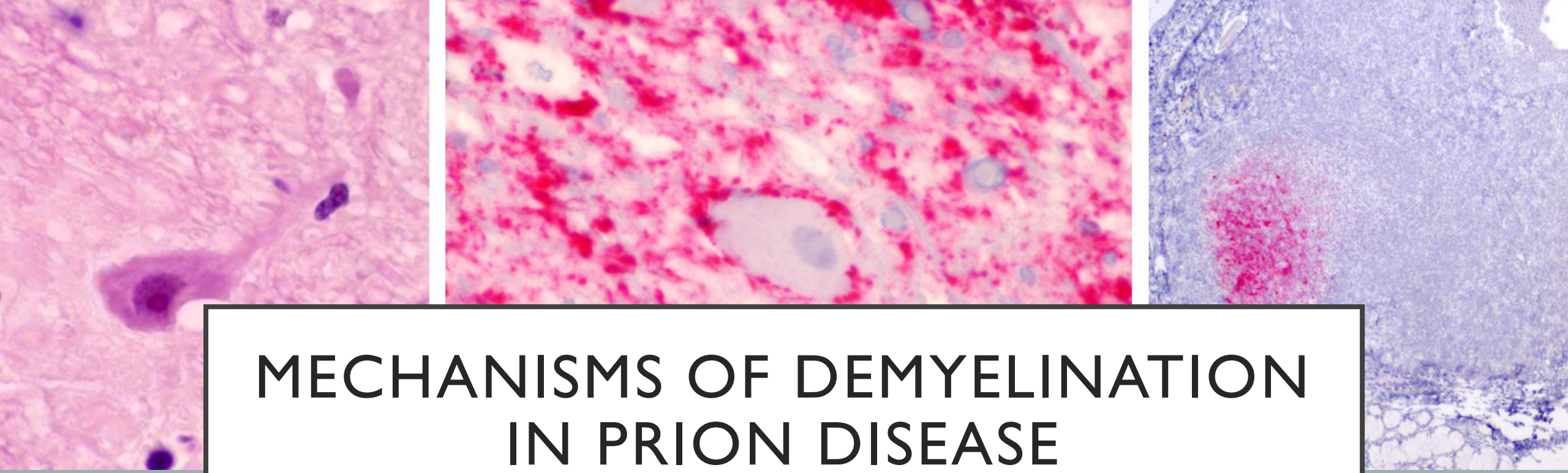
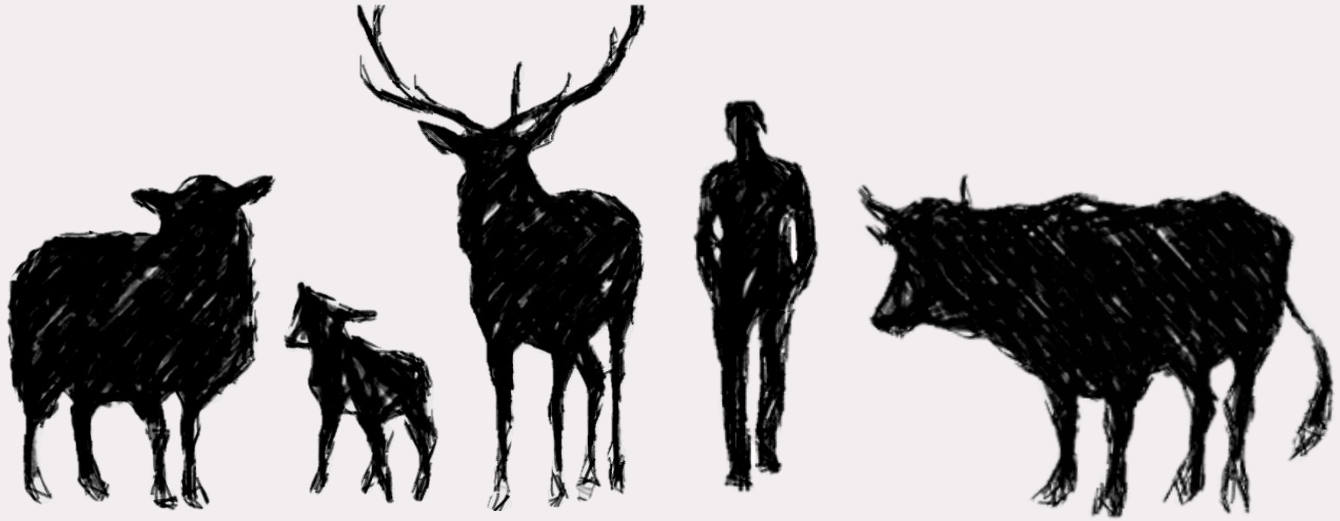


MECHANISMS OF DEMYELINATION IN PRION DISEASE

Joie Lin

Sigurdson Lab

STAR 2020



PRION DISEASES

- progressive, neurodegenerative disorders

- share similarities with age-related neurodegenerative disorders

PRION DISEASE

- neurotoxicity → neuronal death, spongiform encephalopathy
- mechanisms of neurotoxicity still unclear
- protein-only infectious agent, PrP^{Sc}
- PrP^{C} has many functions

PrP^{C}

PrP^{Sc}
(aggregated form)

neuronal death
body dysfunction
death

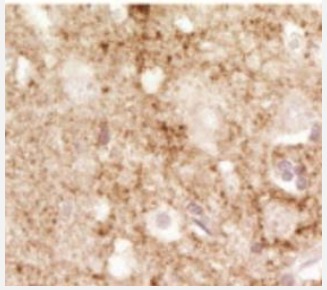
COMMON FEATURES OF PRION DISEASE:

