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Bridging the pre-clinical gap for a small brain-penetrant molecule that reduces PrP^C levels

2025 CJD FOUNDATION FAMILY CONFERENCE

JULY 11-13, 2025
CHICAGO, IL

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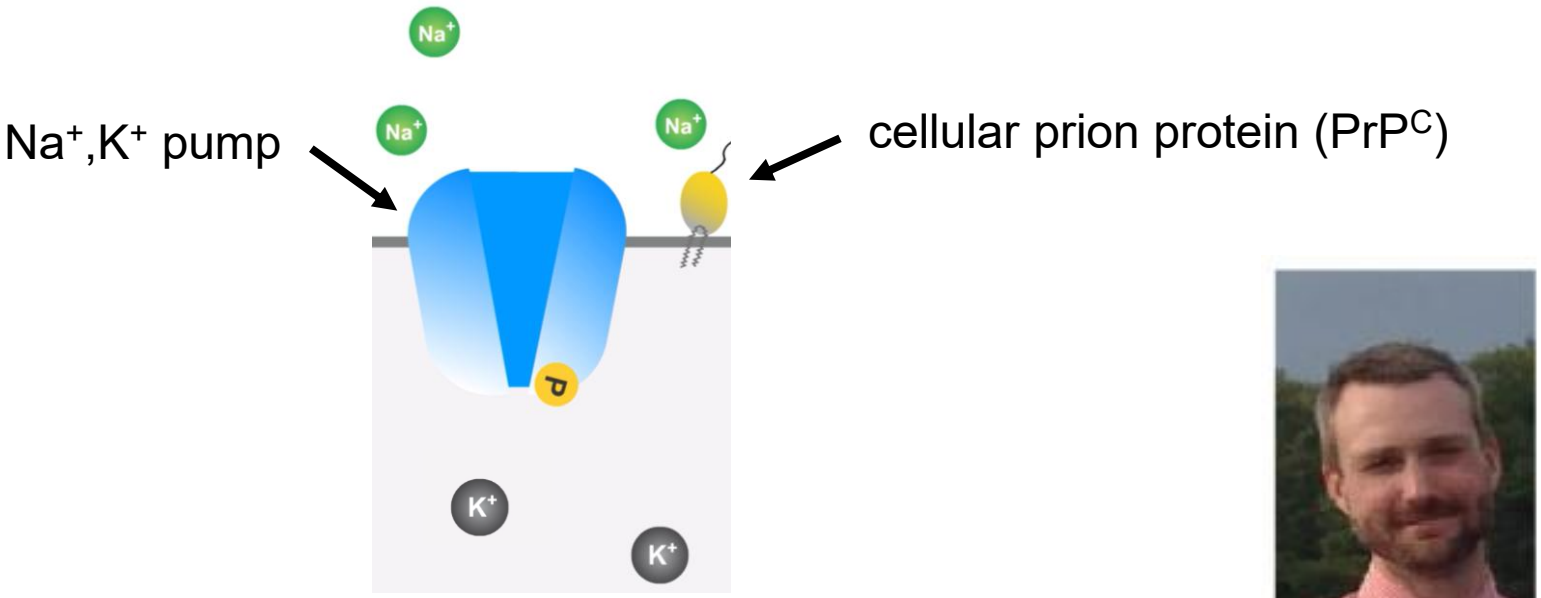
Principal Investigator

