Treatment with a Non-Toxic, Self-Replicating Anti-Prion

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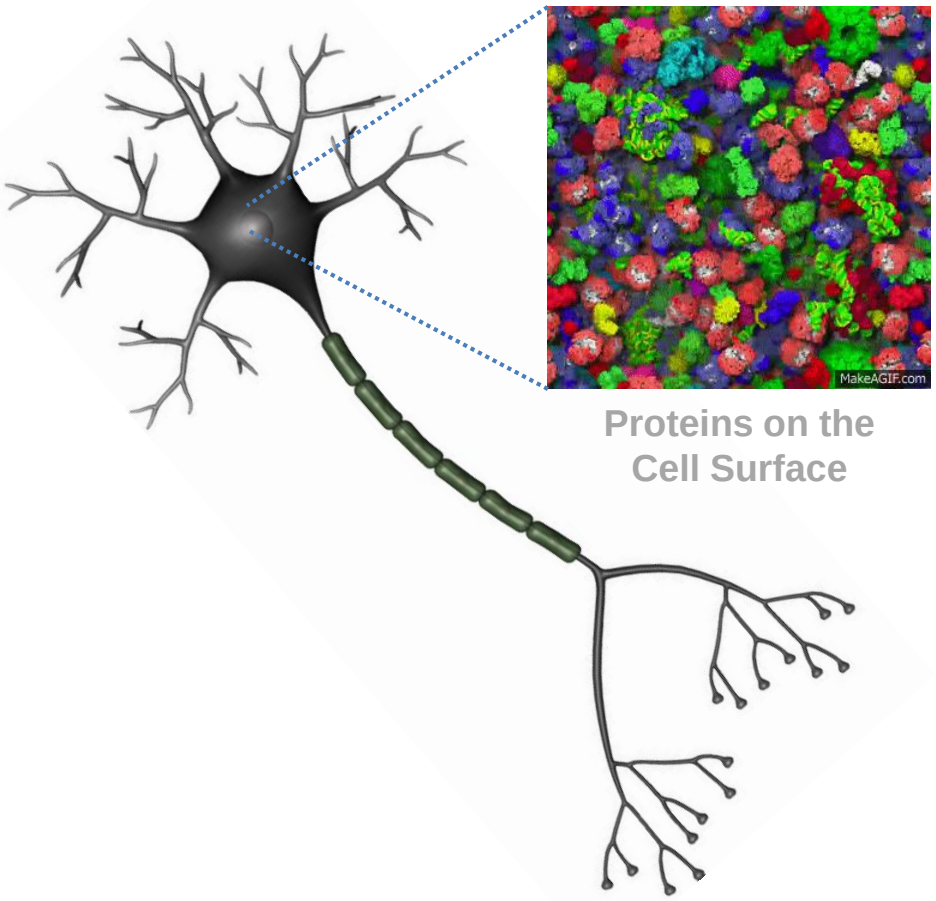
PMDL

Outline

- Prion replication.
  - Brain cell environment.
  - Misfolding of the cellular prion protein (PrP^{C}) into PrP^{Sc}.
- Modeling prion disease.
  - Phases of prion infection.
- Non-pathogenic prions.
  - Synthetic prions.
- Anti-prion concept.
  - Competition between pathogenic and non-pathogenic prions.
- Summary, conclusions, and future directions.

Prion Replication:
Misfolding of the Cellular Prion Protein (PrP^C)

