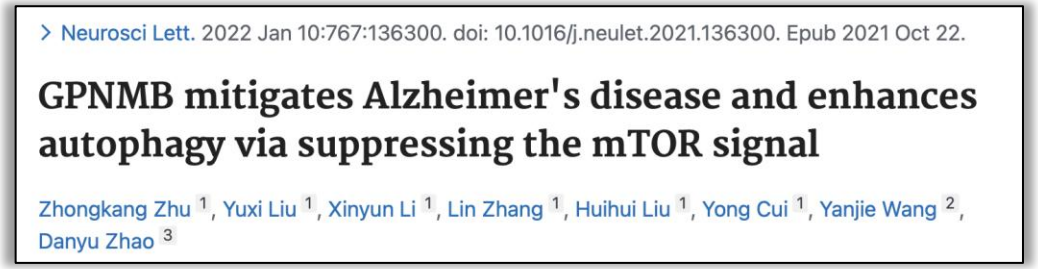
Investigation of Glycoprotein Nonmetastatic Melanoma protein B (GPNMB) as potential therapeutic target in Prion Diseases

Chicago, 12.07.2025

Dr. Elena De Cecco

Many biomarkers, very few targets

In recent years, many CJD-related biomarkers have emerged, but only few hold potential as therapeutic targets


> Neurosci Lett. 2022 Jan 10:767:136300. doi: 10.1016/j.neulet.2021.136300. Epub 2021 Oct 22.

GPNMB mitigates Alzheimer's disease and enhances autophagy via suppressing the mTOR signal

Zhongkang Zhu [1], Yuxi Liu [1], Xinyun Li [1], Lin Zhang [1], Huihui Liu [1], Yong Cui [1], Yanjie Wang [2], Danyu Zhao [3]


Review > Mol Neurobiol. 2018 Jun;55(6):5167-5176. doi: 10.1007/s12035-017-0707-z. Epub 2017 Aug 30.

Glycoprotein NMB: an Emerging Role in Neurodegenerative Disease

Kevin M Budge [1 2], Matthew L Neal [3], Jason R Richardson [3], Fayez F Safadi [4 5]


nature > scientific reports > articles > article

Article | Open access | Published: 13 August 2012

The potential of GPNMB as novel neuroprotective factor in amyotrophic lateral sclerosis

Hirotaka Tanaka, Masamitsu Shimazawa, Masataka Kimura, Masafumi Takata, Kazuhiro Tsuruma, Mitsunori Yamada, Hitoshi Takahashi, Isao Hozumi, Jun-ichi Niwa, Yohei Iguchi, Takeshi Nikawa, Gen Sobue, Takashi Inuzuka & Hideaki Hara

Glycoprotein nonmetastatic melanoma protein B (GPNMB) has recently been linked to neurodegenerative diseases.

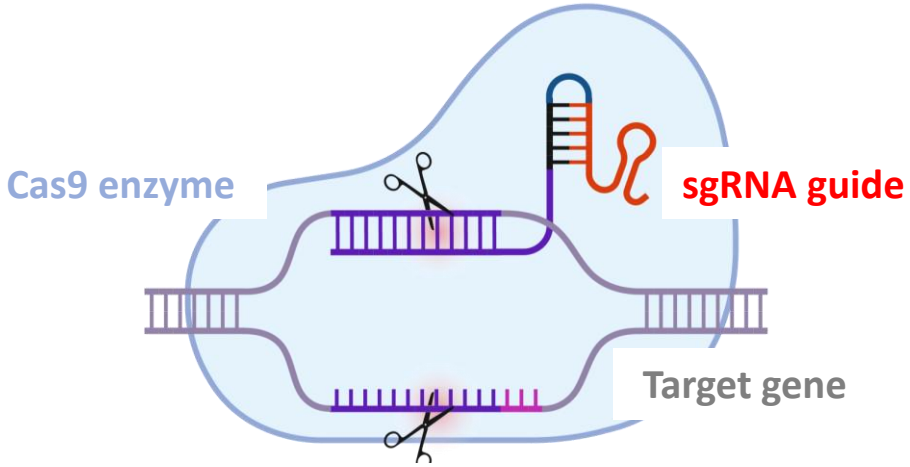
Several studies showed a neuroprotective effect of GPNMB in disease models.

