Worms: a novel genetic model for therapeutic research in prion diseases

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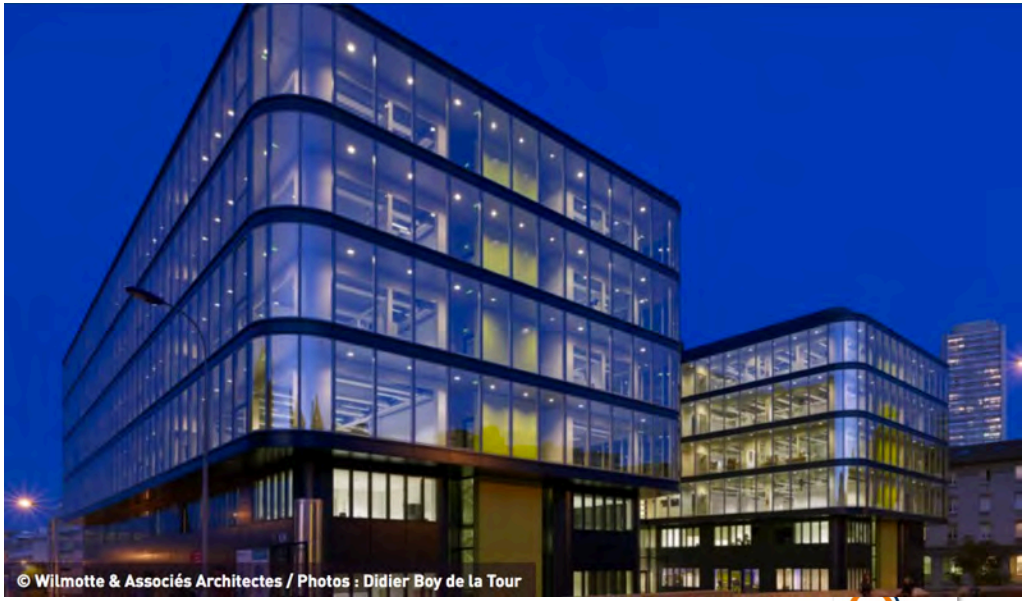
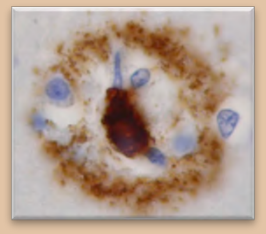
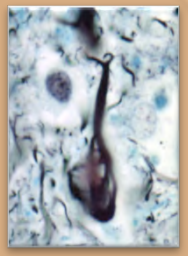


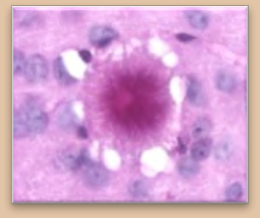
Reiss, 1850; Brouillet 1887

Alzheimer's and Prion diseases Lab

From human neuropathology to cellular mechanisms







- Progression of lesions in human and mouse models
- Cellular effects of Aβ on synapses and endosomes
- Nanobodies-based diagnosis

- Tau pathology
- Strain effects
- Prion-derived amplification methods

- Strains identification and selection
- Strain regional targeting and toxicity
- Prions detection and therapeutics

Alzheimer's

Prions

- French National Center of Reference for human prions
- French National Surveillance Network for CJD
- Biocollection of blood and CNS samples

Long standing interest in prion therapeutics

Compassionate use of quinacrine in Creutzfeldt–Jakob disease fails to show significant effects

S. Haïk, MD, PhD; J.P. Brandel, MD; D. Salomon, BA; V. Sazdovitch, MD; N. Delasnerie-Lauprêtre, MD; J.L. Laplanche, PharmD, PhD; B.A. Faucheux, PhD; C. Soubrié, MD; E. Boher, PharmD; C. Belorgey, MD; J.J. Hauw, MD; and A. Alpérovitch, MD

NEUROLOGY 2004;63:2413–2415

Doxycycline in Creutzfeldt-Jakob disease: a phase 2, randomised, double-blind, placebo-controlled trial

Stéphane Haïk, Gabriella Marcon*, Alain Mallet, Mauro Tettamanti, Arlette Welaratne, Giorgio Giaccone, Shohreh Azimi, Vladimiro Pietrini, Jean-Roch Fabreguettes, Daniele Imperiale, Pierre Cesaro, Carlo Buffa, Christophe Aucan, Ugo Lucca, Laurène Peckeu, Silvia Suardi, Christine Tranchant, Inga Zerr, Caroline Houillier, Veronica Redaelli, Hervé Vespignani, Angela Campanella, François Sellal, Anna Krasnianski, Danielle Seilhean, Uta Heinemann, Frédéric Sedel, Mara Canovi, Marco Gobbi, Giuseppe Di Fede, Jean-Louis Laplanche, Maurizio Pocchiari, Mario Salmona, Gianluigi Forloni, Jean-Philippe Brandel†, Fabrizio Tagliavini†*

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Minimal properties of an antiprion compound usable in clinical trials

- Active against prion propagation or the effects of prion propagation on neuronal cells
- Validated efficacy against human prions
- Efficacy validated in several models including *in vivo*
- Cross the blood-brain barrier
- Low toxicity profile in humans and known pharmacokinetics (ideally FDA-approved)

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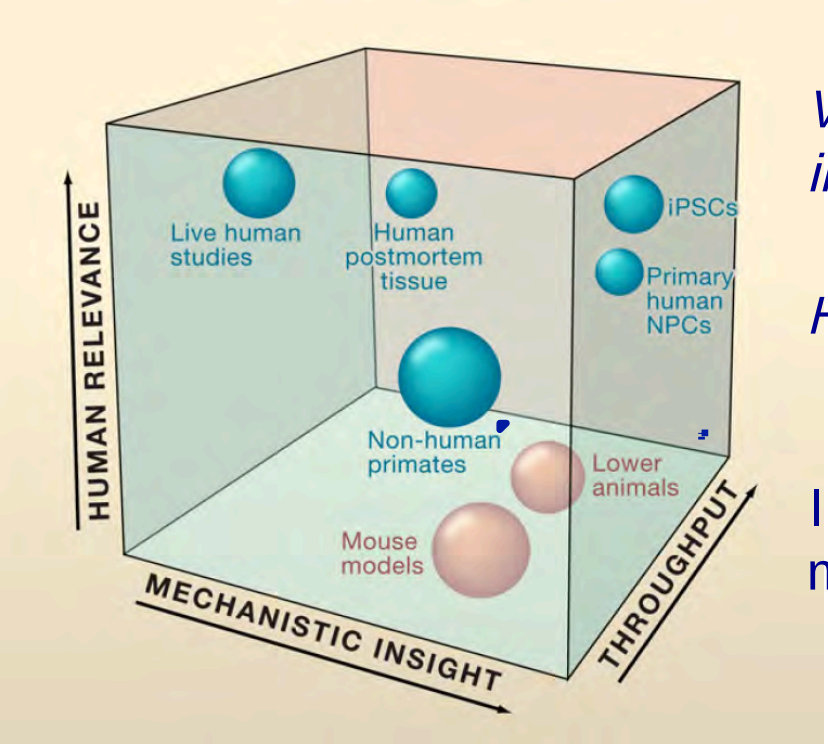
- Cross the blood-brain barrier ✔
- Low toxicity profile in humans and known pharmacokinetics (ideally FDA-approved) ✔