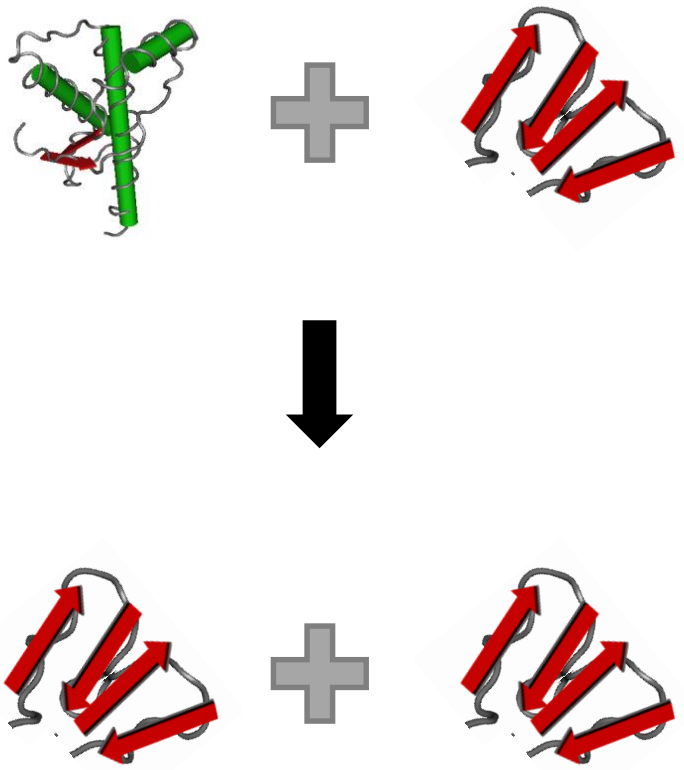
Brain Neuron



Proteins on the Cell Surface

PrP^C
Healthy

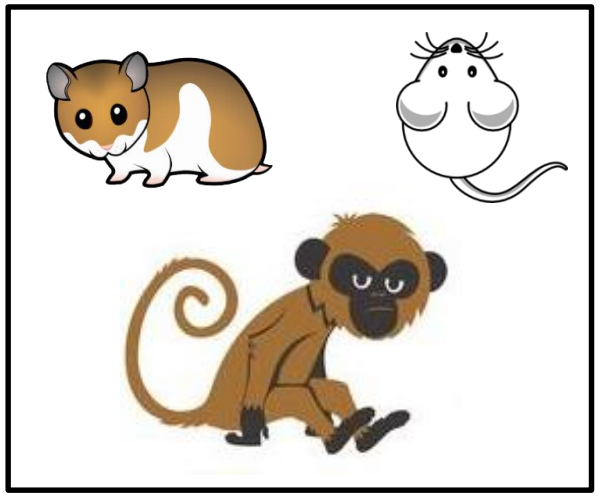
PrP^{Sc}
Disease

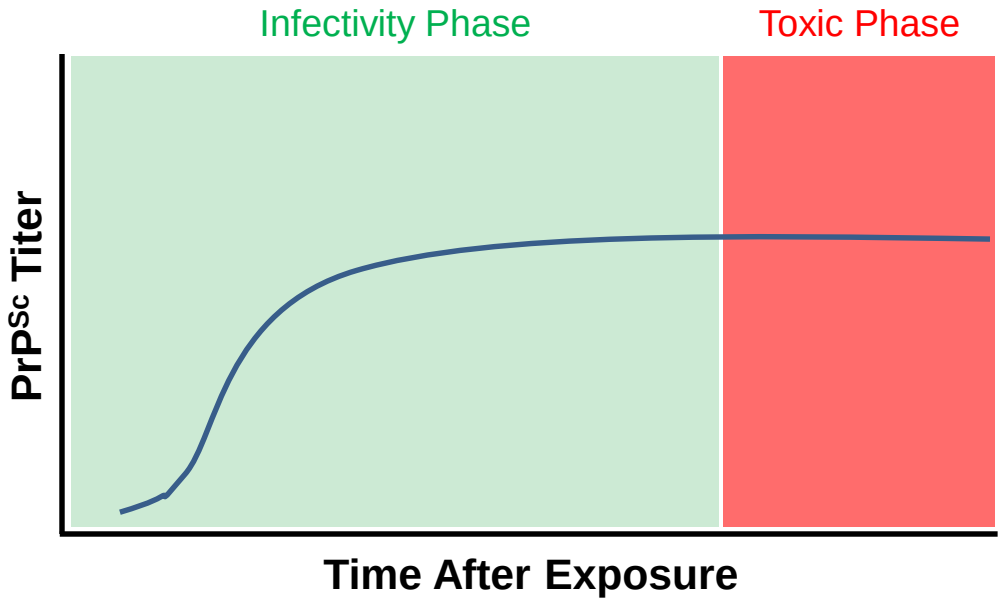


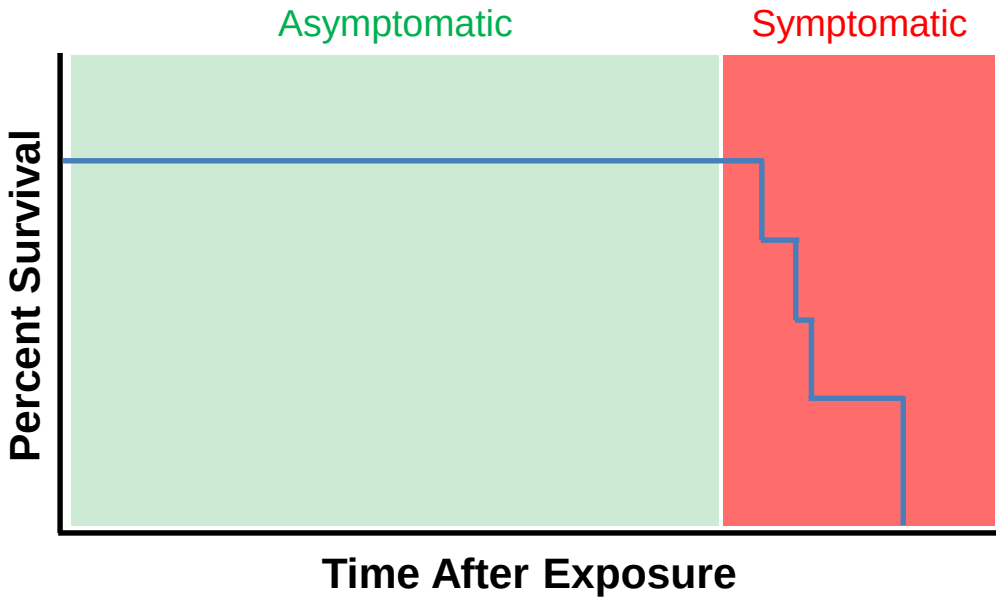
McGuffee and Elcock, PLoS Comput. Biol. 2010; NCBI Database MMDBID:19134