- protein misfolding
- protein aggregates

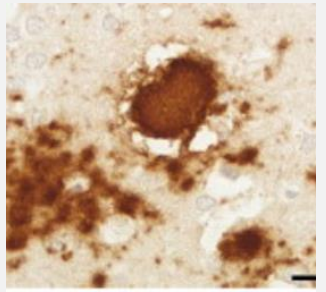
HUMAN PRION DISEASES

PrP^{Sc} plaques

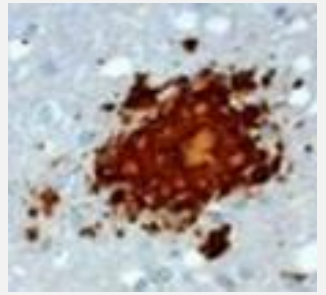
Sporadic Creutzfeldt-Jakob disease



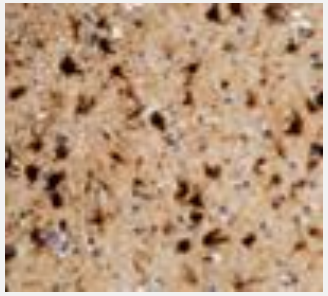
Variant Creutzfeldt-Jakob disease



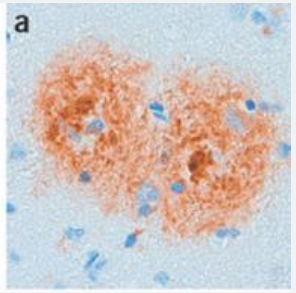
Gerstmann-Sträussler-Scheinker disease



Fatal Familial Insomnia

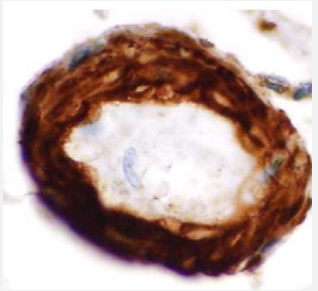


Alzheimer's disease



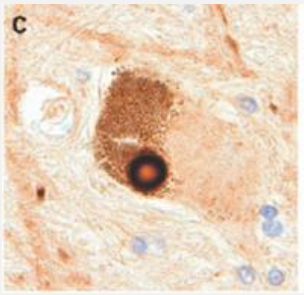
Amyloid-β plaques cortex

Cerebral amyloid angiopathy



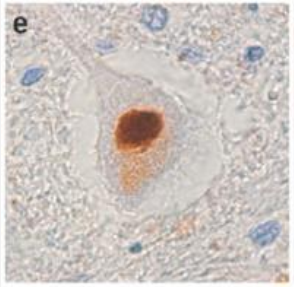
Amyloid-β plaques meninges

Parkinson's disease



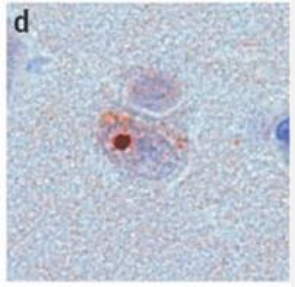
α-synuclein substantia nigra

Amyotrophic lateral sclerosis



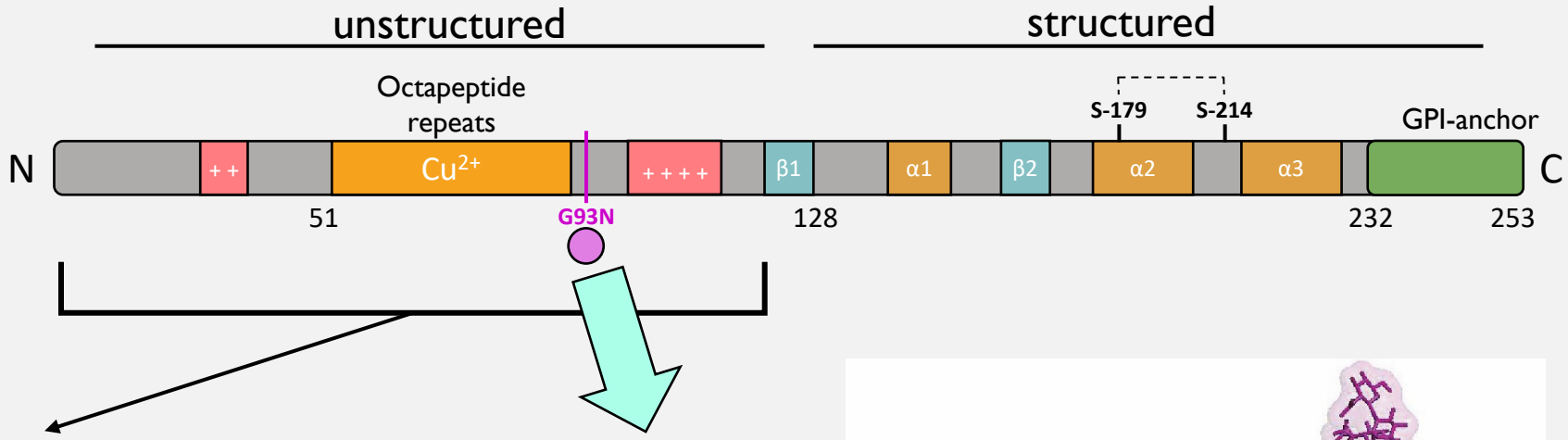
Ubiquitin inclusions spinal cord

Huntington's disease



Poly-Q inclusions striatum

THE ROLE OF PrP^C IN PRION DISEASE

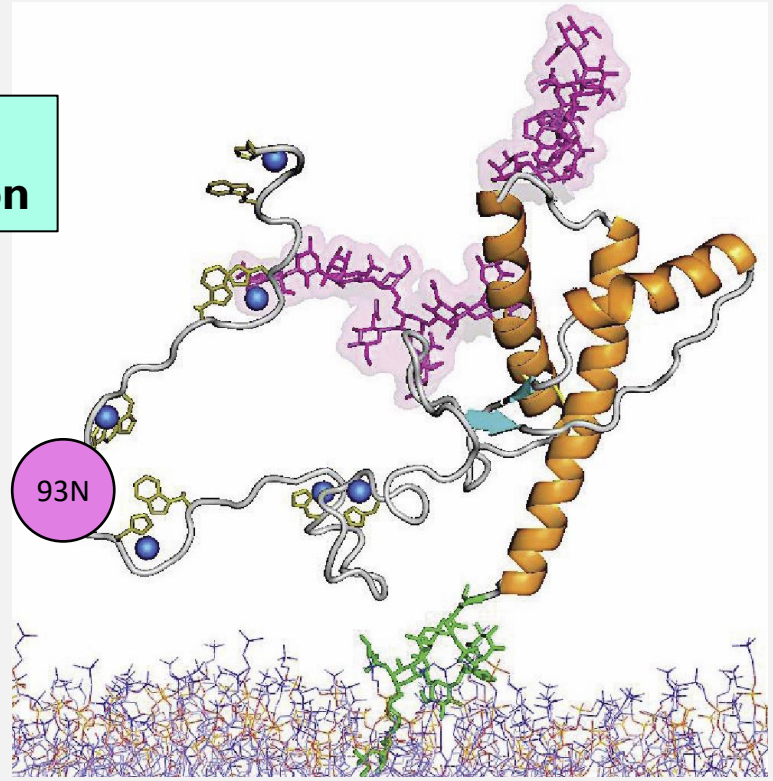


N-terminus is linked to toxic signaling

- Δ32-134 mutant
  → neuronal toxicity
- Antibodies that bind to C-term and prevent N-C interaction in cis
  → neuronal toxicity

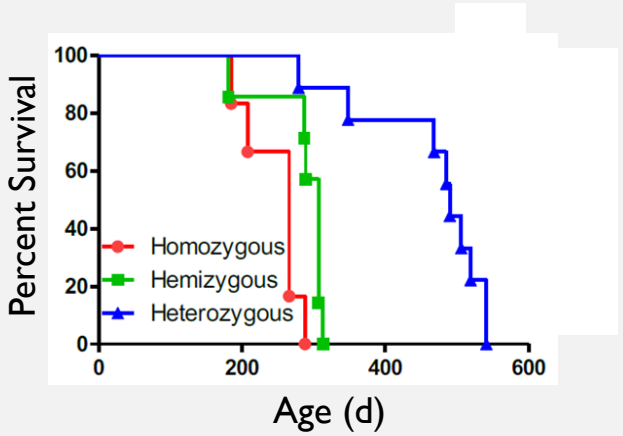
Spontaneous neurodegeneration

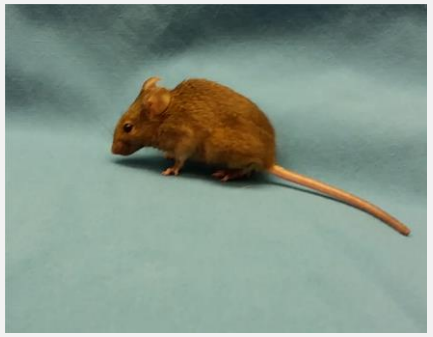
PrP^C itself can mediate neurotoxicity, in the absence of PrP^{Sc}