➔ *Drug repositioning using FDA approved library of compounds targeting the CNS*

Need for a screening approach



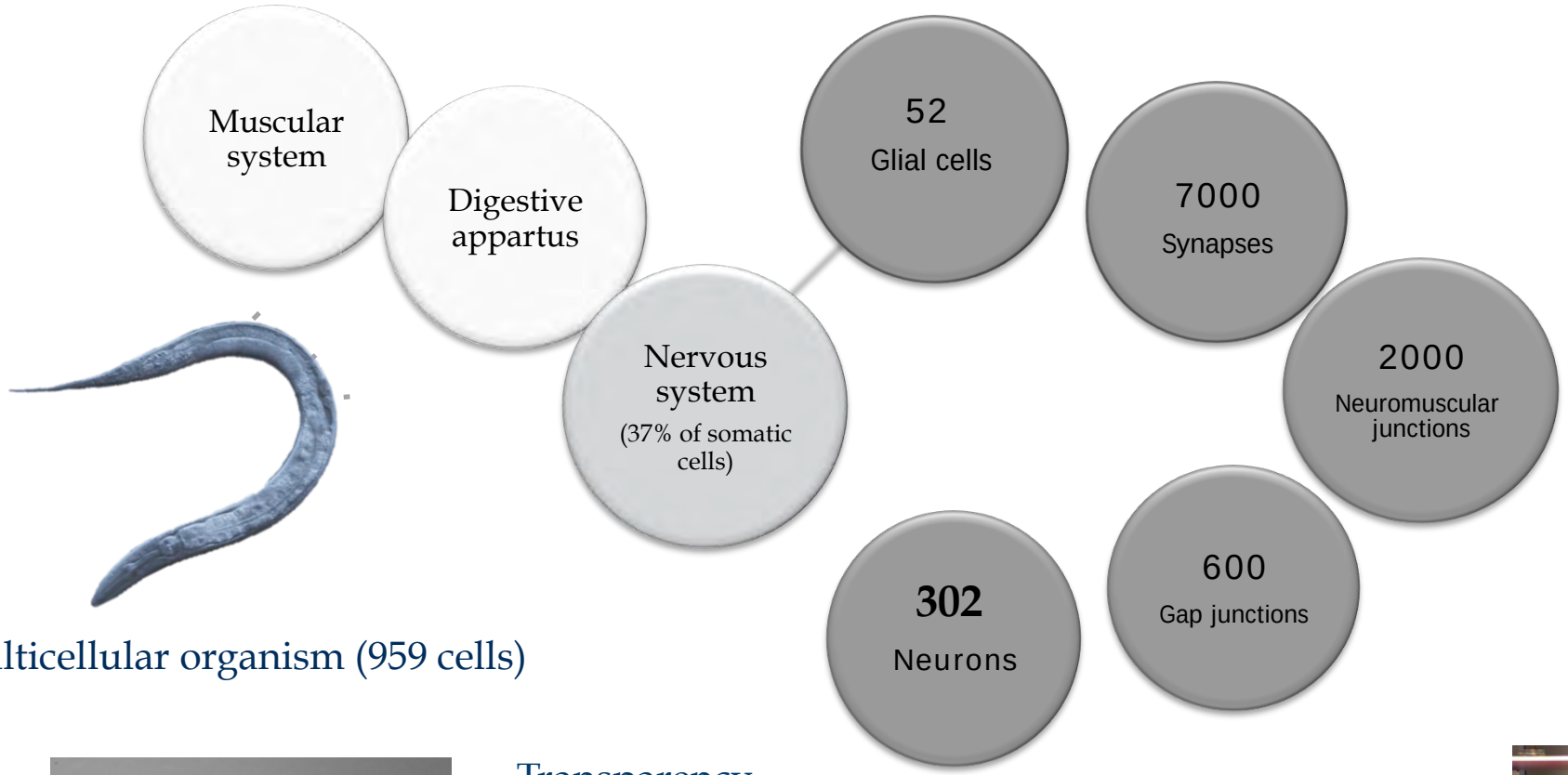
Niches occupied by various experimental approaches (Dolmetsch, Cell 2011)

Validation in mammalian cells infected using CJD isolates

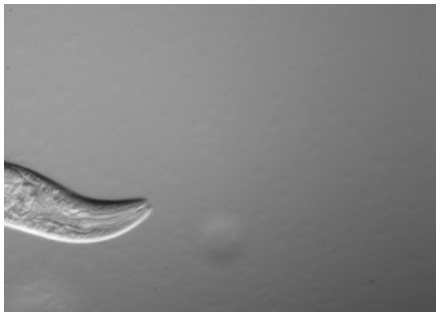
Human PrP (E200K)

In vivo simplified genetic model

In vivo simplified genetic model: nematode *Caenorhabditis elegans*

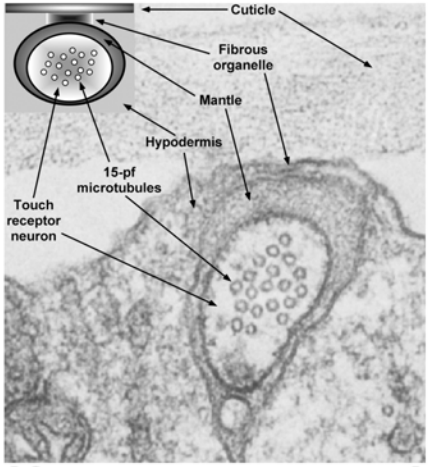


Multicellular organism (959 cells)



Transparency
Fully characterized cell lineage and inter-connectivity
Short cycle of developpment and important progeny
Self-fertilization
High gene homology with humans (≈75%)
Devoid of prion protein