Is GPNMB involved in prion diseases?

Can it become a therapeutic target?

Our approach: CRISPR-based forward genetics

Genome-wide arrayed CRISPR activation screen for modifiers of GPNMB expression and secretion

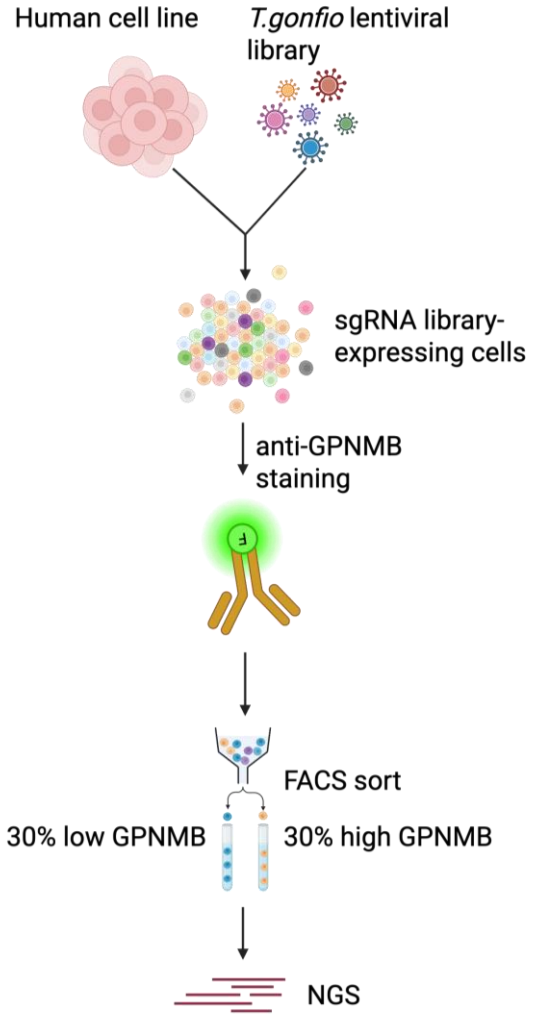


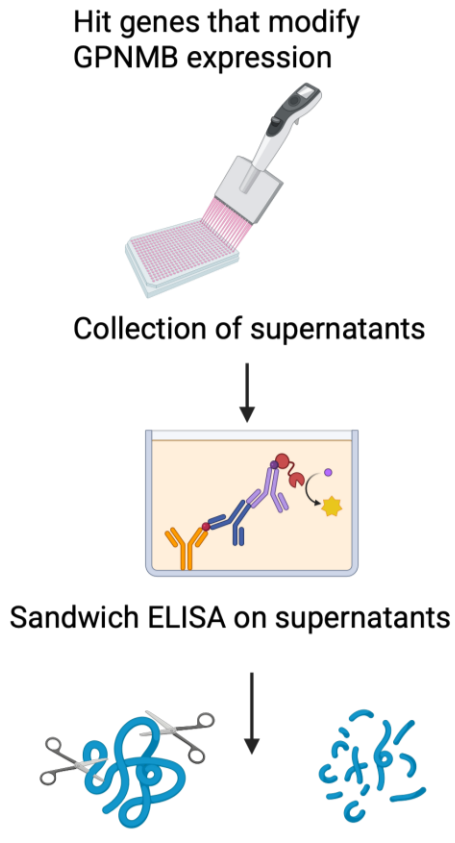
CRISPR-Cas9 system allows direct manipulation of individual genes, and potentially of the entire genome.