Wille, Virology, 2014

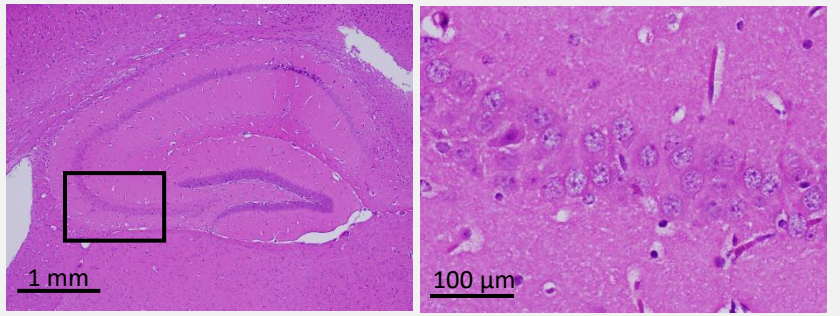
G93N-PrP^{C} MICE SPONTANEOUSLY DEVELOP NEURODEGNERATIVE DISEASE

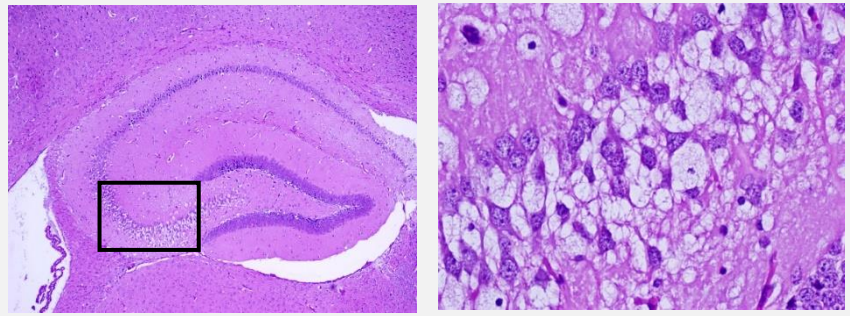


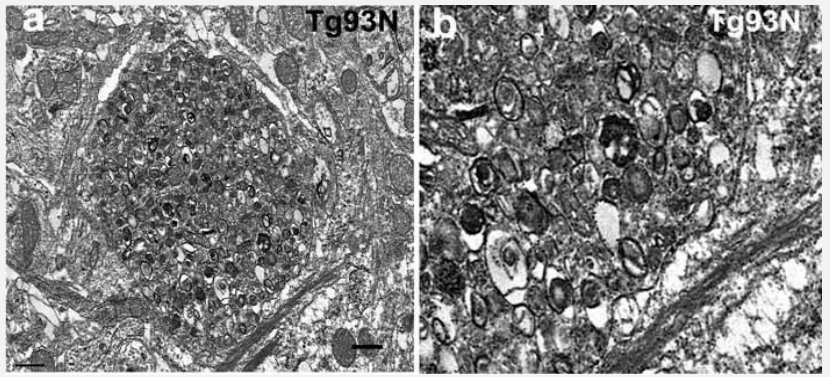


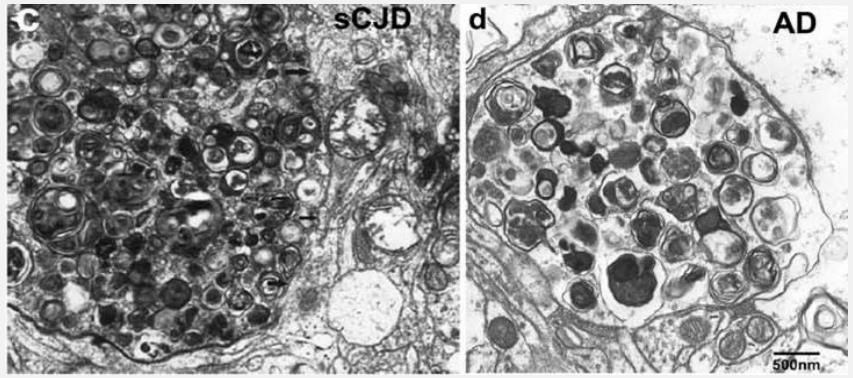
WT hippocampus

93N-PrP^{c} hippocampus



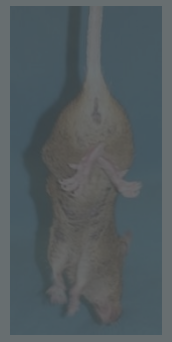


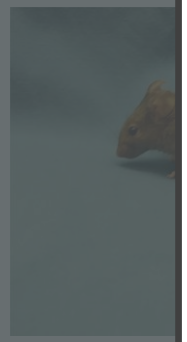




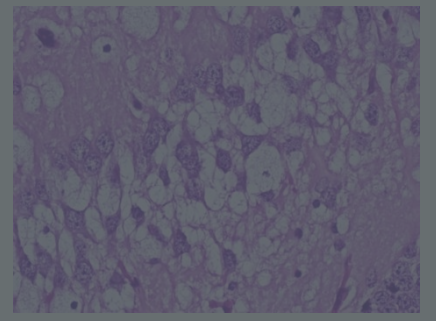
Nixon *et al.* (2005) J. Neuropathol Exp Neurol

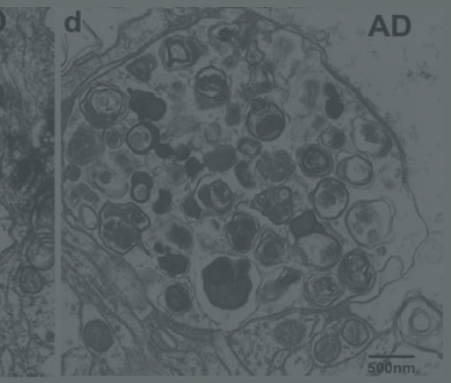
G93N-PrP^{C} MICE SPONTANEOUSLY DEVELOP NEURODEGNERATIVE DISEASE





Pc hippocampus





et al. (2005) J. Neuropathol Exp Neurol

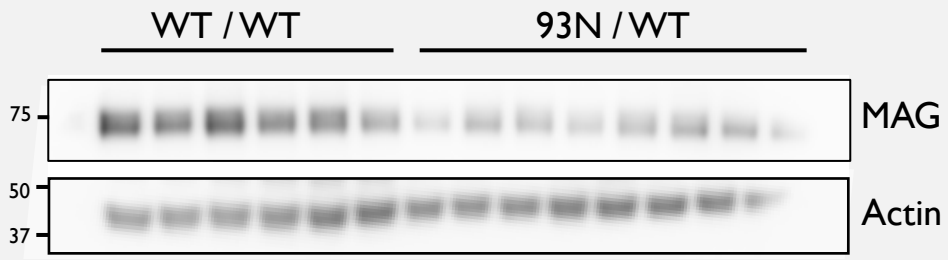
THERE IS NO PRP^{Sc} IN THE 93N MOUSE MODEL, BUT NEUROTOXICITY IS STILL OCCURRING.

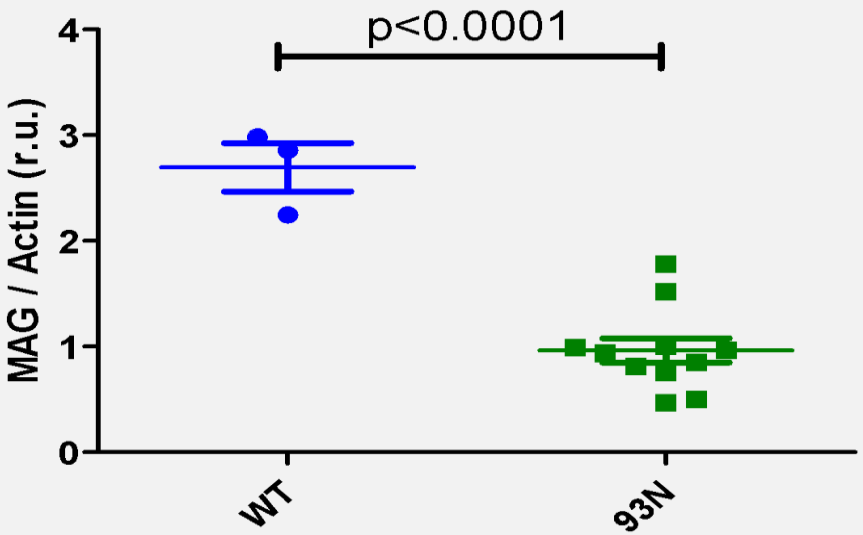
PRP^{SC} = INFECTIOUS AGENT

IN THE ABSENCE OF PRP^{Sc}, HOW DOES PRP^{C} CAUSE NEUROTOXICITY?

PrP^{Sc} = infectious agent

PrP^C AND DEMYELINATION



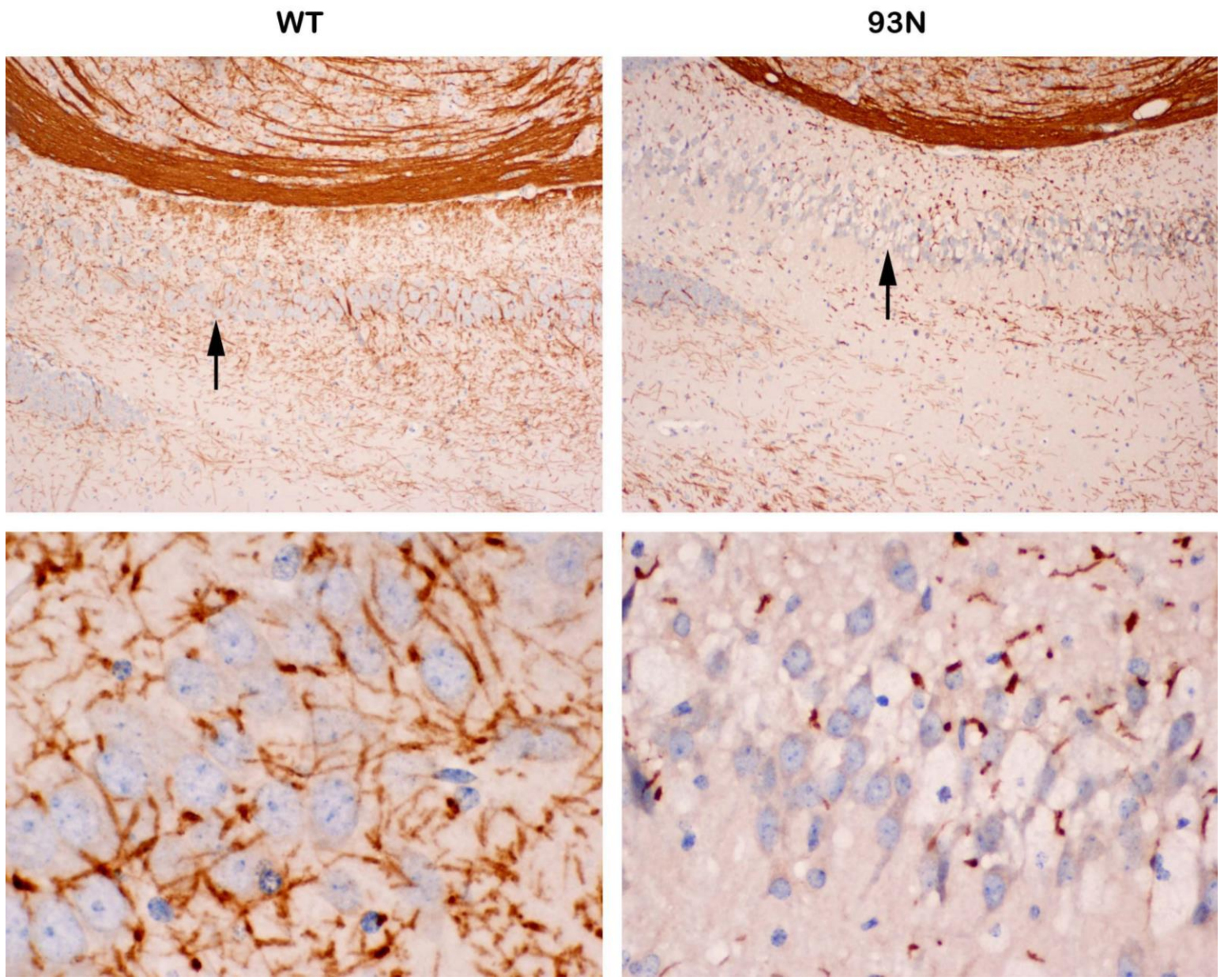


At terminal disease (550 d), 93N brains exhibited **decreased (>50%)** myelin-associated glycoprotein (MAG) levels.