Tanz Centre for Research
in Neurodegenerative Diseases
UNIVERSITY OF TORONTO

The cellular prion protein resides next to Na^+,K^+ pumps

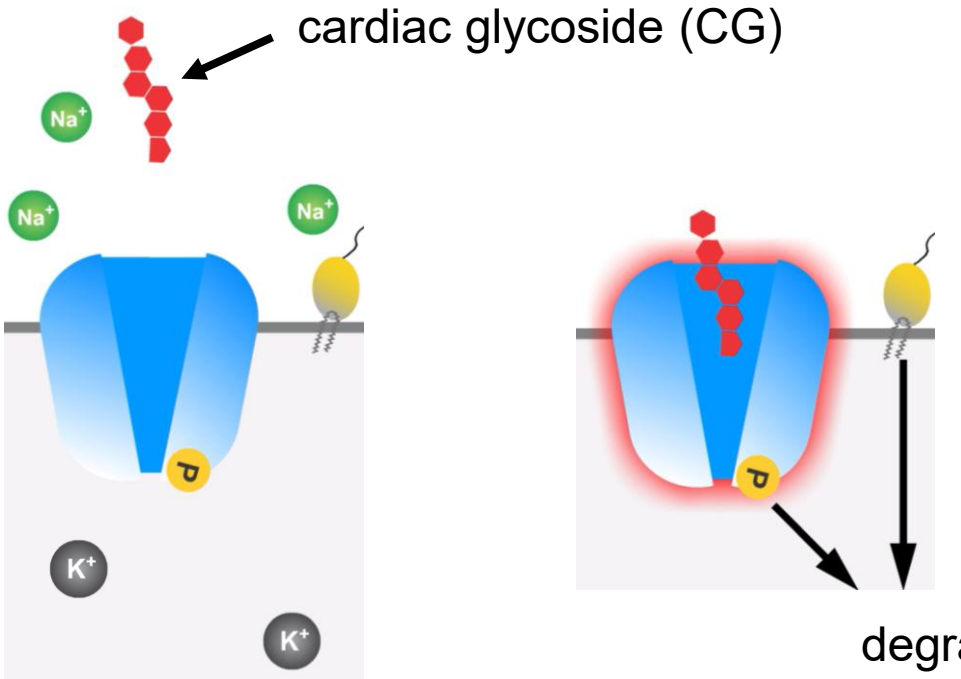


Declan Williams

Williams et al. (2021), PLoS One 16(11): e0258682

Hypothesis

Natural inhibitors of these pumps, known as cardiac glycosides, will cause cells to internalize the inhibited pumps and degrade them, with PrP^C coming along for the ride and getting co-degraded.