Gene knockout

Gene activation

Gene silencing



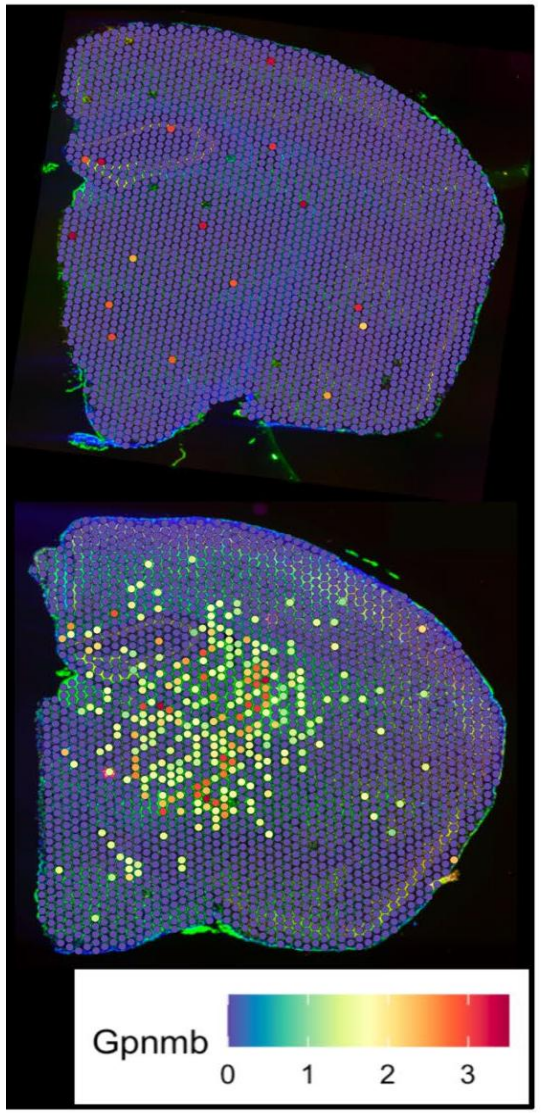


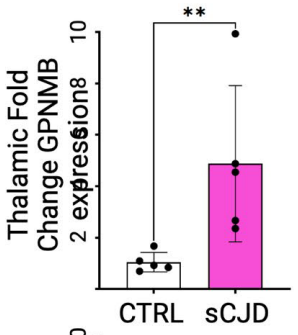
Highly phagocytic microglia upregulated GPNMB upon prion infection

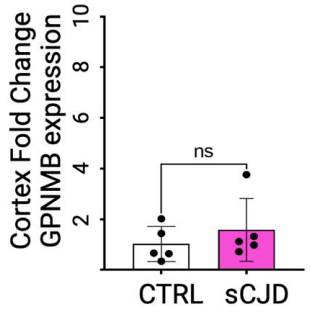
Terminal Stage

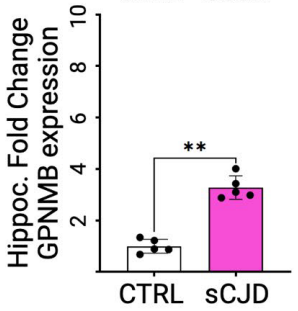
Control (NBH)