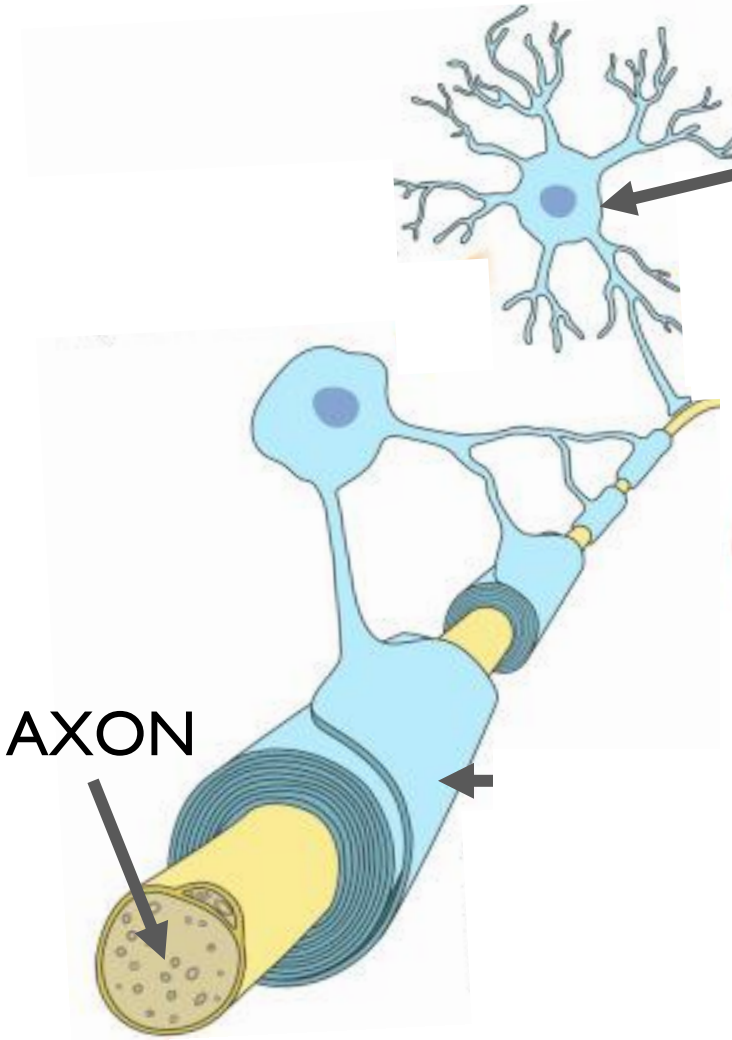
PrP^{C} AND DEMYELINATION

WHERE IS THE MYELIN LOSS HISTOLOGICALLY?

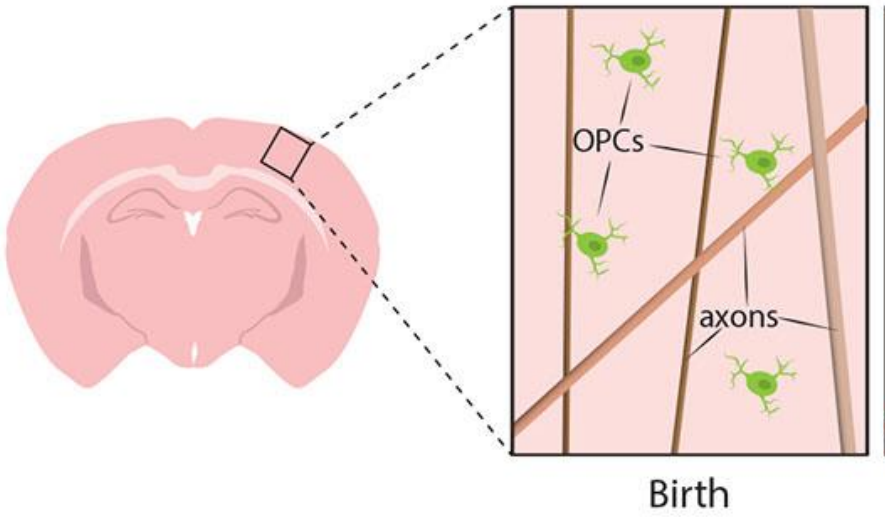
MYELIN BASIC PROTEIN (MBP) STAINING



PrP^C AND DEMYELINATION



Adapted from Mount & Monje. (2017) *Neuron*



/disease

Adapted from Williamson & Lyons. (2018) *Front. Cell. Neurosci.*

cognitive deficits

HYPOTHESIS

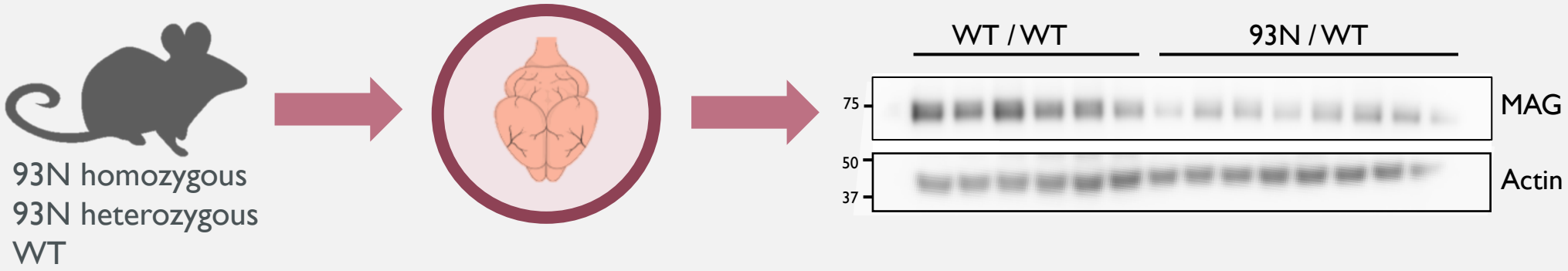
In prion disease, oligodendrocytes develop normally and then degenerate due to excitotoxicity.

excitotoxicity = when neurons die from overactivation of glutamate receptors

AIM 1: To determine (i) the timing and extent of myelin loss and (ii) the maturity of the oligodendrocyte population in the *Prnp*^{93N} knock-in mice (homozygous, heterozygous, and WT littermate controls).

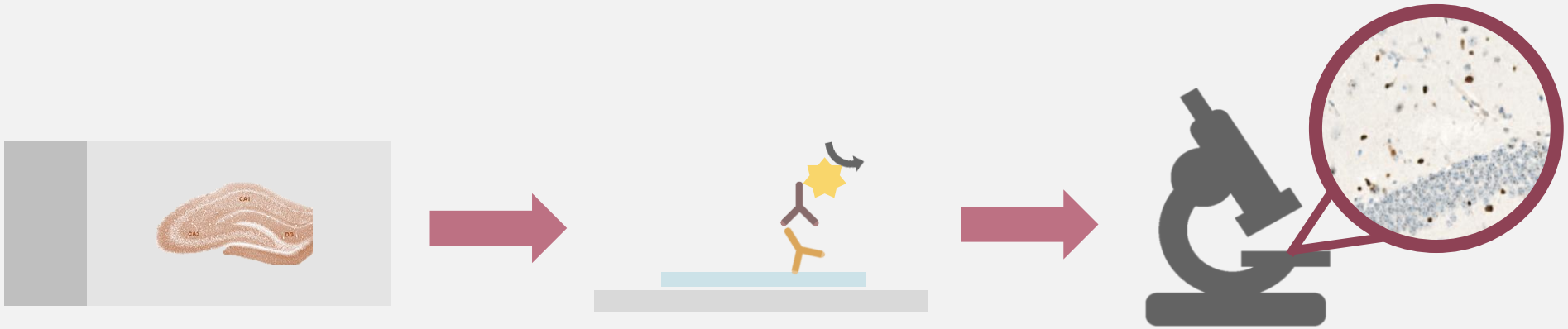
AIM 2: To compare the PrP interactome in the *Prnp*^{93N} knock-in mice (homozygous vs. WT littermate controls) and analyze the differences in interacting proteins or pathways involved in myelin homeostasis.

AIM 1 METHODS: DETERMINE THE TIMING AND EXTENT OF MYELIN LOSS AND MATURITY OF THE OLIGODENDROCYTE POPULATION.