Targeting a specific group of neurons: mechano-sensitive neurons

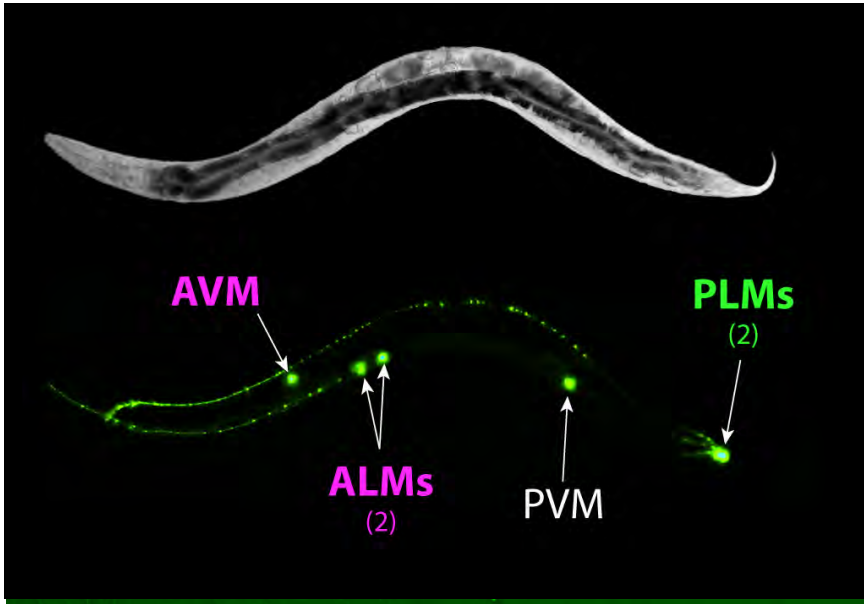


Mechanosensitive neurons

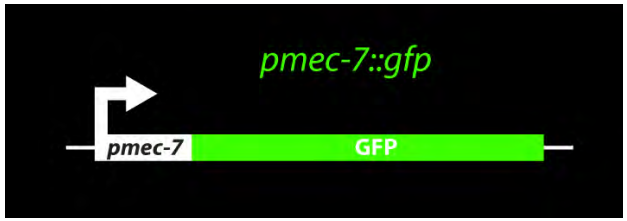
Microtubules

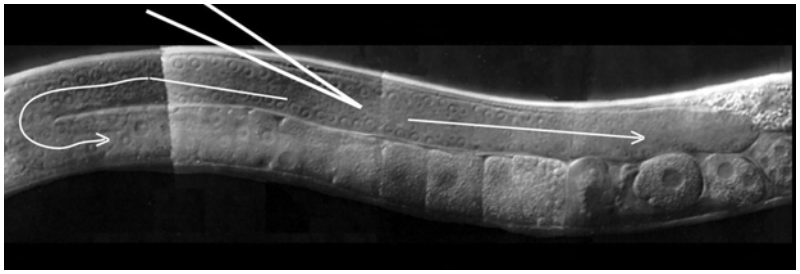
15 protofilaments

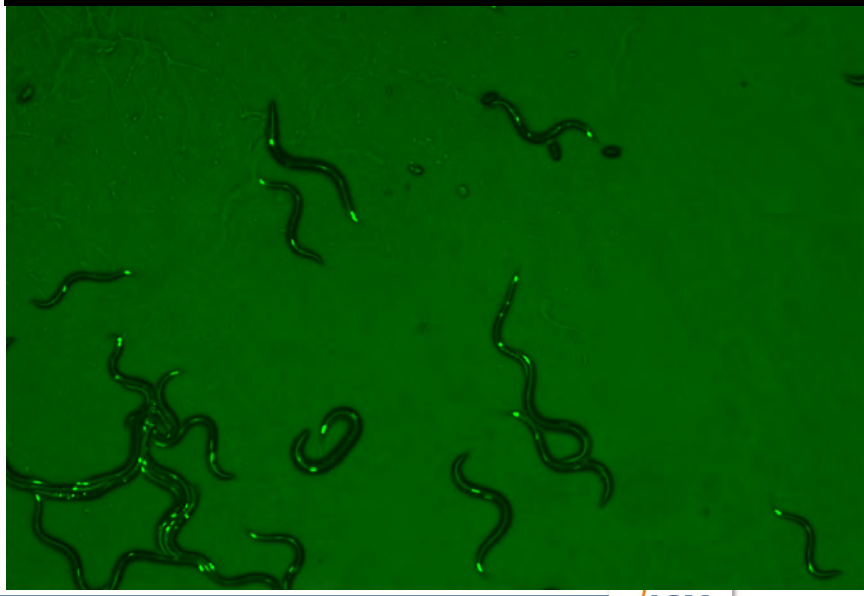
ß-tubulin (**MEC-7**)



Transgenesis

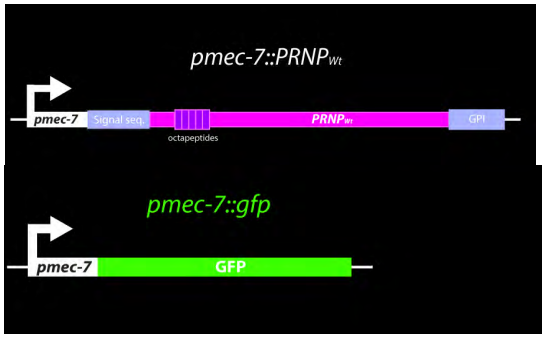


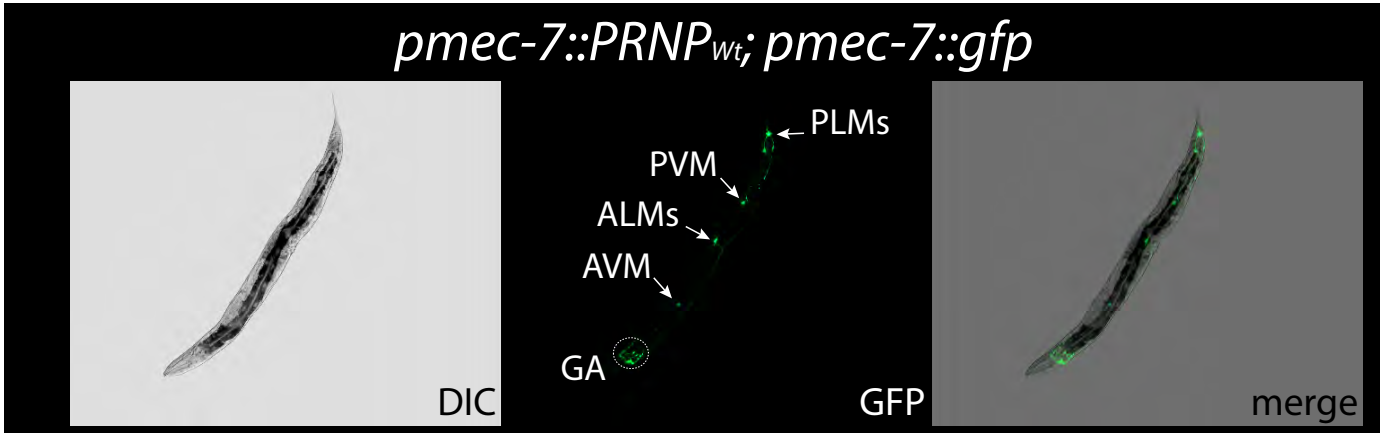




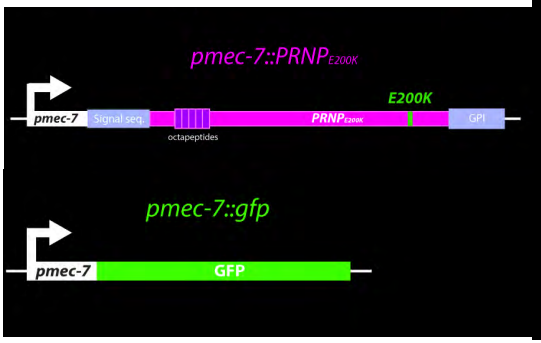
Wild-type PrP or E200K PrP expression in mechano-sensitive neurons