Modeling Prion Disease: Clinical Phenotype

Common Models

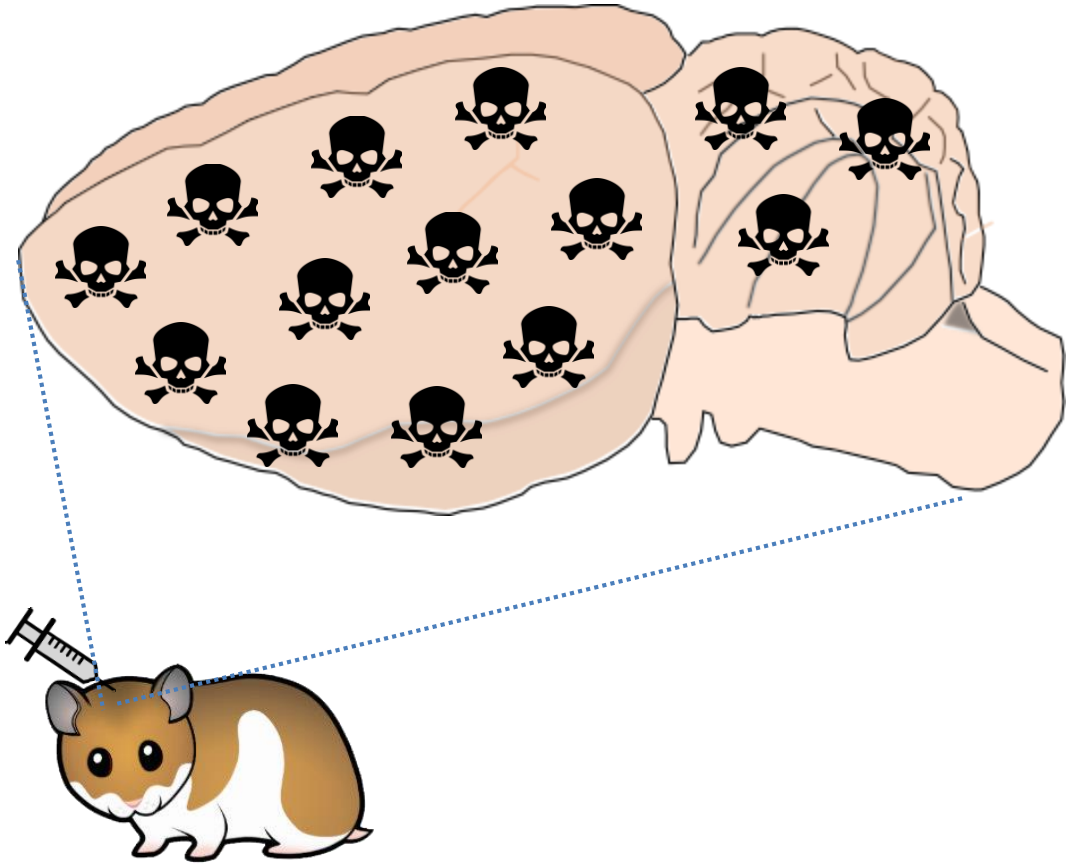


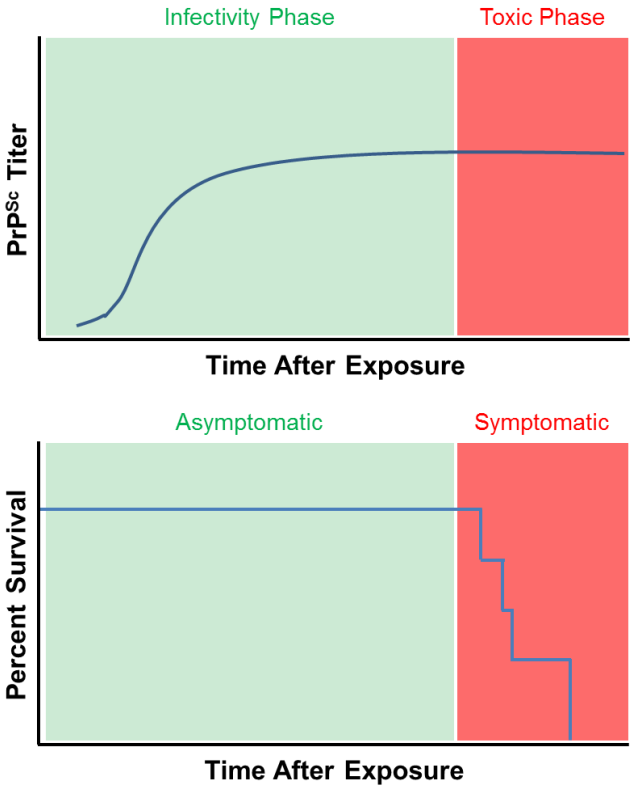




Protein Misfolding Diseases Lab

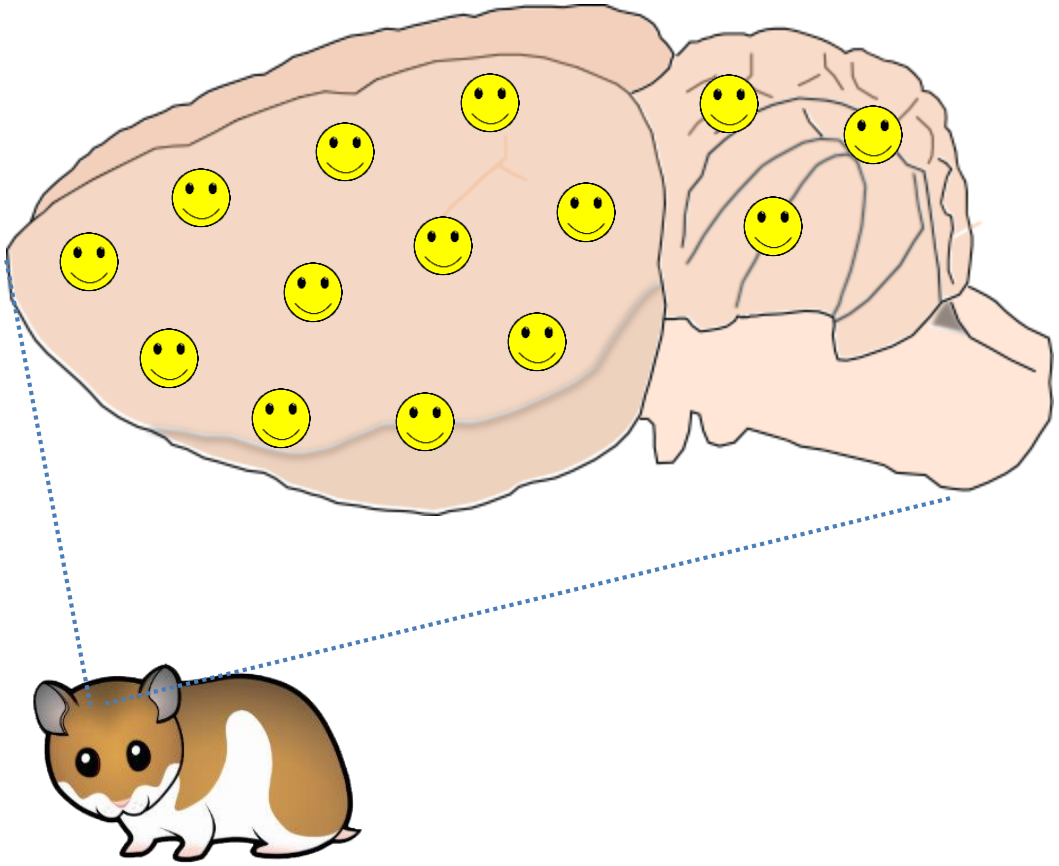
Modeling Prion Disease: Brain Damage

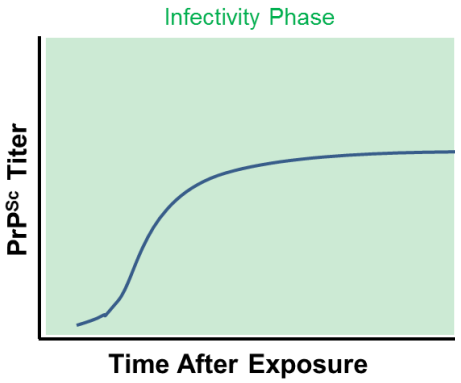


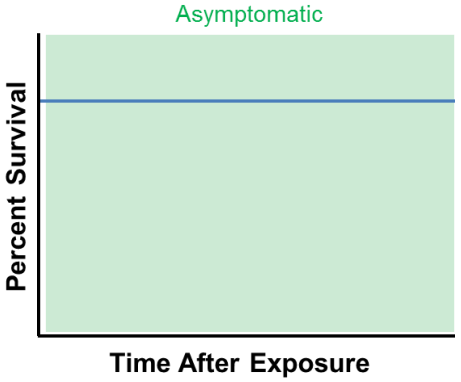


- Exposure to pathogenic prions.
  - Toxicity and clinical onset.
  - Tendency to be rapid and aggressive.