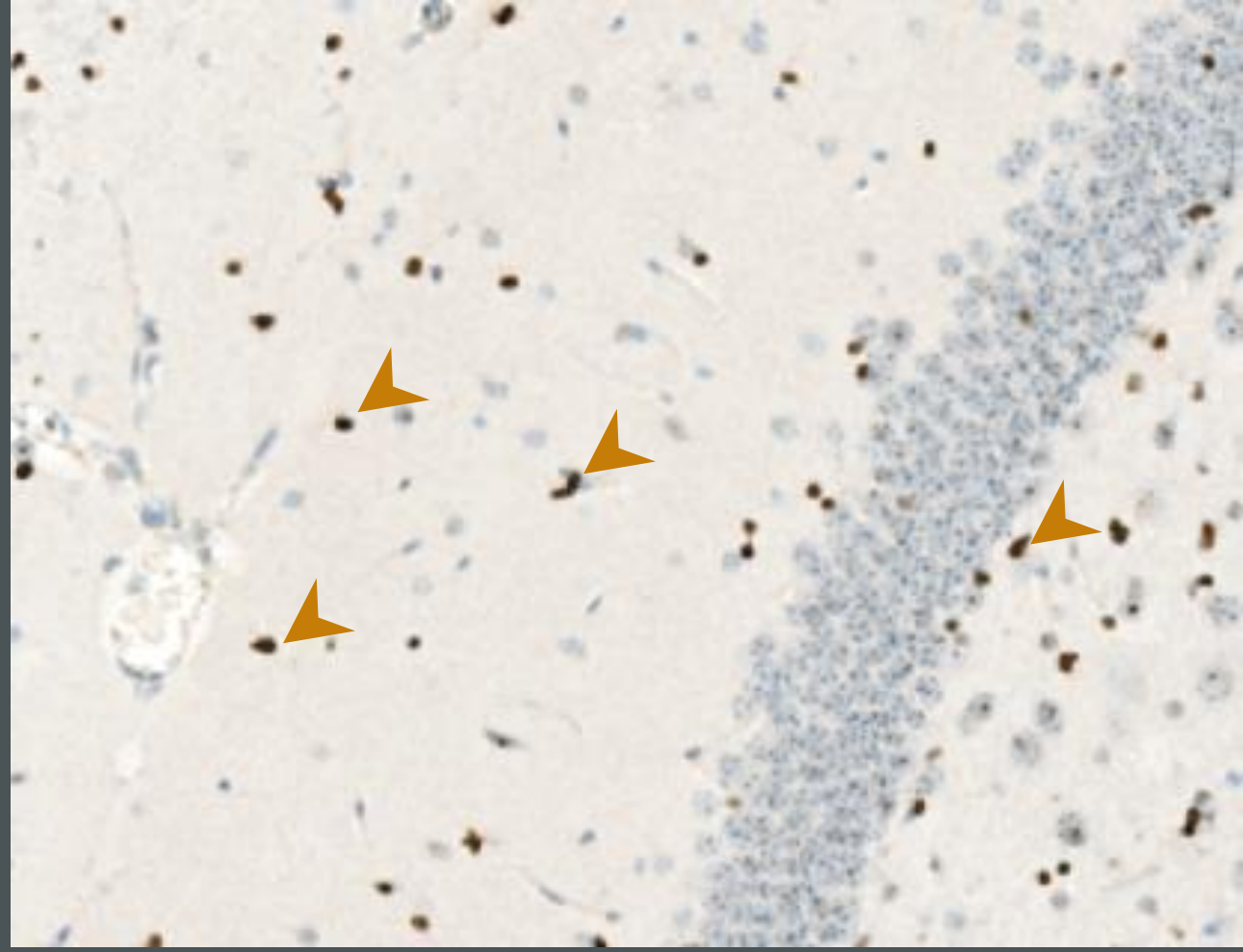


Collect brain and spinal cord samples for biochemical and histologic analyses of myelin proteins and oligodendrocyte populations.

AIM 1 METHODS: DETERMINE THE TIMING AND EXTENT OF MYELIN LOSS AND MATURITY OF THE OLIGODENDROCYTE POPULATION.

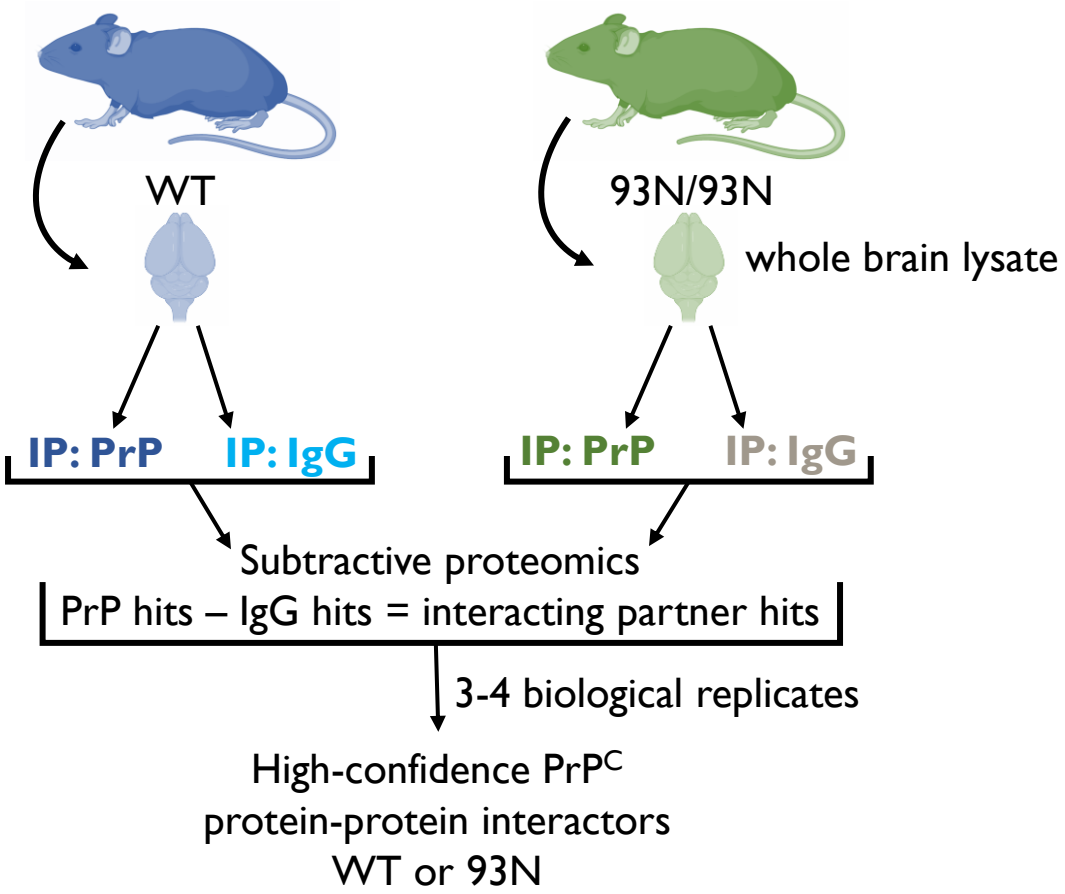


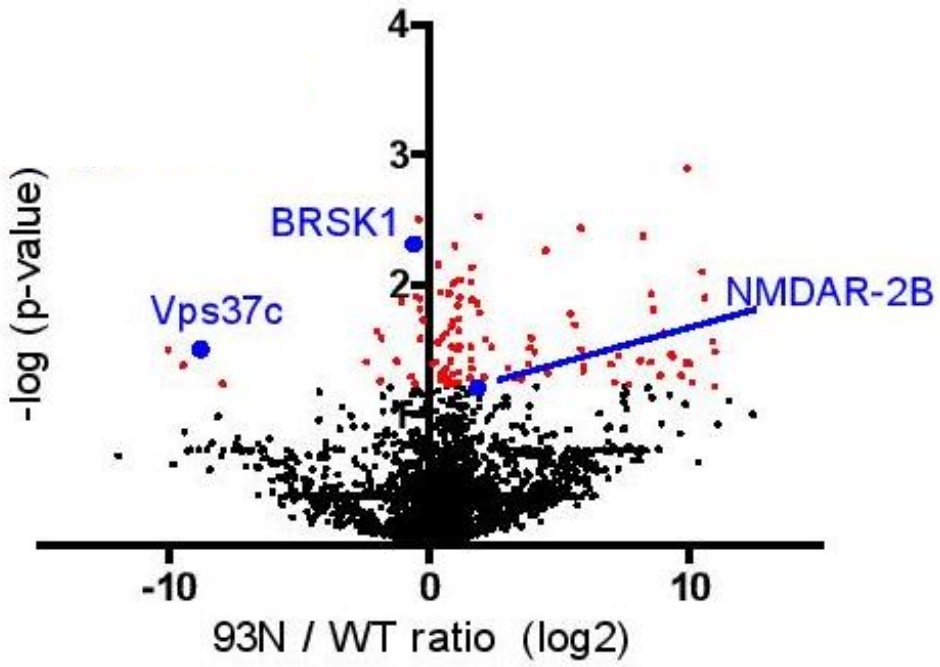
Characterize and quantify precursor and mature oligodendrocyte populations in the brain.



OLIG2

AIM 2: COMPARE THE PRP INTERACTOME & ANALYZE DIFFERENCES IN INTERACTING PROTEINS/PATHWAYS INVOLVED IN THE CONTROL OF MYELINATION.