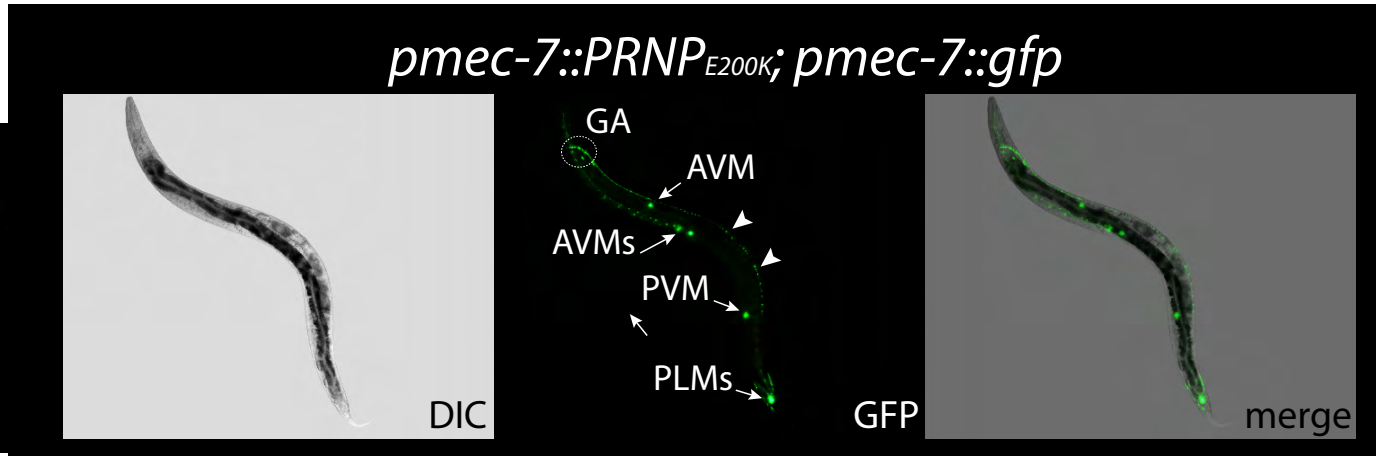
Wild-type PrP



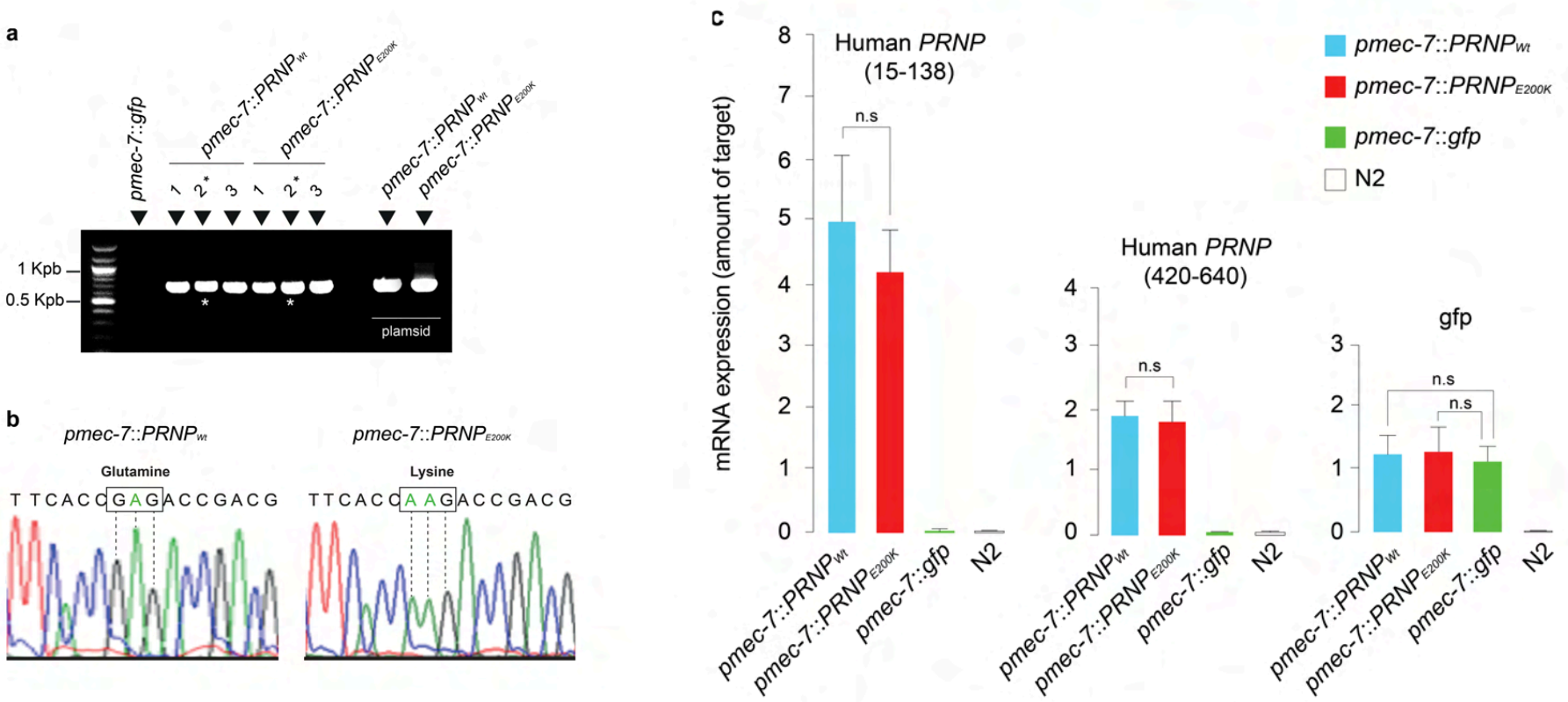


E200K PrP



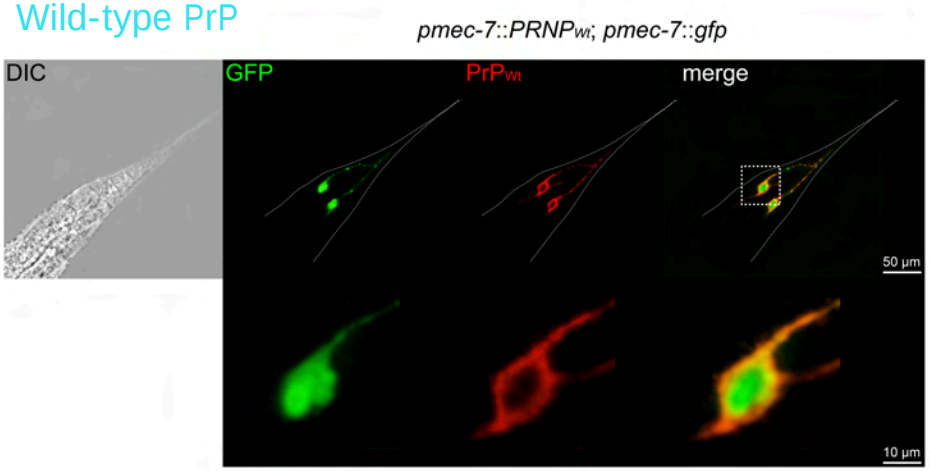


Selected wild-type and E200K PrP expressing lines showing similar levels of PrP expression