Do Non-Pathogenic Prions (Anti-Prions) with Therapeutic Potential Exist?





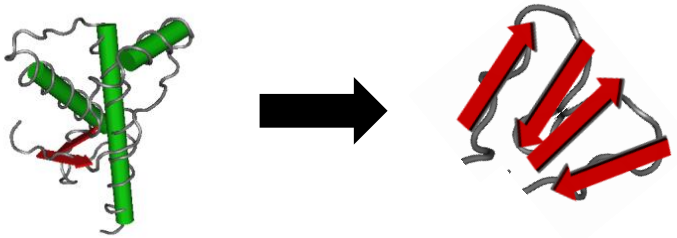


- Exposure to nonpathogenic, nontoxic anti-prions.
  - Accumulation without disease.
  - Tendency to replicate slowly.

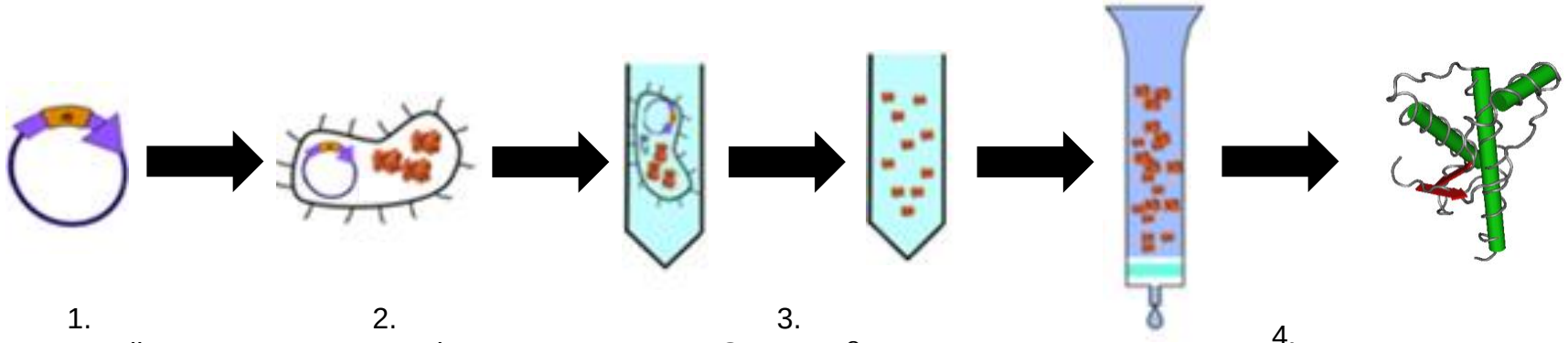
Synthetic Prions: Promising Anti-Prion Candidates

PrP^{C}
Healthy

PrP^{Sc}
Disease



Large Scale Production of PrP^{C} by Bacteria



1. DNA Encoding PrP^{C}
2. Insert DNA into Bacteria
3. Grow PrP^{C} Producing Bacteria
4. Purify PrP^{C}

- Recapitulating PrP misfolding in the laboratory.
  - Highly pathogenic and infectious conformations are rare.
  - Some self-replicate *in vitro* and *in vivo* without clinical onset.

Wang et al., 2010 Science; Makarava et al., 2010 Acta Neuropathol

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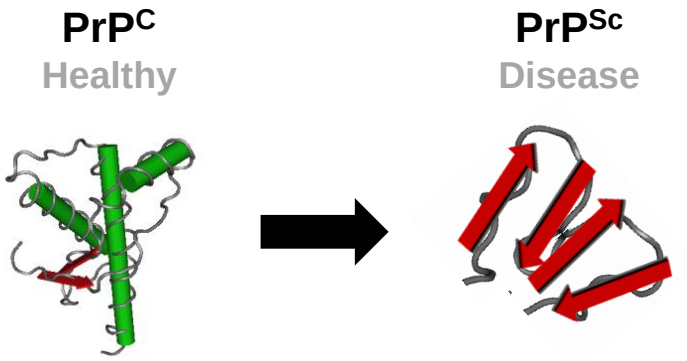