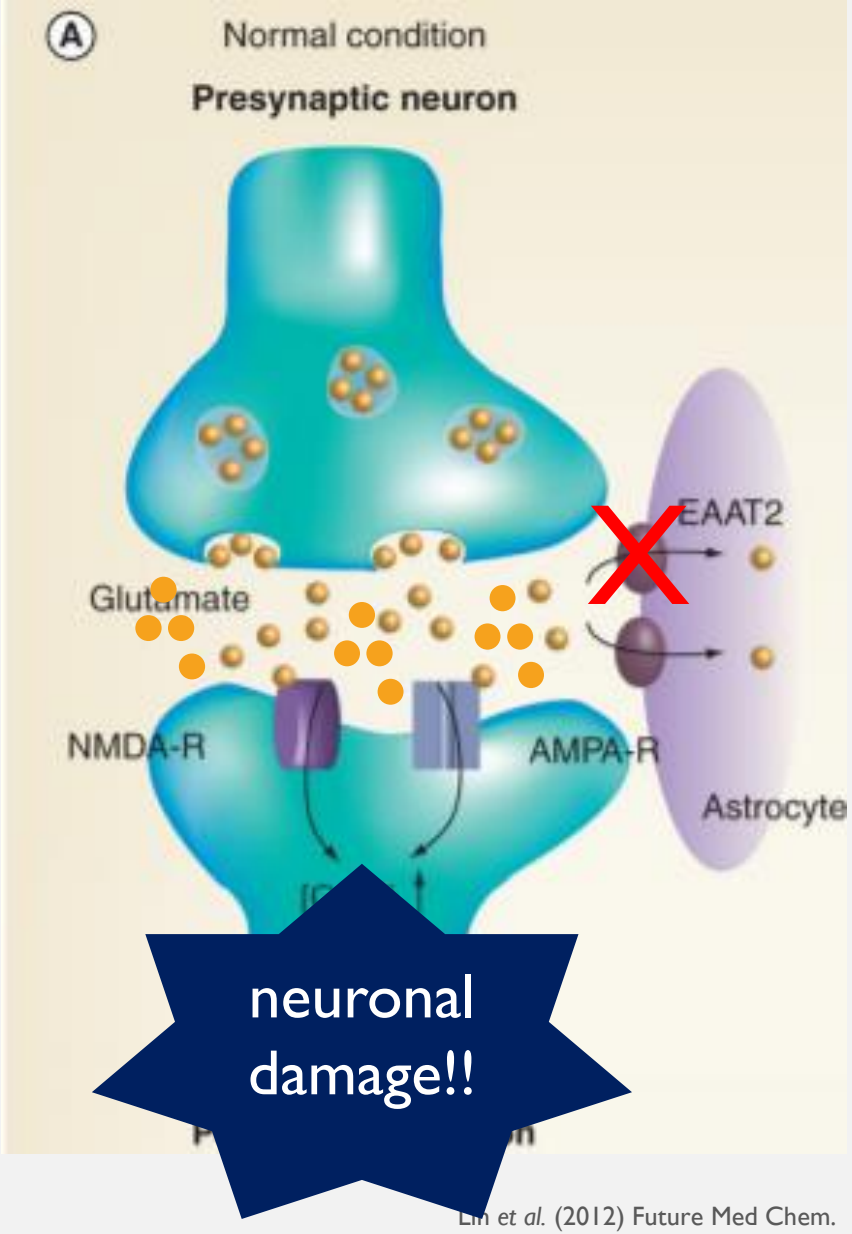




EAAT2 TRANSPORTER

DECREASED INTERACTIONS WITH PRP IN THE 93N MOUSE MODEL

- excitatory amino acid transporter 2 (EAAT2)
  - sodium-dependent glutamate transporter
  - glutamate = excitatory neurotransmitter
- decreased PrP interactions with EAAT2
  - → lack of glutamate reuptake
  - → excess glutamate
  - → increased excitotoxicity?



Lin *et al.* (2012) Future Med Chem.

NEXT STEPS

- Continue with image analysis (oligodendrocyte markers)
- Investigate EAAT2 levels
  - Plus other glutamate transporters and receptors

SUMMARY

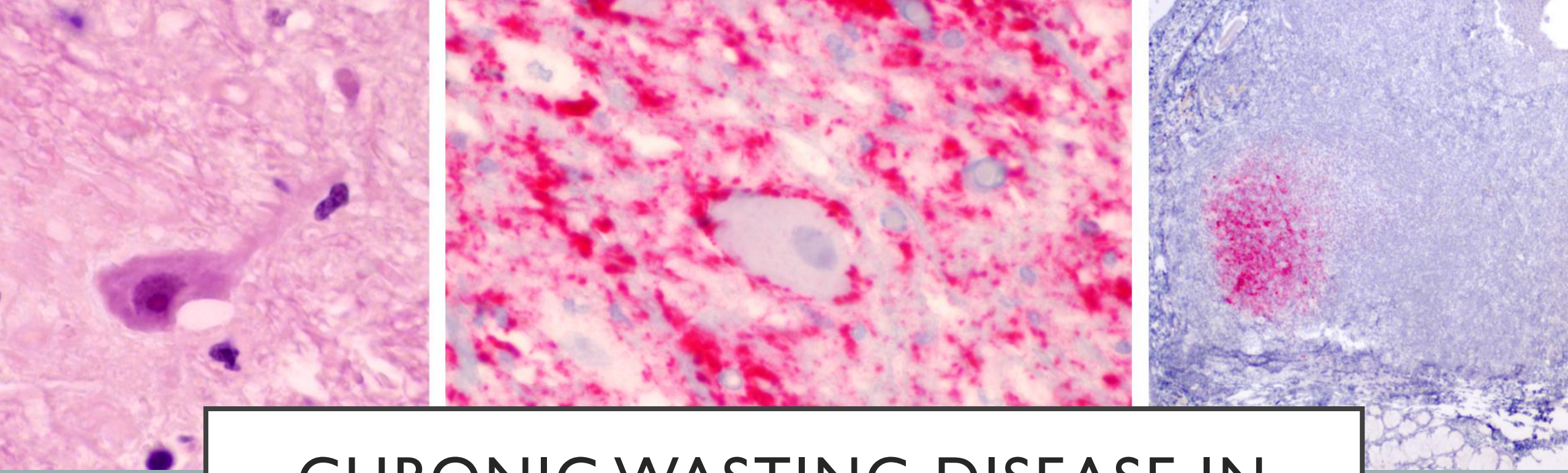
- Prion diseases are progressive, neurodegenerative diseases
- Our mouse model shows that prion neurotoxicity can occur in the absence of prion aggregates
  - Modified PrP^{C} can be neurotoxic
- In prion disease, we hypothesize that oligodendrocytes (cells responsible for myelinating the CNS) degenerate over time, leading to demyelination

ACKNOWLEDGEMENTS

- **Christina Sigurdson**
- **Julia Callender**
- Sigurdson Lab
- Donald Pizzo
- Alexandra Marquez
- Nigel Calcutt
- Samantha Darling
- STAR Program