Mohadeseh Mehrabian

Challenge 1: Only a small amount of CGs gets into the brain

Mehrabian et al. (2022), PLoS One 17(07): e0270915

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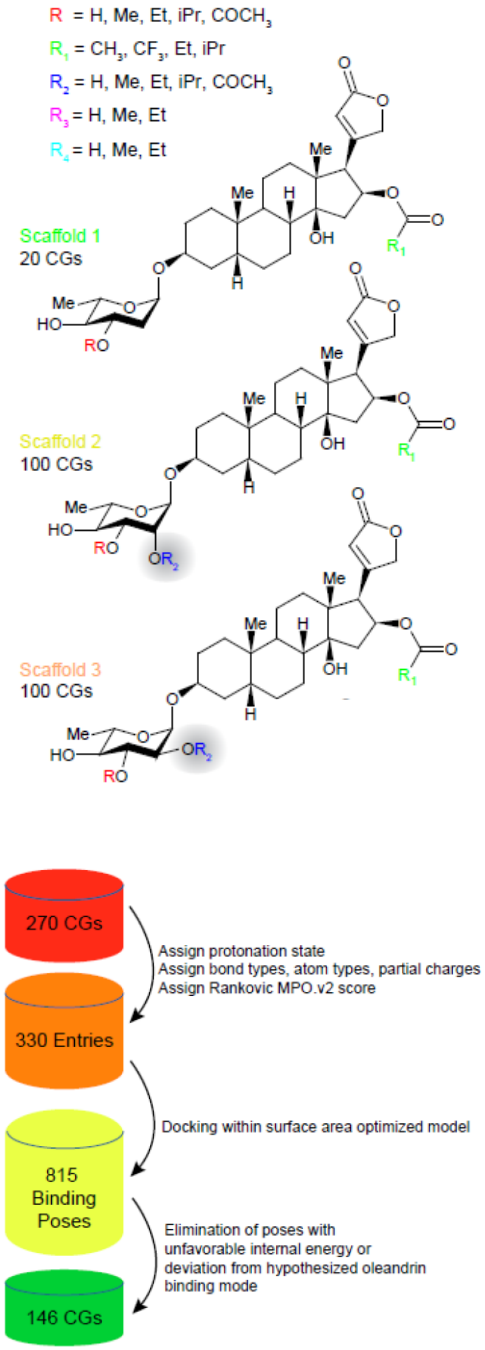
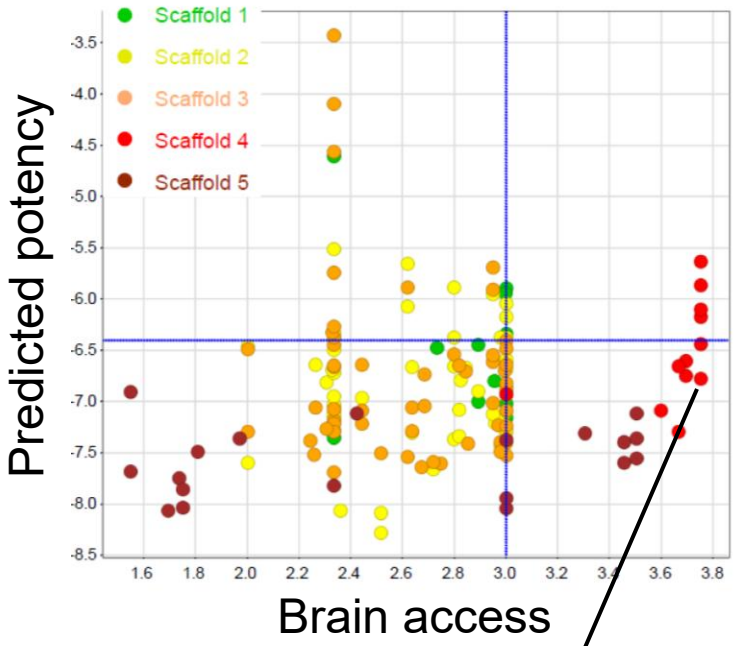
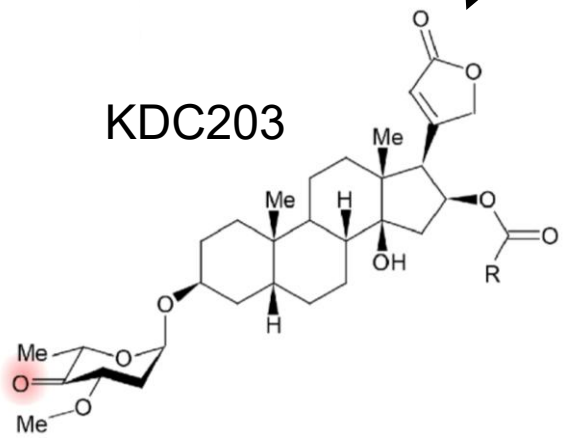
Identification of KDC203, a CG that can pass the blood brain barrier efficiently

Pavel Nagorny





KDC203



Eid et al. (2022), IJMS 23(23):14823

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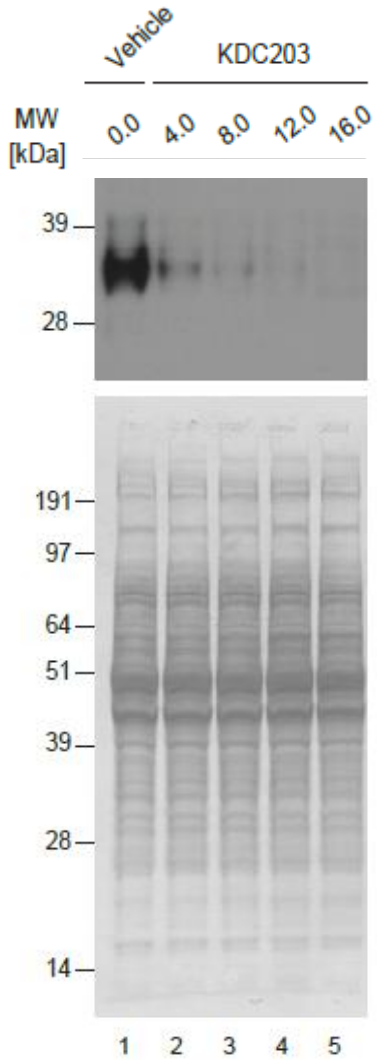
Miniscule levels of KDC203 reduced levels of the cellular prion protein (PrP^C) by 85%