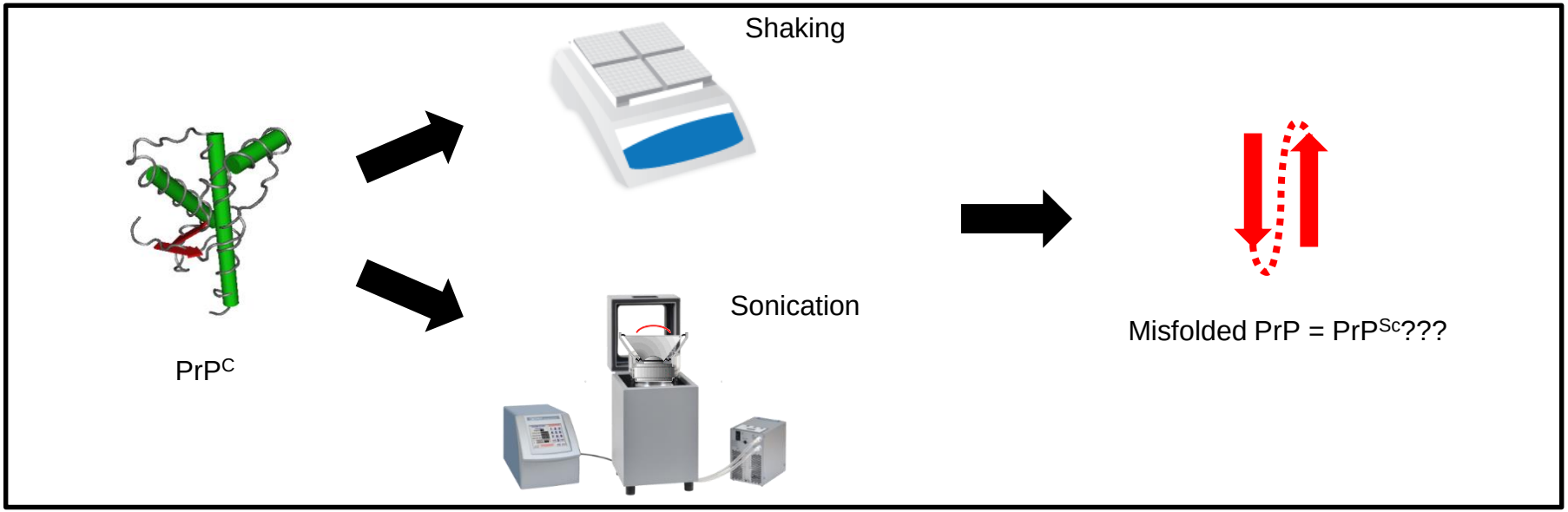

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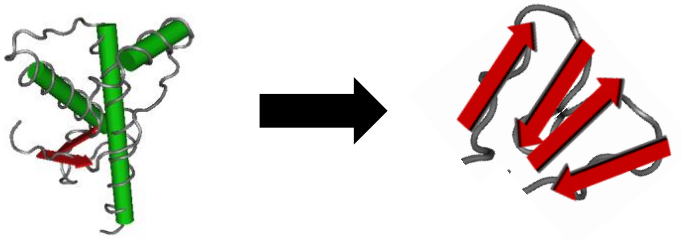

Some Synthetic Prions Appear Non-Pathogenic

Misfolded PrP

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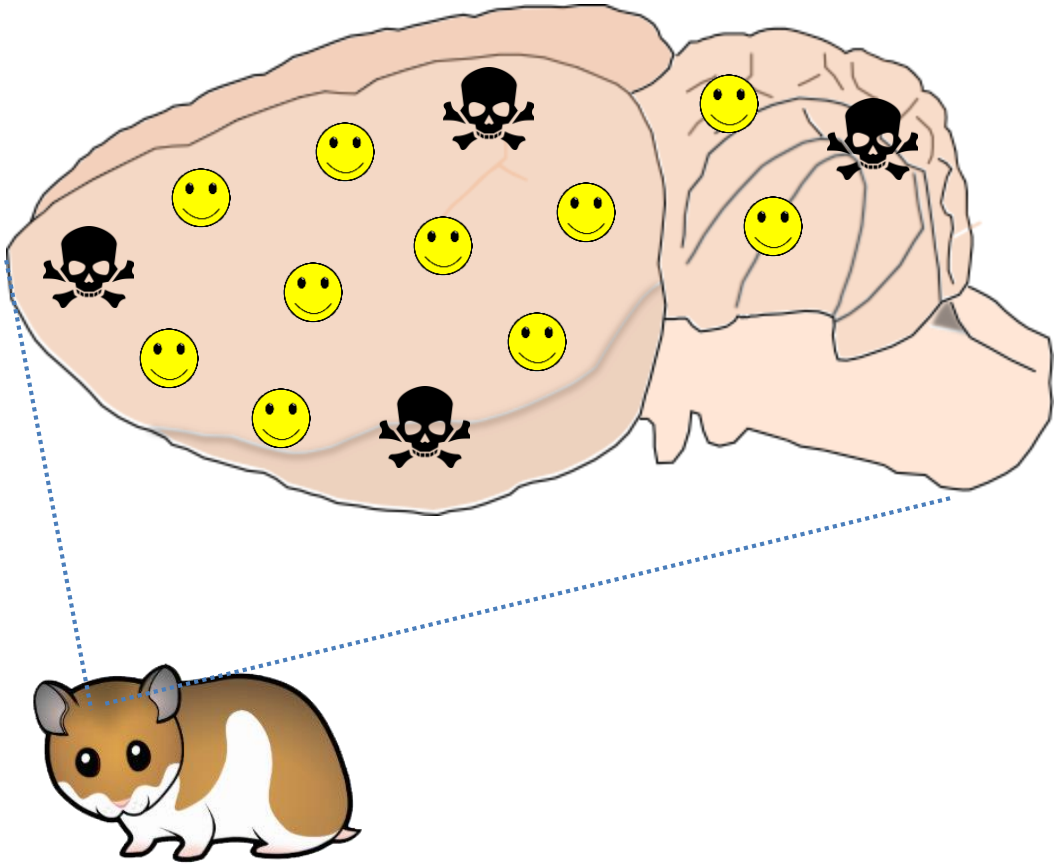
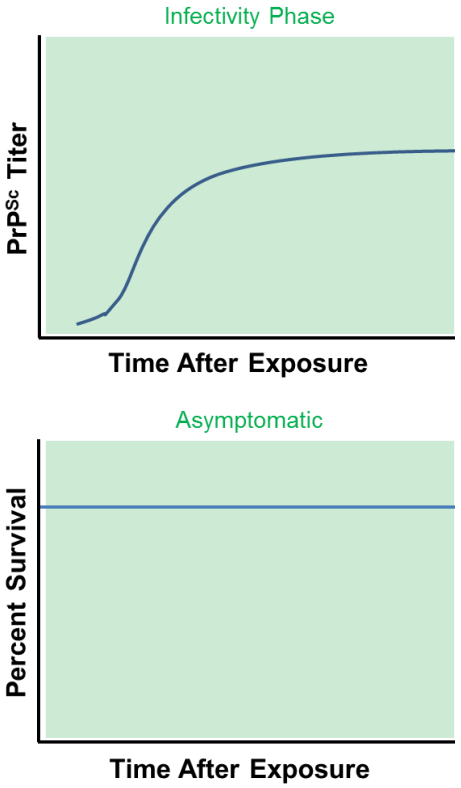
Anti-Prion Concept





- Simultaneous replication of pathogenic prions and anti-prions.
  - Competition will reduce the amount of toxic prions, lower brain damage, and delay disease.