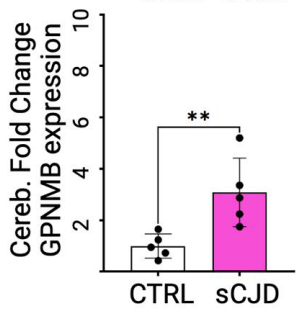
Prions





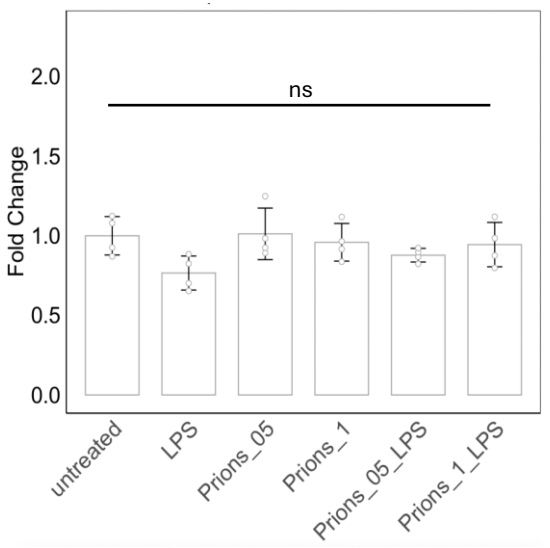




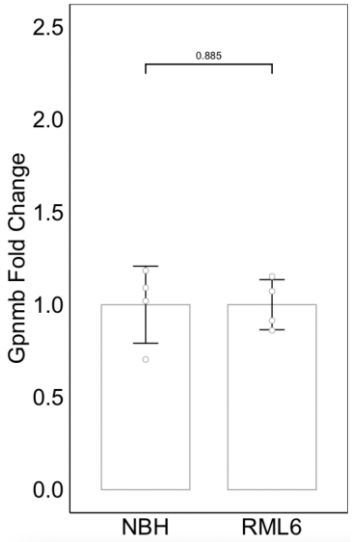


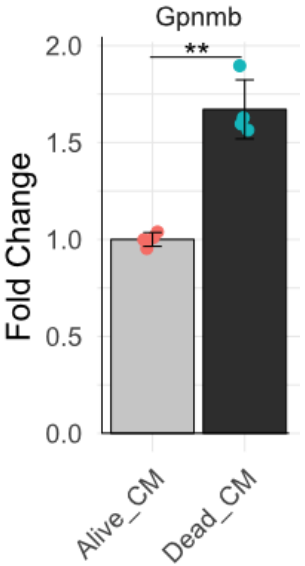
GPNMB is upregulated in prion-infected mice starting from 30 weeks post-inoculation and it increases over time.