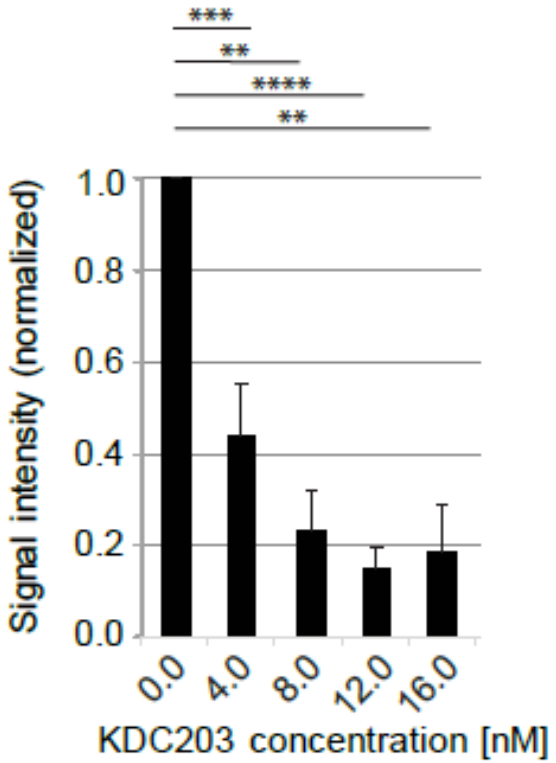


nanomolar [nM]