Anti-Prions Competing with Pathogenic Prions

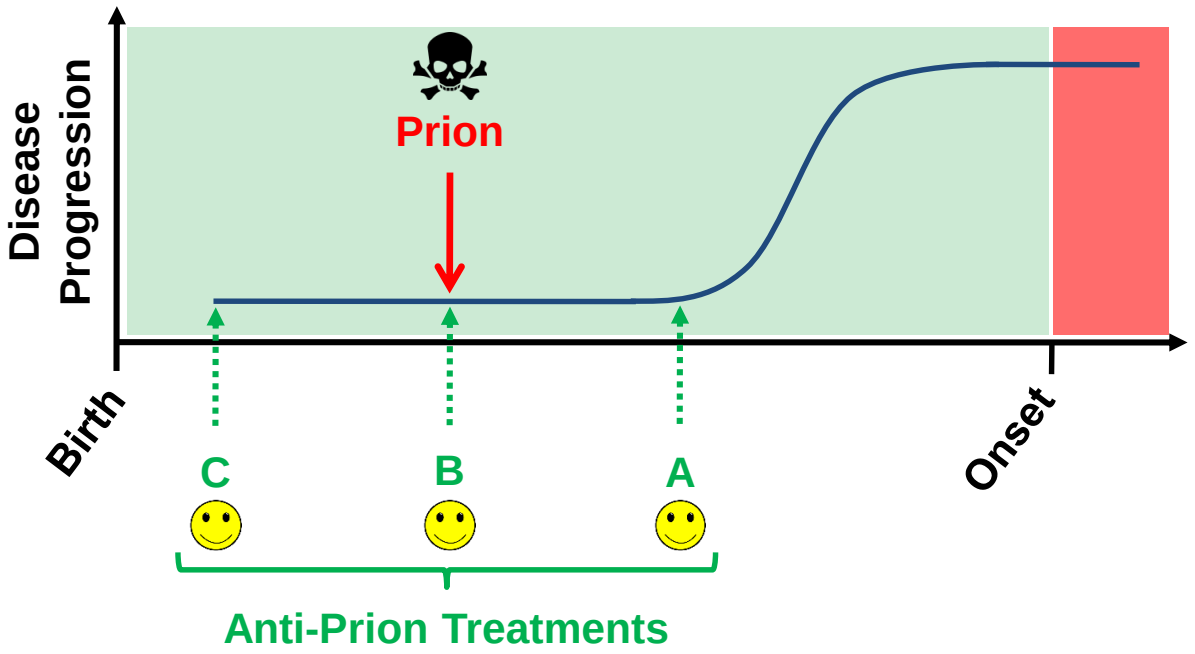
USAIN BOLT'S MAX. SPEED
27.7 MPH

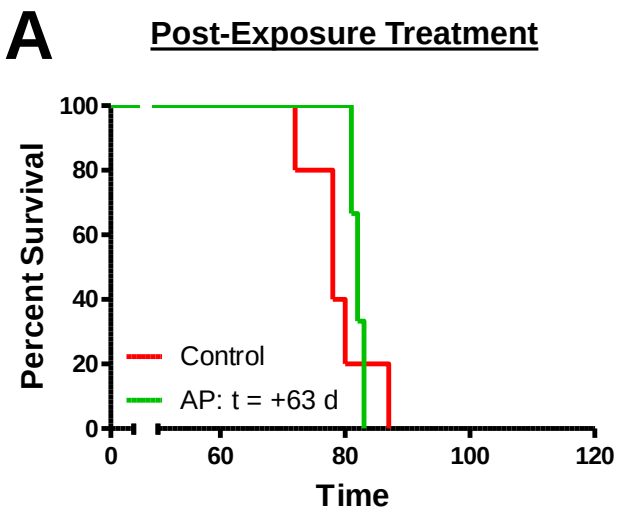
AVERAGE HUMAN WALKING
3 MPH

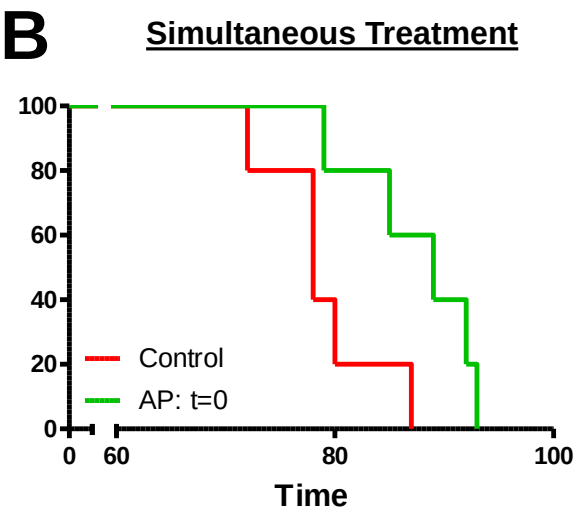
SOURCES: Illinois State University ISU ReD: Research and eData; Atlas Obscura; Live Science; Atkins Bookshelf