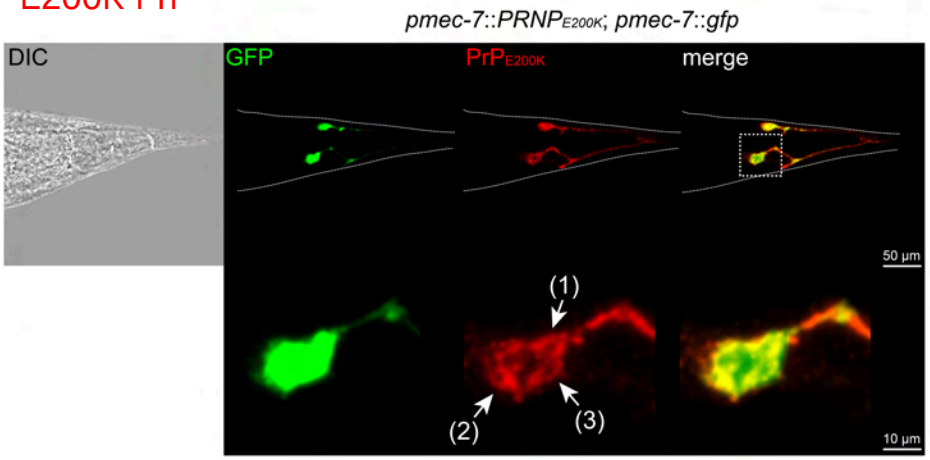


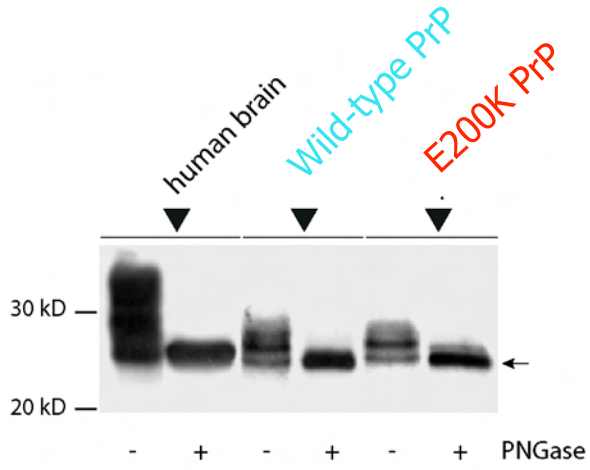
Wild-type and E200K PrP expression is detectable in mechano-sensitive neurons from transgenic animals