PrP^C levels

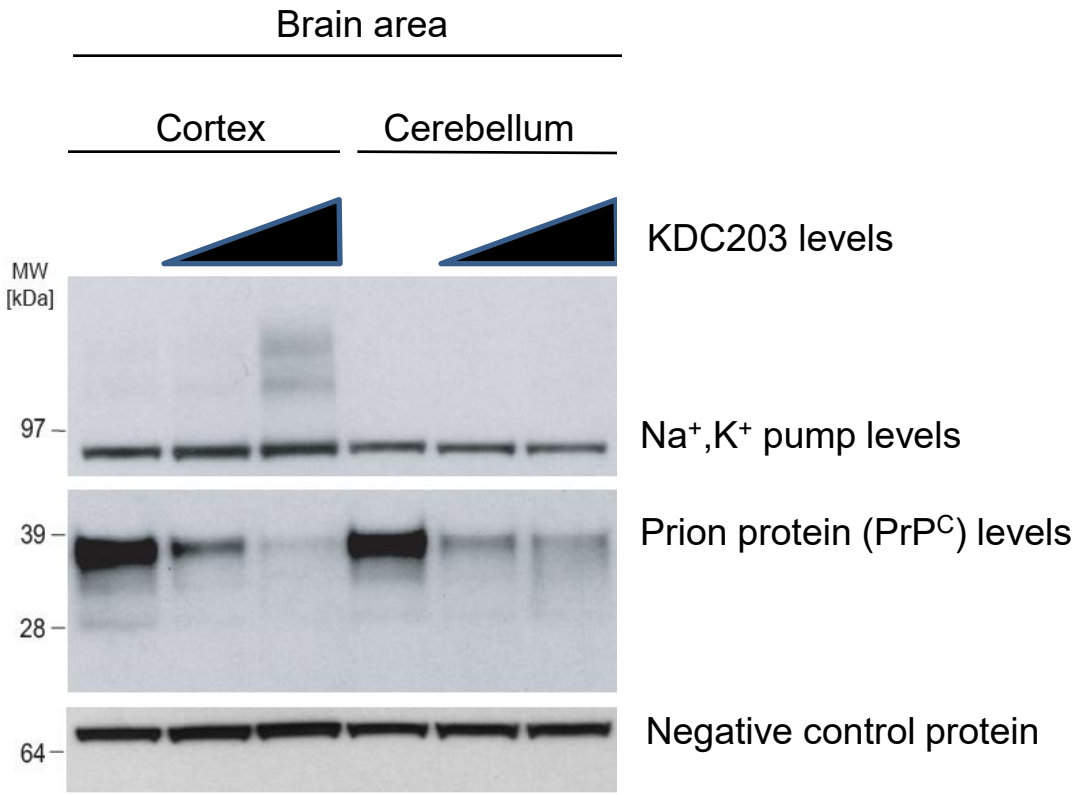
All proteins

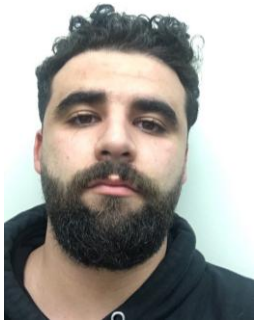
PrP^C levels



Eid et al. (2022), IJMS 23(23), 14823

KDC203 reduces PrP^C levels even in brain-in-a-dish slice cultures





Shehab Eid

Eid et al. (2024), PLoS One 19(9), e0308821

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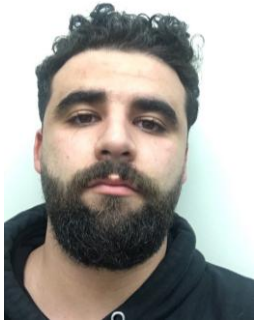
Challenge 2: When tested in a mammalian model, orally administered KDC203 did not consistently lower PrP^C levels!

A chemical analysis revealed that most of KDC203 was inadvertently converted by gut bacteria to a related substance. The latter lacks the efficiency of KDC203 and does not cross the blood-brain barrier.



Shehab Eid

Possible solutions:

1. Develop a stealth KDC203 resistant to inadvertent conversion.

2. Move from oral to blood-based administration.

Pavel Nagorny

Eid et al. (2025), unpublished.
Nagorny et al. (2025), unpublished

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Characteristics of a CGs that could accelerate their clinical translation

1. CGs are a class of compounds for which a wealth of pharmacological data in humans are available.

2. CGs are not toxic at their PrP^C lowering concentrations.

3. A future CG-based oral treatment could be offered for ~$1 per day, which would make it hundred times, if not thousand times, more affordable than alternative approaches.

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This work would not be possible without your help and the outstanding community effort spearheaded by the CJD Foundation

Special thanks go to:

The Michael R. Creutz Memorial Grant, by The Family of Michael R. Creutz

The Davey L. Kock Memorial Research Grant, by Janine Kock

The Anna Mazzola Memorial Grant, by Henry Mazzola and Family and Friends

The James McGill Memorial Grant, by The Family of Jim McGill

The José A. Piriz and Sonia E. Piriz Memorial Research Grant, by Karla Piriz and Lauren Esposito

Thank you so much for your support!!!

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Bridging the pre-clinical gap for a small brain-penetrant molecule that reduces PrP^C levels

Summary / SCHMITT-ULMS, Gerold

1. Optimized cardiac glycosides, like KDC203, can lower levels of the cellular prion protein (PrP) indirectly by binding to a nearby pump molecule, causing cells to internalize and replace the pump and to degrade PrP.

2. Their administration for the treatment of prion diseases would most likely require individuals to take one tablet per day orally.

3. For this therapy to work, we next need to engineer a stealth version of KDC203 that is not inadvertently modified and rendered ineffective as it passes the gut.

4. If successful, such a treatment would have the benefit that it could be offered at costs of ~$1 per day.

5. There is a wealth of pharmacological data available because similar compounds have been in the clinic for decades for the treatment of heart diseases. This clinical experience would add to the safety profile.

Thank you for your time and for sharing our dedication to finding a cure for prion diseases!