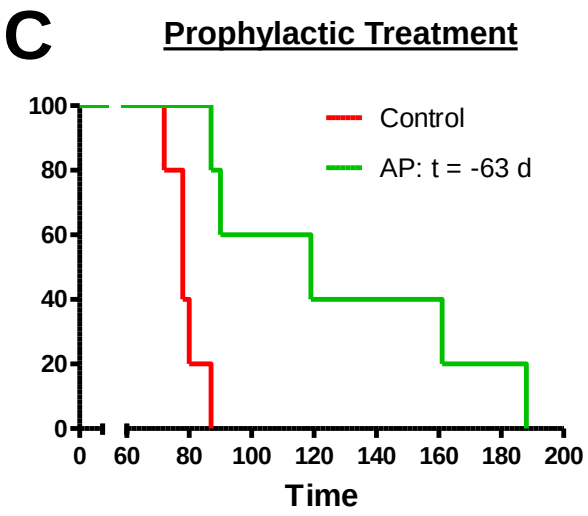
TECH INSIDER

Efficiency Dependent on Treatment Timing



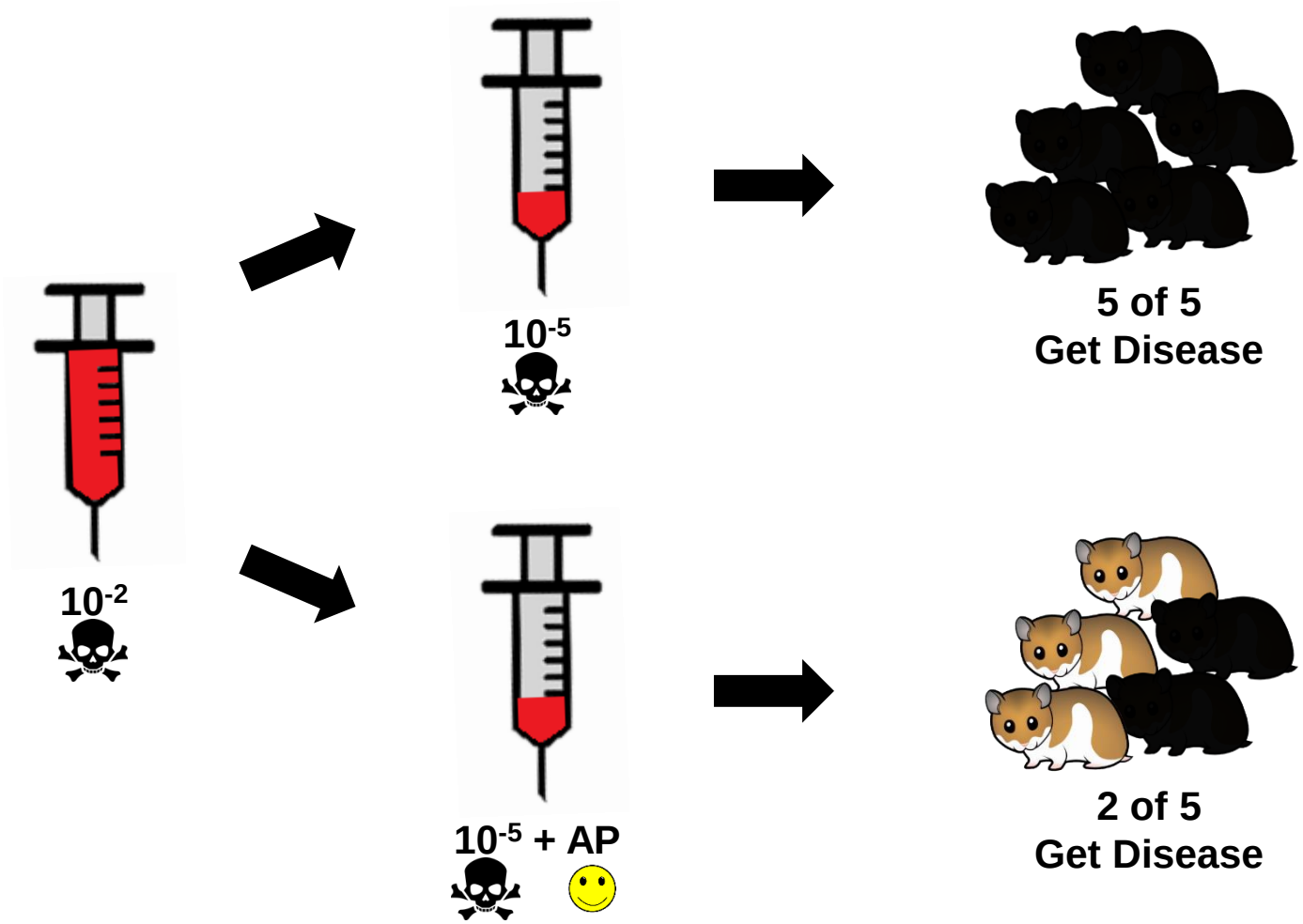






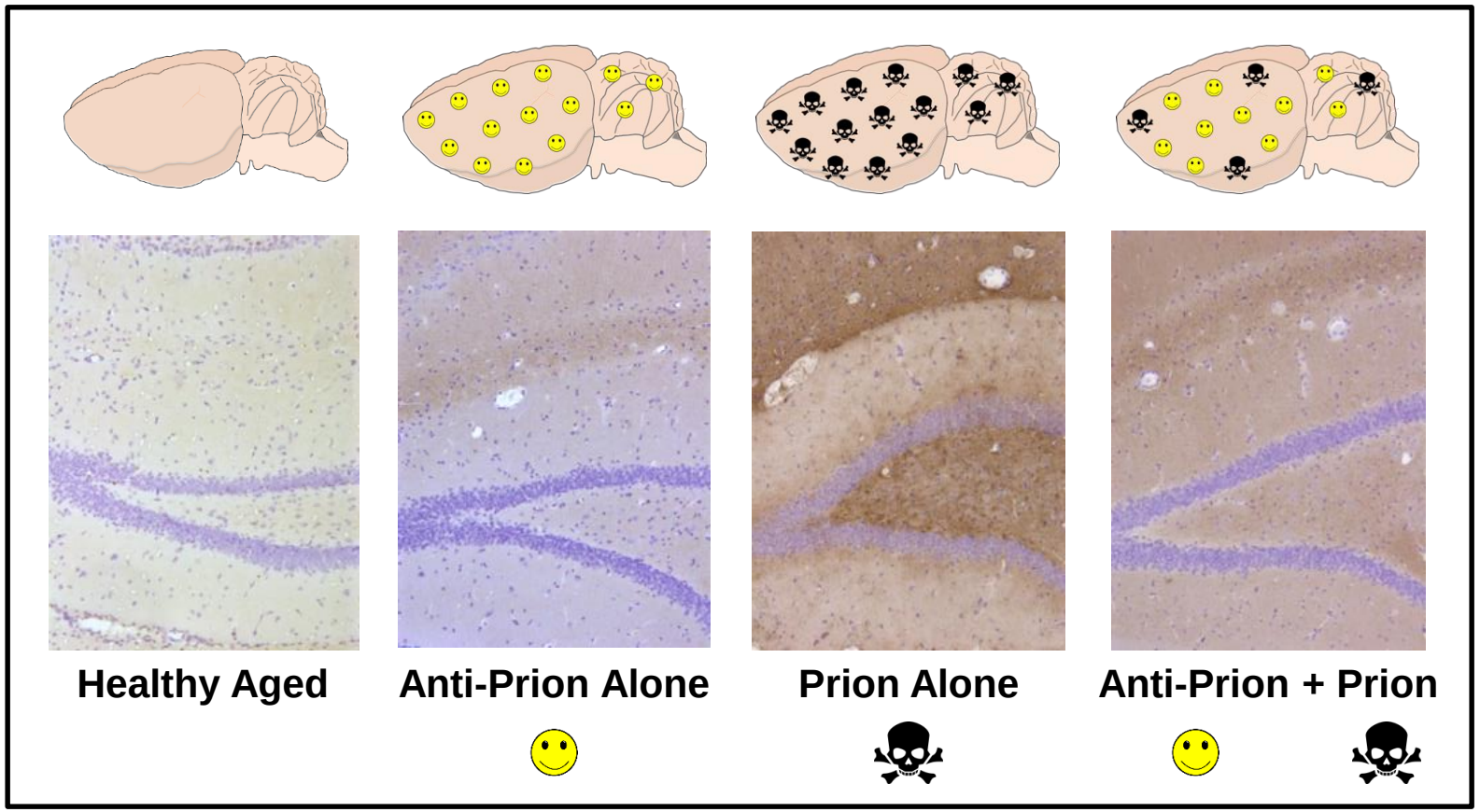
Protein Misfolding Diseases Lab

Dependency on Pathogenic Prion Dose



- Prophylactic anti-prion treatment reduced infectivity by ~99%.