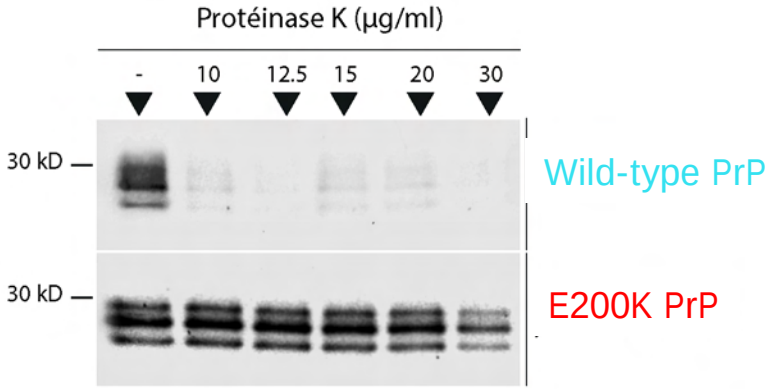
Wild-type PrP



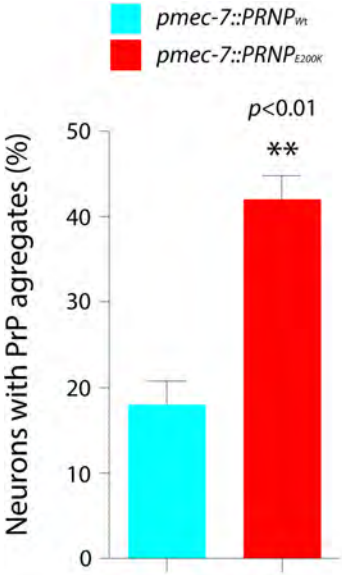
E200K PrP

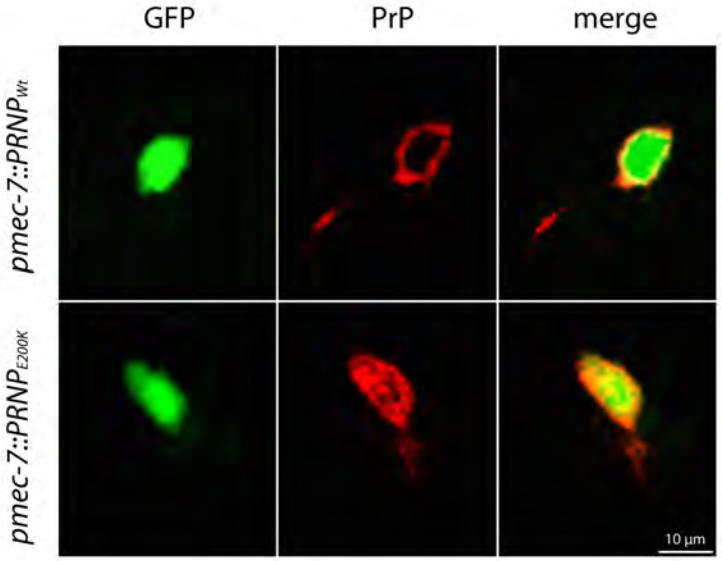


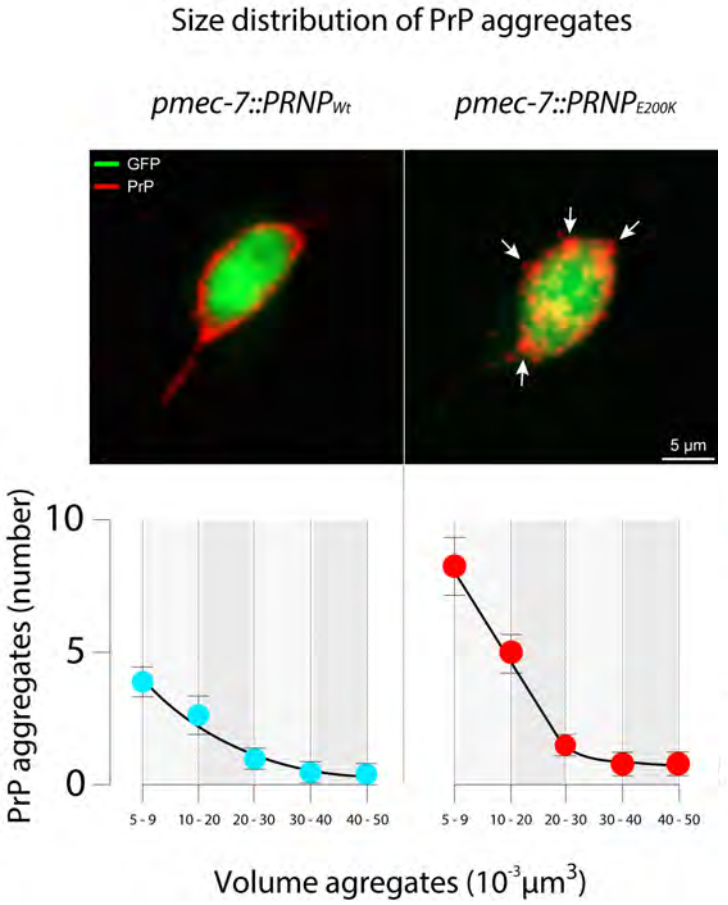




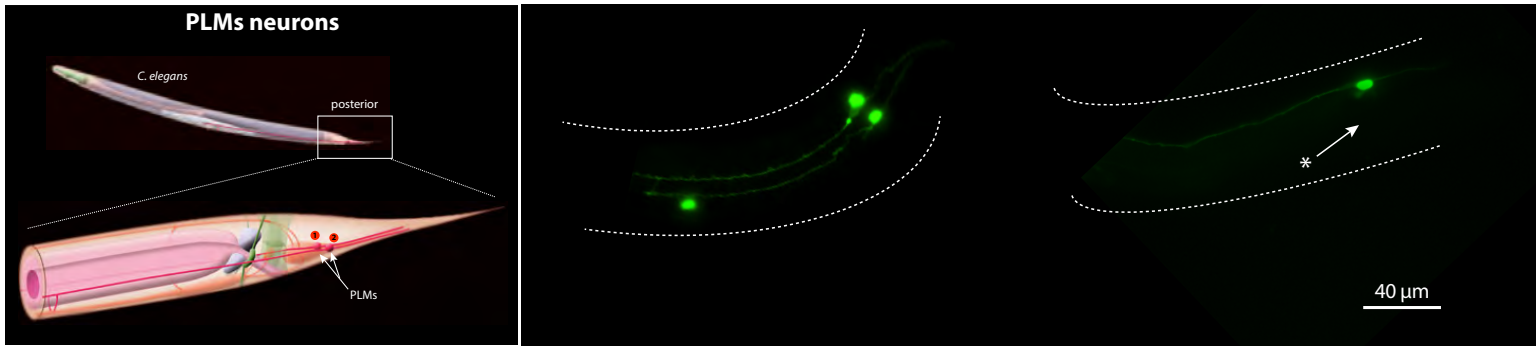
PrP aggregates observed in mechano-sentive neurons from animals expressing E200K PrP