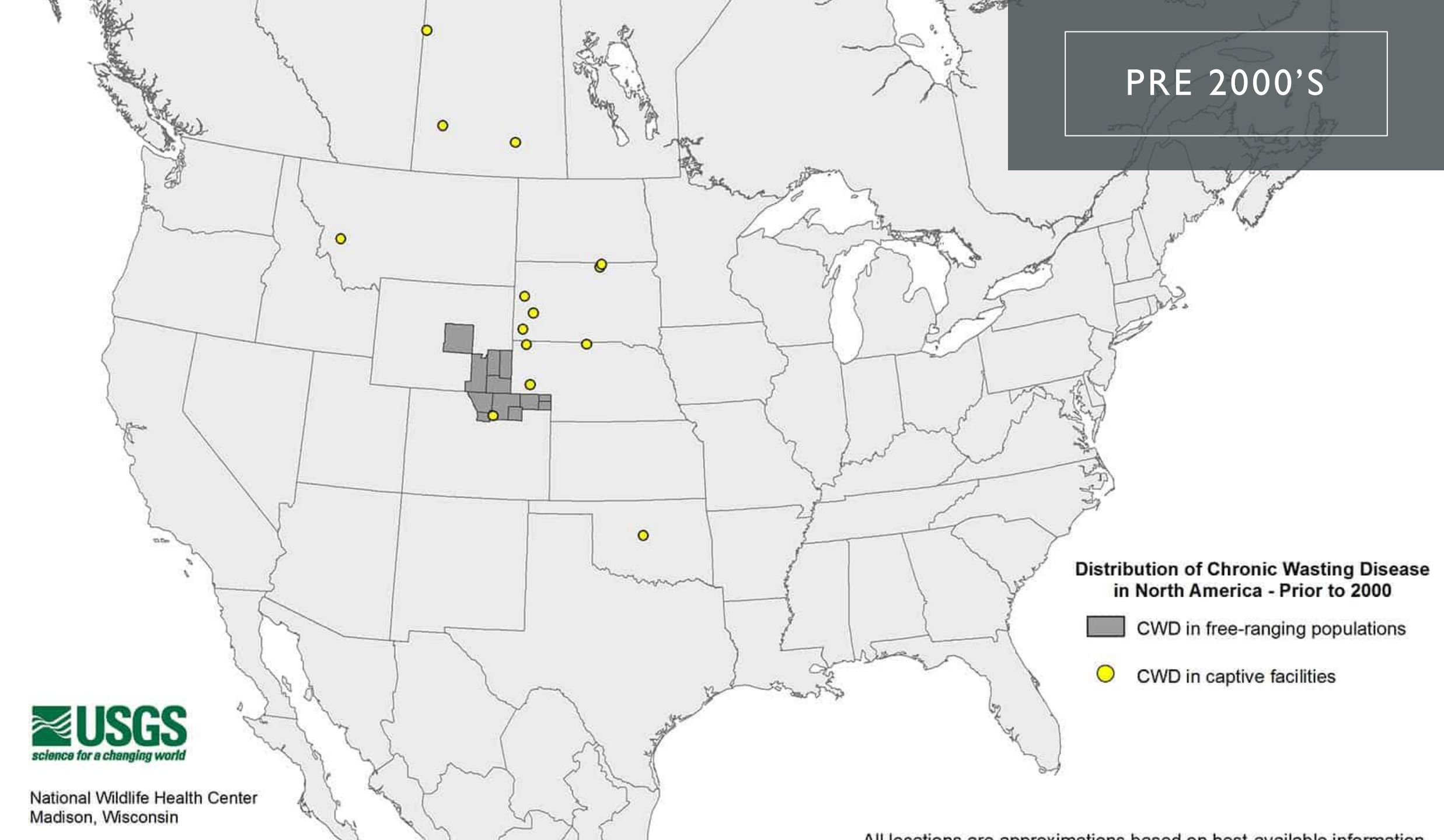
- Funding provided by NIH T35 OD010956


QUESTIONS?

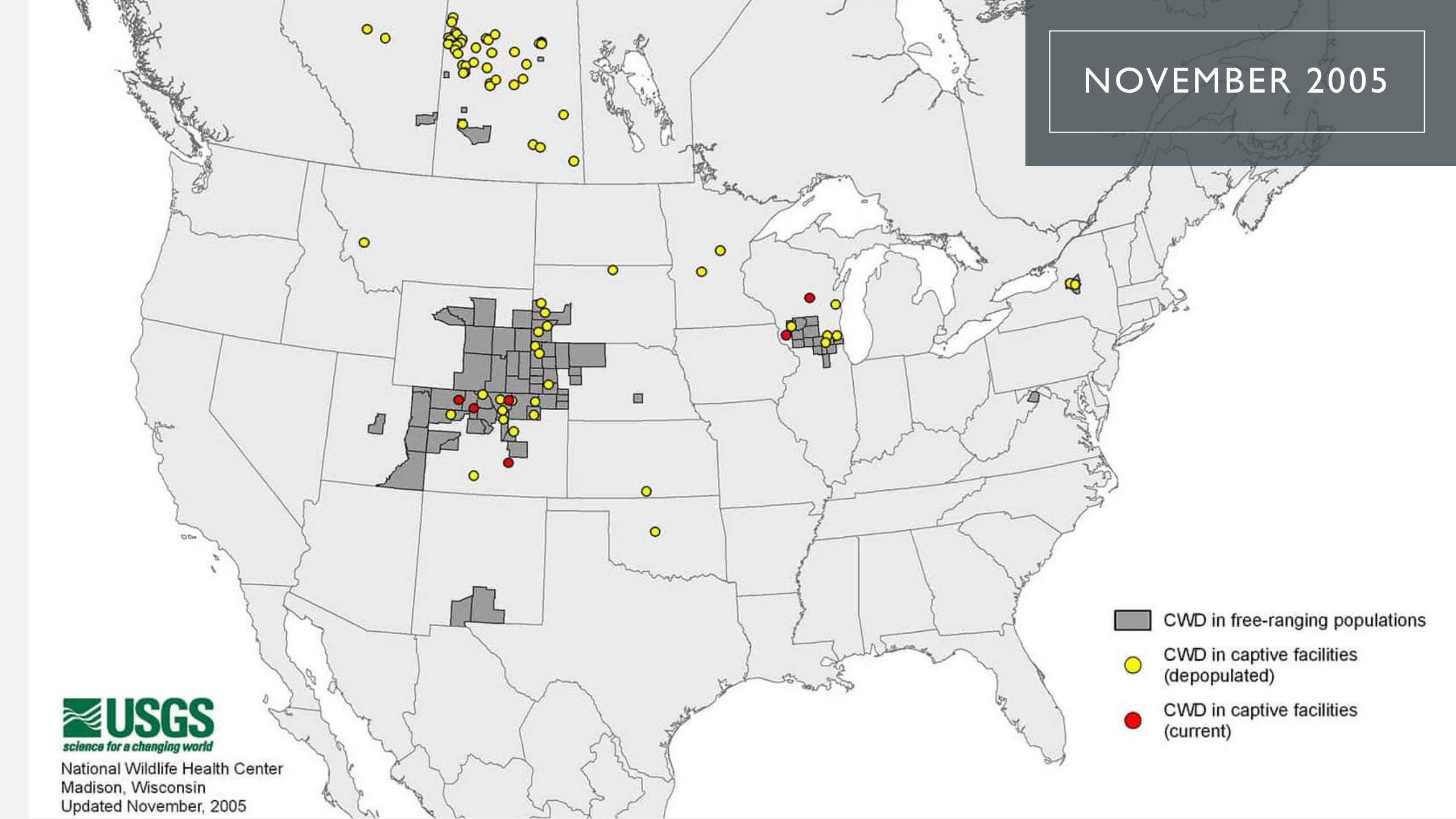


CHRONIC WASTING DISEASE IN CERVIDS

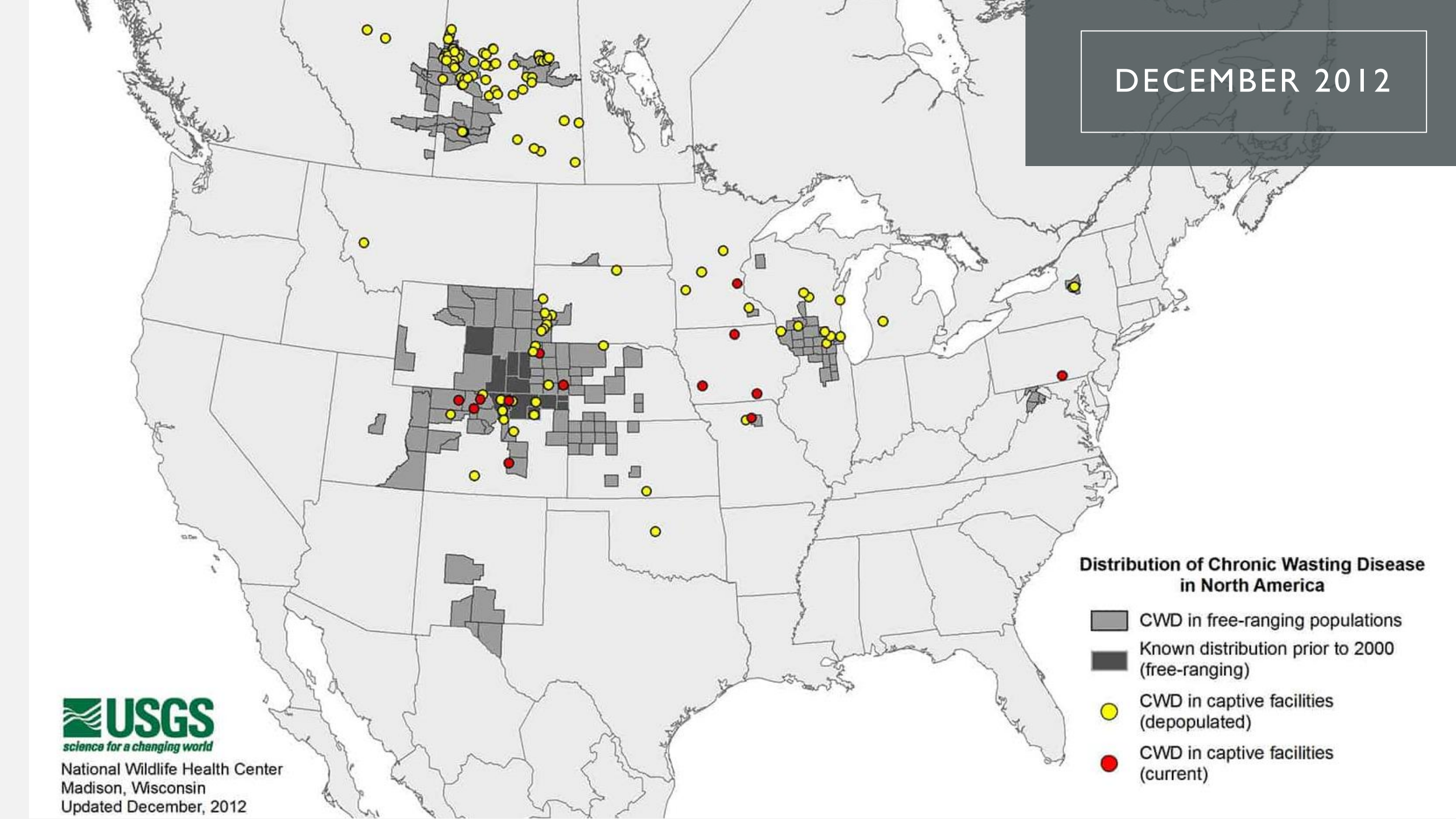
PRE 2000'S


Distribution of Chronic Wasting Disease
in North America - Prior to 2000
CWD in free-ranging populations
CWD in captive facilities
USGS
science for a changing world
National Wildlife Health Center
Madison, Wisconsin
All locations are approximations based on best available information