Anti-Prions Inhibit Pathogenic PrP^{Sc} Replication



- PrP^{Sc} deposition was low, but detectable, in the brains of anti-prion treated asymptomatic animals.

Summary and Conclusions

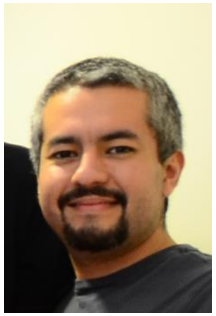
- A non-toxic, self-replicating anti-prion was generated from full-length recombinant PrP^{C}.
  - Mild PrP^{Sc} deposition observed > 400 dpi.
  - No clinical signs (> 600 dpi).
- The anti-prion significantly inhibited pathogenic prions in hamsters.
  - Simultaneous and prophylactic treatment.
  - Efficiency was dependent on time and the pathogenic prion dose.
- After anti-prion treatment, PrP^{Sc} accumulation was significantly lower, and disease was occasionally prevented.
  - Prion infectivity was reduced by approximately 2 logs.
- **Conclusion:** Prion replication can be separated from toxicity, thus providing a novel target for therapeutic intervention.

Future Directions

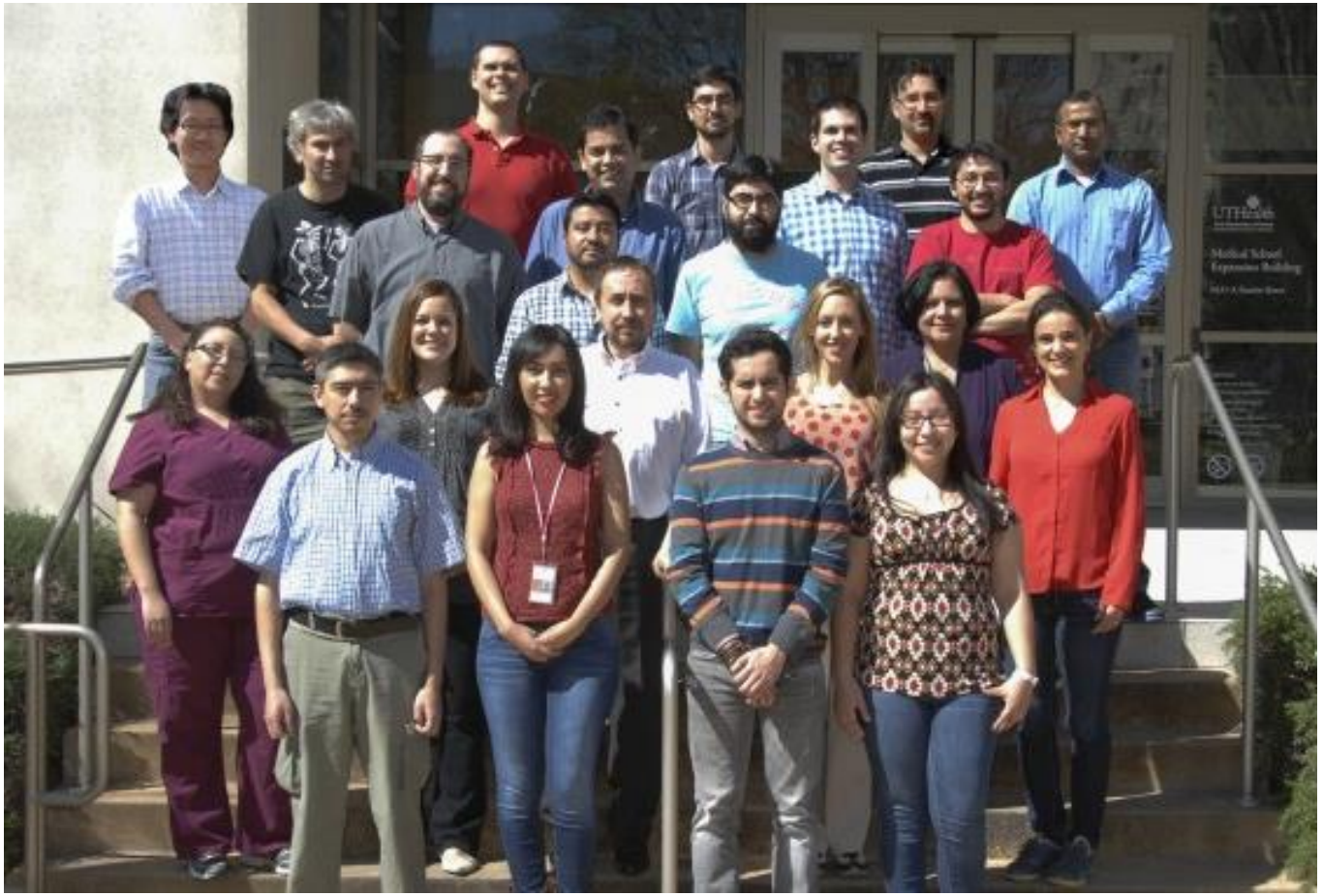
- Define the underlying mechanism for the anti-prions.
  - Competition for PrP^C substrate, host response to prophylactic treatment, etc.
- Determine whether anti-prions are applicable to diverse prion diseases of different species.
  - Utilize established transgenic mouse models.
- Attempt to obtain more potent anti-prions.
  - Do non-pathogenic prions that replicate faster exist?

Acknowledgements

Dr. Claudio Soto, PhD



Dr. Rodrigo Diaz, PhD



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