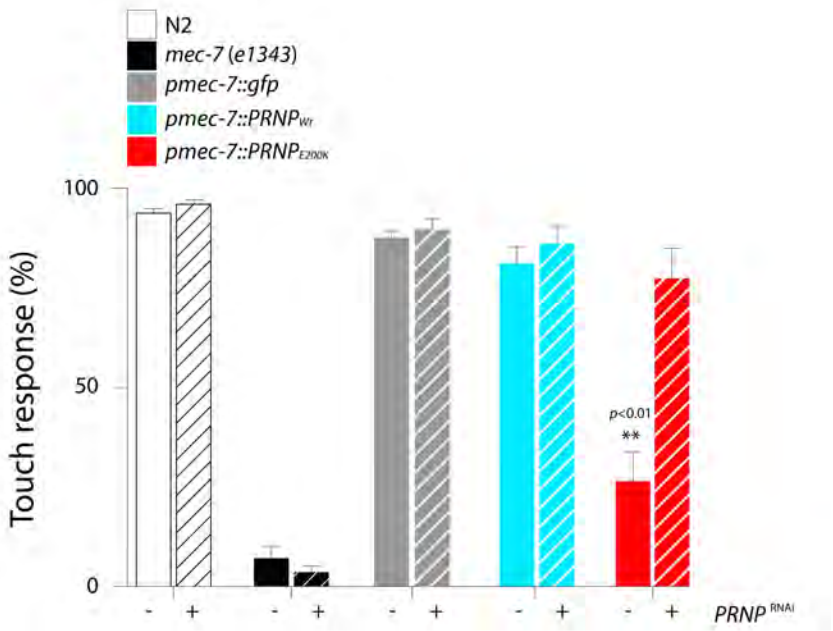


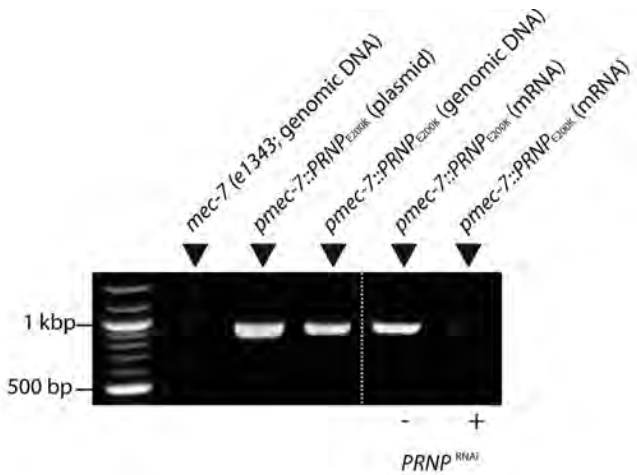


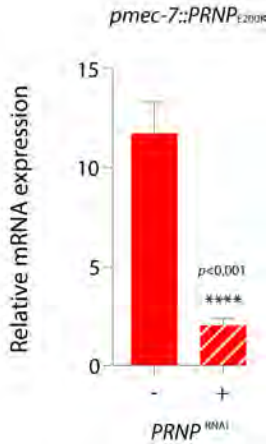


Neuronal loss in nematodes expressing E200K PrP





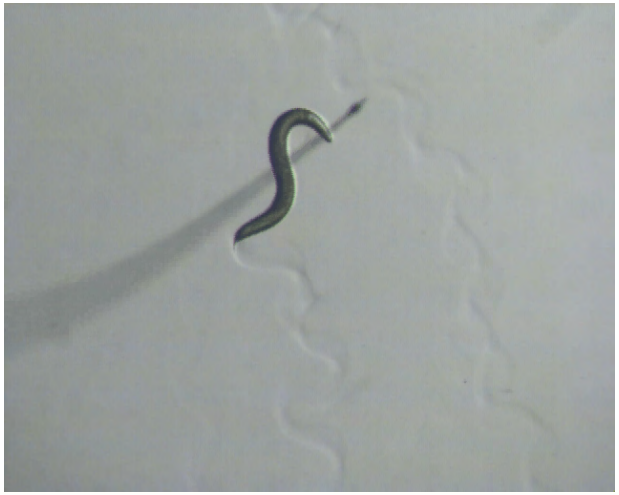


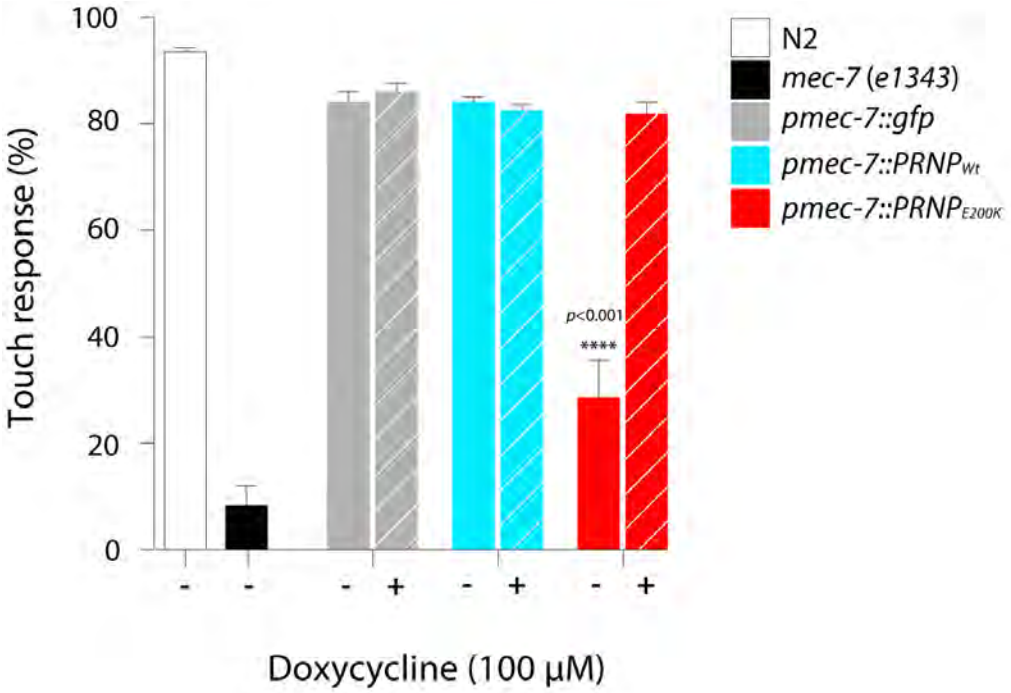


Loss of touch response in nematodes expressing E200K PrP in mechanosensitive neurons