Purified prions



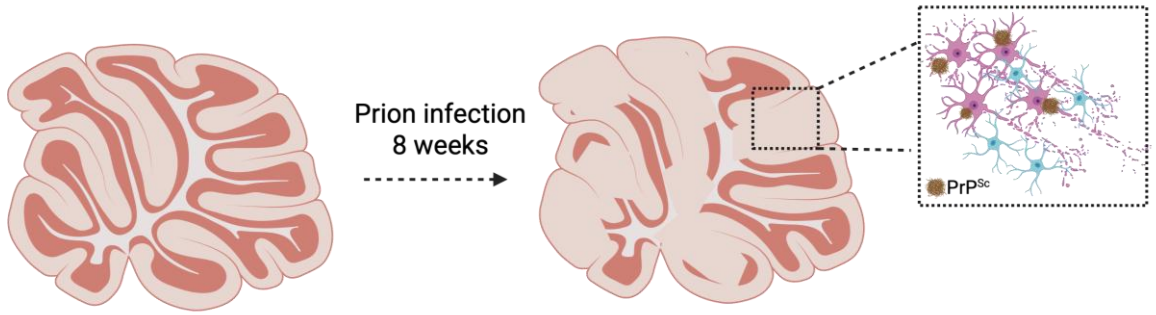
Brain homogenate

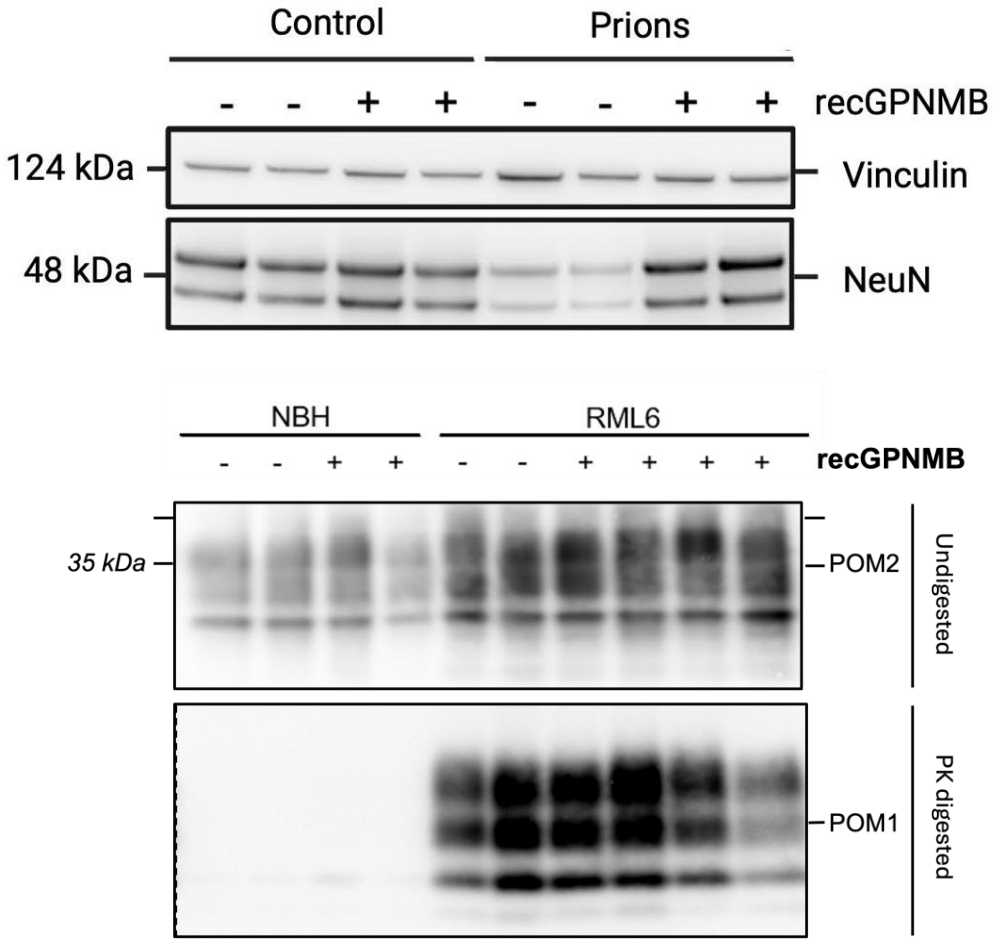




Apoptotic bodies, but not prions, trigger GPNMB upregulation

Soluble GPNMB shows neuroprotective effects ex-vivo





Cerebellar organotypic cultured slices mimic neurodegeneration ex-vivo.

Massive neuronal death at 56 days post infection.

Administration of recombinant soluble GPNMB prevents neuronal loss without reducing prion levels

What are the implications and what remains to be done?

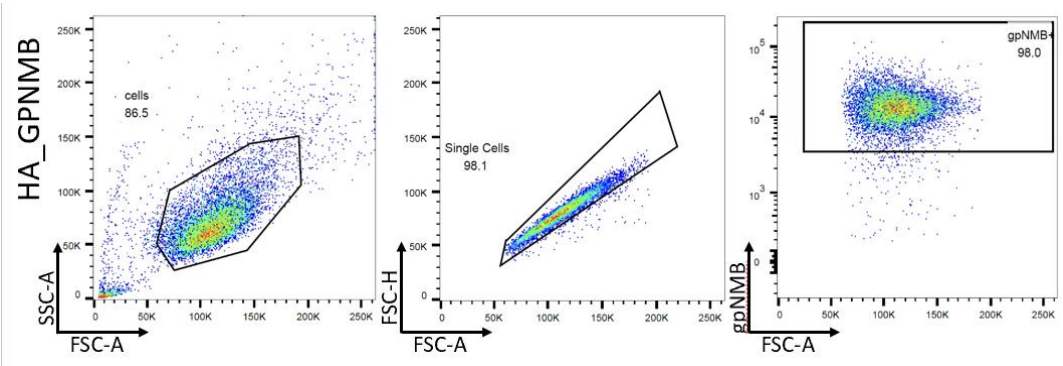
Increasing GPNMB expression and shedding could counteract neurotoxicity

Step 1 Increase GPNMB expression

Step 2 Increase shedding

Step 3 Compounds against selected genes

Cell model and screen readouts: ready ✓



CRISPR library: ready ✓

Screen: starting soon

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Gpnmb Defines a Phagocytic State of Microglia Linked to Neuronal Loss in Prion Disease

Davide Caredio, Giovanni Mariutti, Martina Cerisoli, Lisa Polzer, Yasmine Laimeche, Giulia Miracca, Marc Emmenegger, Matthias Schmitz, Inga Zerr, Elena De Cecco, Adriano Aguzzi

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