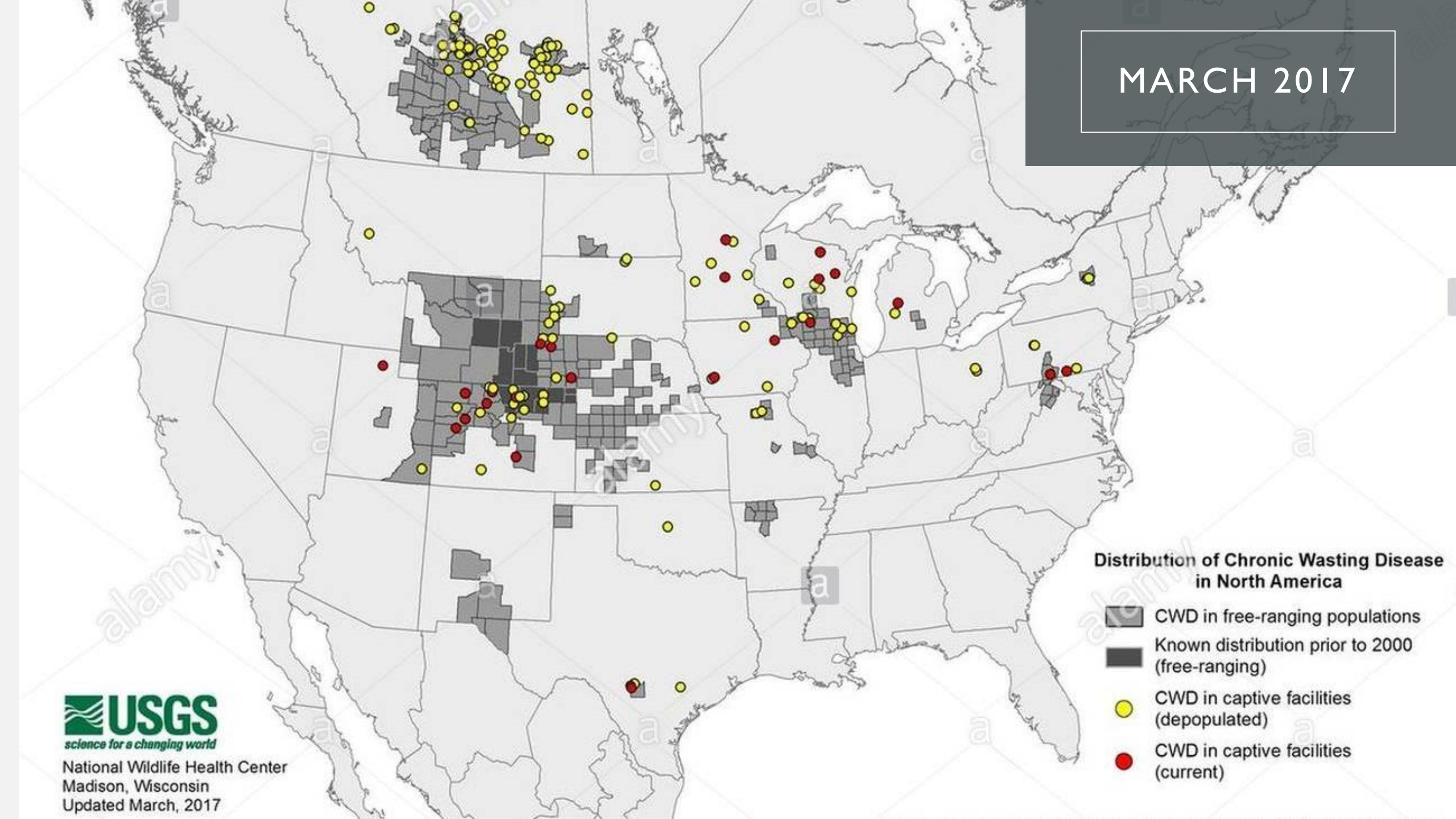
NOVEMBER 2005

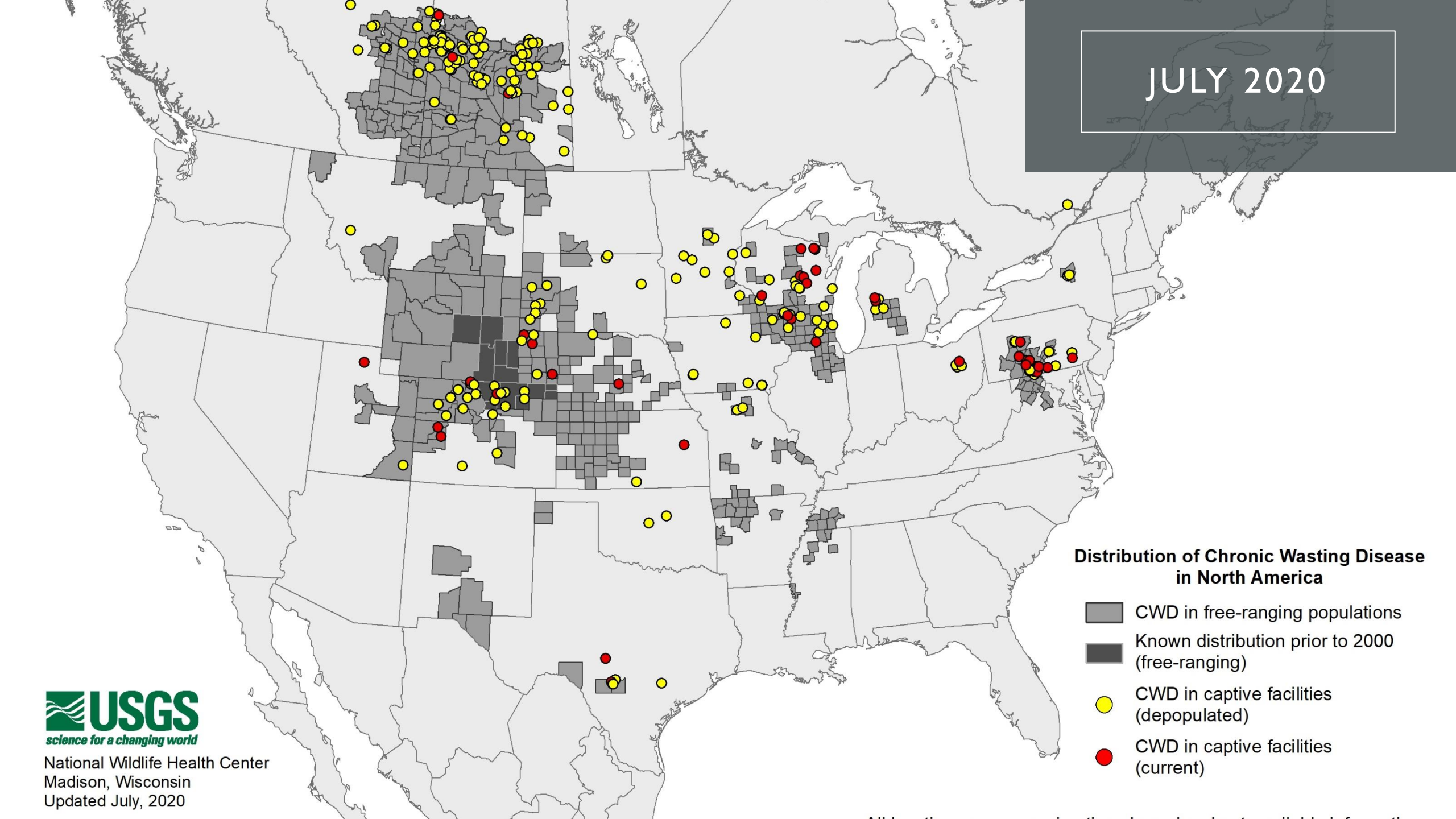


DECEMBER 2012



MARCH 2017


Distribution of Chronic Wasting Disease in North America
CWD in free-ranging populations
Known distribution prior to 2000 (free-ranging)
CWD in captive facilities (depopulated)
CWD in captive facilities (current)
USGS
science for a changing world
National Wildlife Health Center
Madison, Wisconsin
Updated March, 2017


JULY 2020
Distribution of Chronic Wasting Disease in North America
CWD in free-ranging populations
Known distribution prior to 2000 (free-ranging)
CWD in captive facilities (depopulated)
CWD in captive facilities (current)
USGS
science for a changing world
National Wildlife Health Center
Madison, Wisconsin
Updated July, 2020

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- Williamson JM and Lyons DA (2018) Myelin Dynamics Throughout Life: An Ever-Changing Landscape?. *Front. Cell. Neurosci.* 12:424. doi: 10.3389/fncel.2018.00424