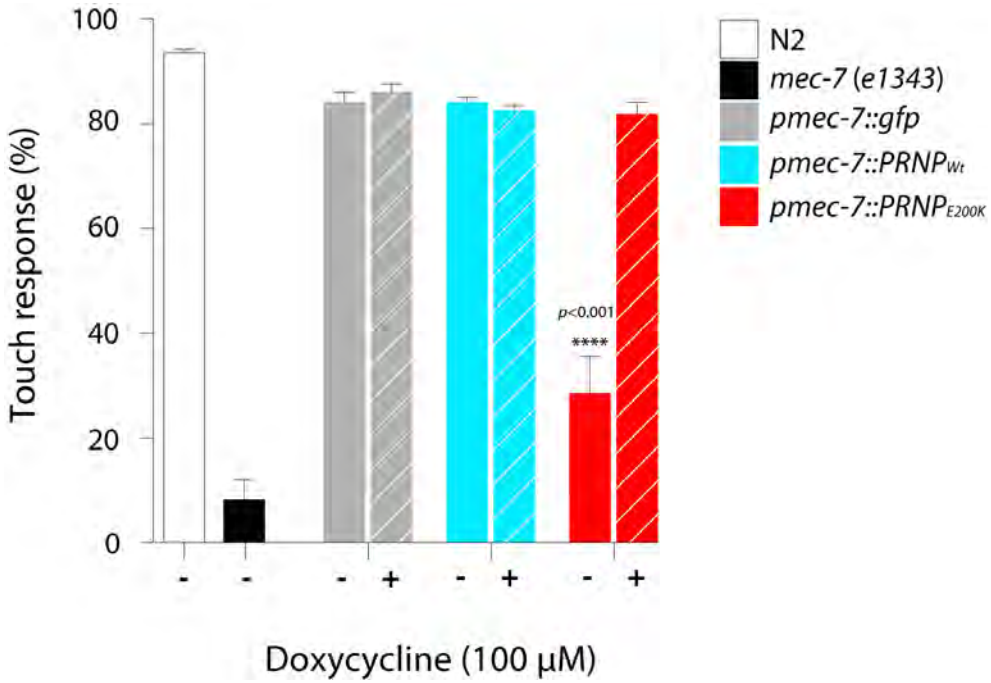
Normal response

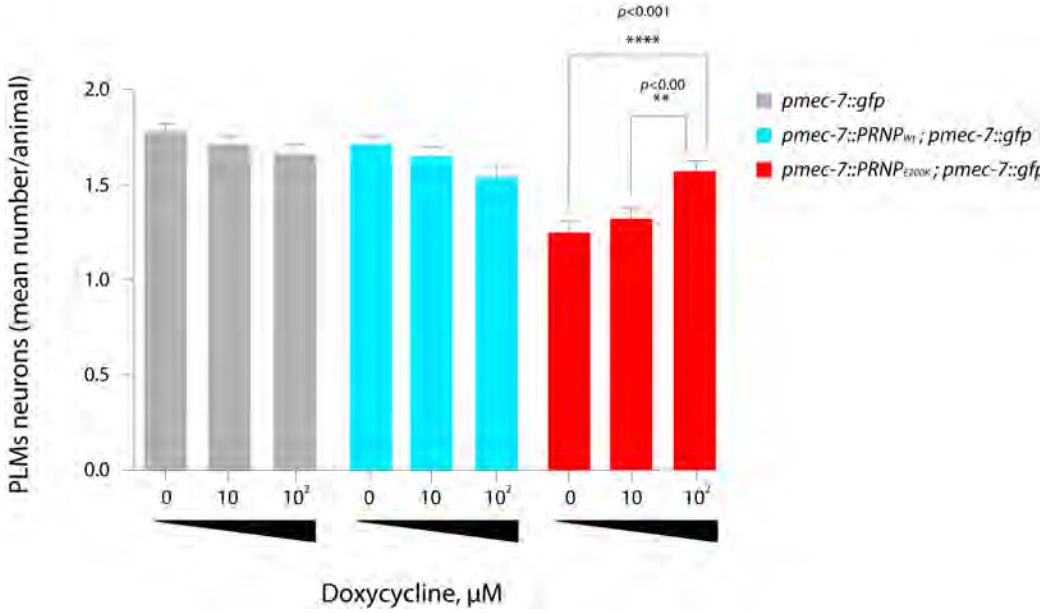
Impaired response





Detecting anti-prion activity in nematodes expressing E200K PrP

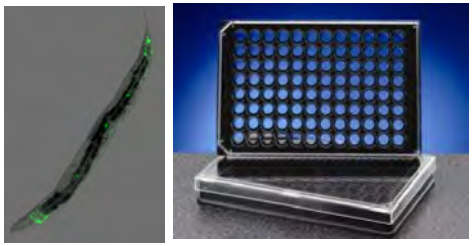




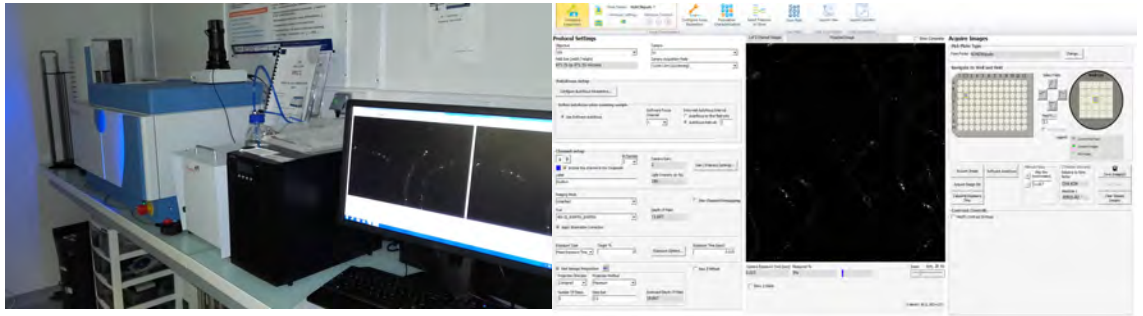
Screening strategy

FDA approved library of compounds targeting
the CNS (N=320+78)
at 3 concentrations

Human PrP E200K



ArrayScan High-Content Systems, ThermoFisher Scientific



Semi-automatized screening setup, number of GFP+ PLM neurons

No effect on neuronal loss

Restauration of mechano-sensitive neurons

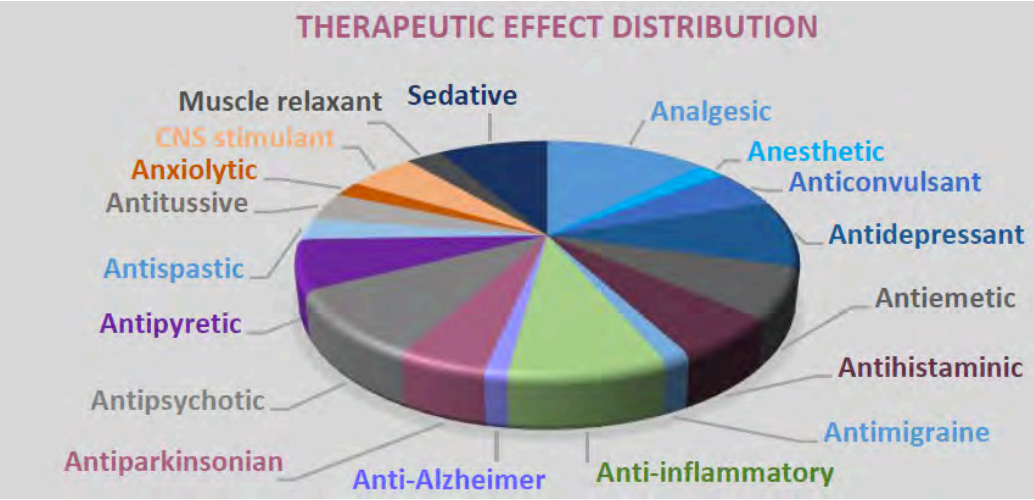
Only neuroprotective drug

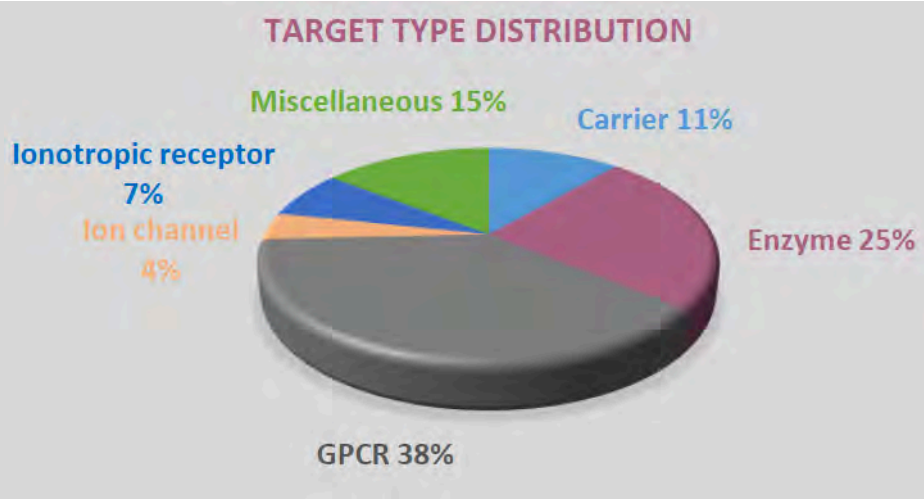
Effect of PrP aggregation (IHC, WB, e-QuIC)

Validation in mammalian cells infected using CJD isolates (Hannoui et al. JID 2013)

Prestwick CNS drug library

"New uses for old drugs", Chong & Sullivan, Nature 2007





+ antibiotics, antiviral and antifungal agents crossing the BBB (n=78)

First results of library screening

Experiences and analysis are on going.

Short overview in laymen's terms

Existing *in vivo* models of inherited forms do not allow high-throughput approaches that may facilitate the discovery of novel anti-prion compounds.

Our main objective is to take advantage of a simplified model of genetic prion disease that we developed in the nematode *C. elegans* to screen a library of *FDA*-approved compounds in a drug repositioning strategy (to find new use for old drugs).

The expression of human PrP with the E200K mutation induces the formation of PrP aggregates and the death of the targeted neurons in nematodes.

Using a semi-automatized system, we are able to screen the effect of hundreds of drugs on prion-induced neuronal death in transgenic animals.

The most promising molecules will be validated in CJD-infected mammalian cells & mice.

Lab members involved in the project:

Nicolas Bizat
Sofian Laoues,
Sebastien Normand
(Valeria Parrales)

Nicolas Privat
Alexianne gougerot
Katarina Grznarova
(Samia Hannaoui)

Audrey Culeux
Serfildan Yildirim

Jean-Philippe Brandel
Véronique Sazdovitch

Creutzfeldt-Jakob Disease Foundation, Inc.
Supporting Families Affected by Prion Disease

Inserm
Institut national de la santé et de la recherche médicale

cnrs

UPMC Sorbonne Universités

ANR

Santé publique France

Assistance Publique Hôpitaux de Paris

JPND research
EU Joint Programme – Neurodegenerative Disease Research

Alliance BioSecure
Sous égide de la Fondation pour la Recherche Médicale

ICM