Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Risk of cancer from reduced expression of PrP^C-implications for prion disease treatment

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CJD FOUNDATION

CREUTZFELDT-JAKOB DISEASE FOUNDATION, INC.

Supporting Families Affected by Prion Disease

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I acknowledge the Traditional Owners of the land on which this work was performed, the land of the Wurundjeri, and pay respect to their Elders and families.

WiNN

A Network that supports, inspires and celebrates Women in Neuroscience. That's a WiNN

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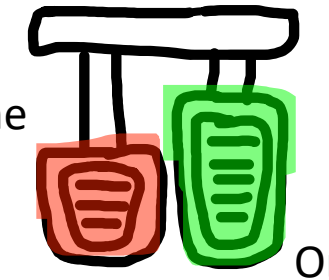
Summary

- Cancer progression is *driven* (🚗) by the deletion of tumor suppressor genes (*brake off*) and activation of oncogenes (*accelerator on*).

Tumor suppressor gene

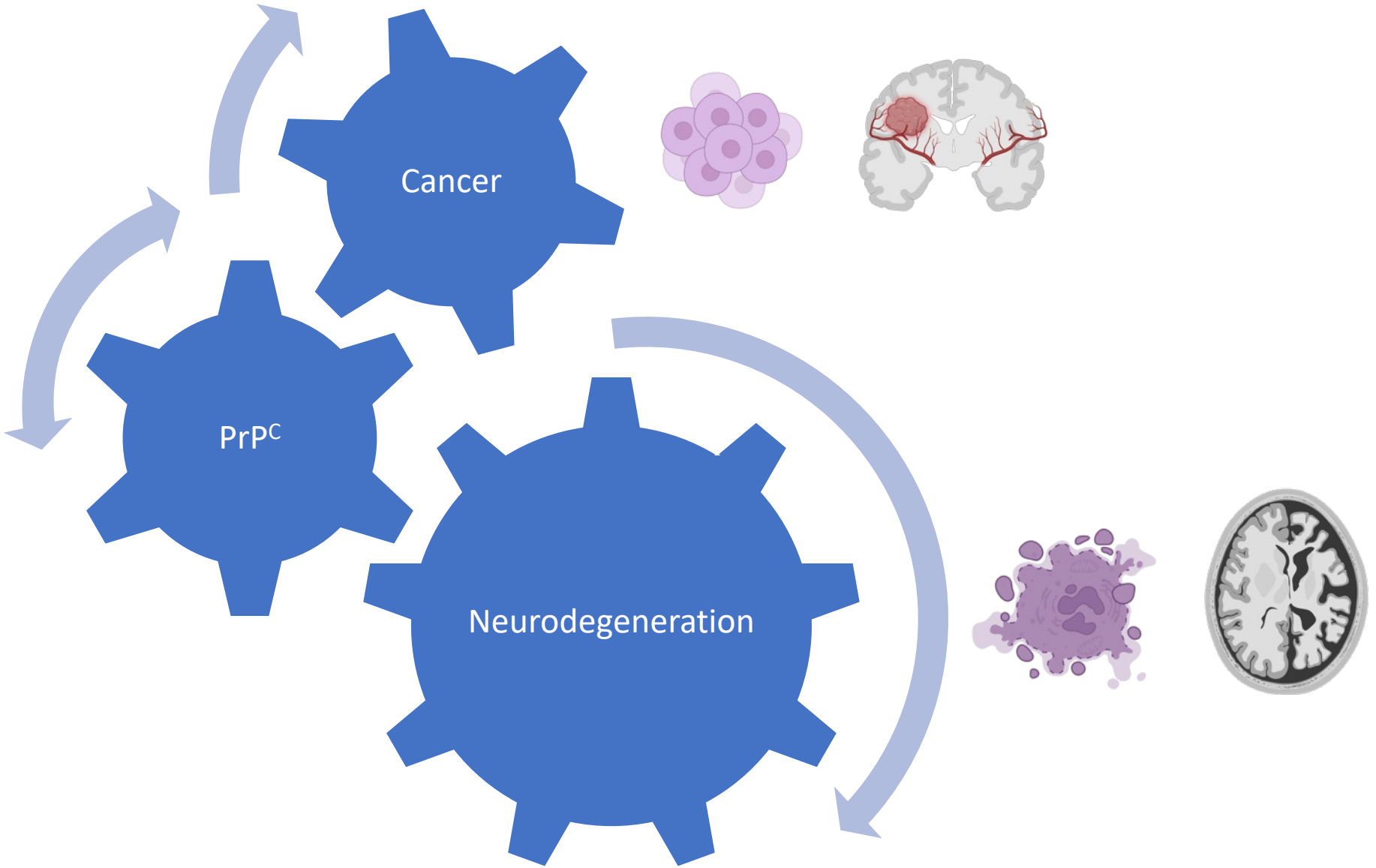


Oncogene

- We have investigated the effect of PrP^C expression in two models of brain cancer to determine whether treatment of prion disease with ASO to decrease expression of PrP^C could affect cancer risk.

- In a low-grade brain cancer model (brake off) the absence of PrP^C expression was associated with larger more invasive tumor cells.
- In a high-grade brain cancer model (brake off/accelerator on) the absence of PrP^C expression was associated with reduced tumor cell proliferation.
- These observations suggest that PrP^C has a complex role in cancer progression and that prolonged changes in PrP^C expression through therapeutic intervention could inadvertently increase the risk of cancer in some individuals.
- We are using spatial gene expression to better understand how PrP^C contributes to brain cancer.

PrP^C : cell death or proliferation



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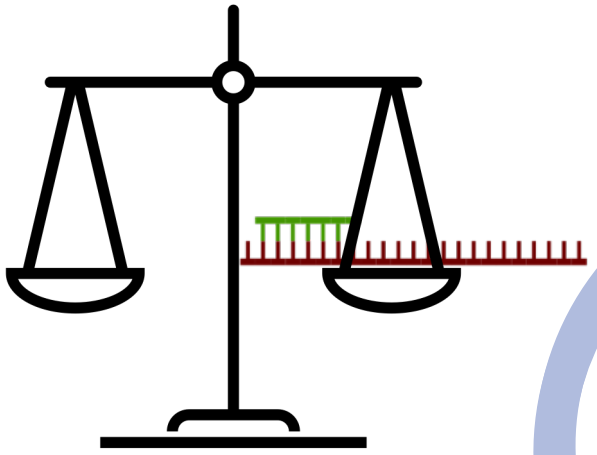
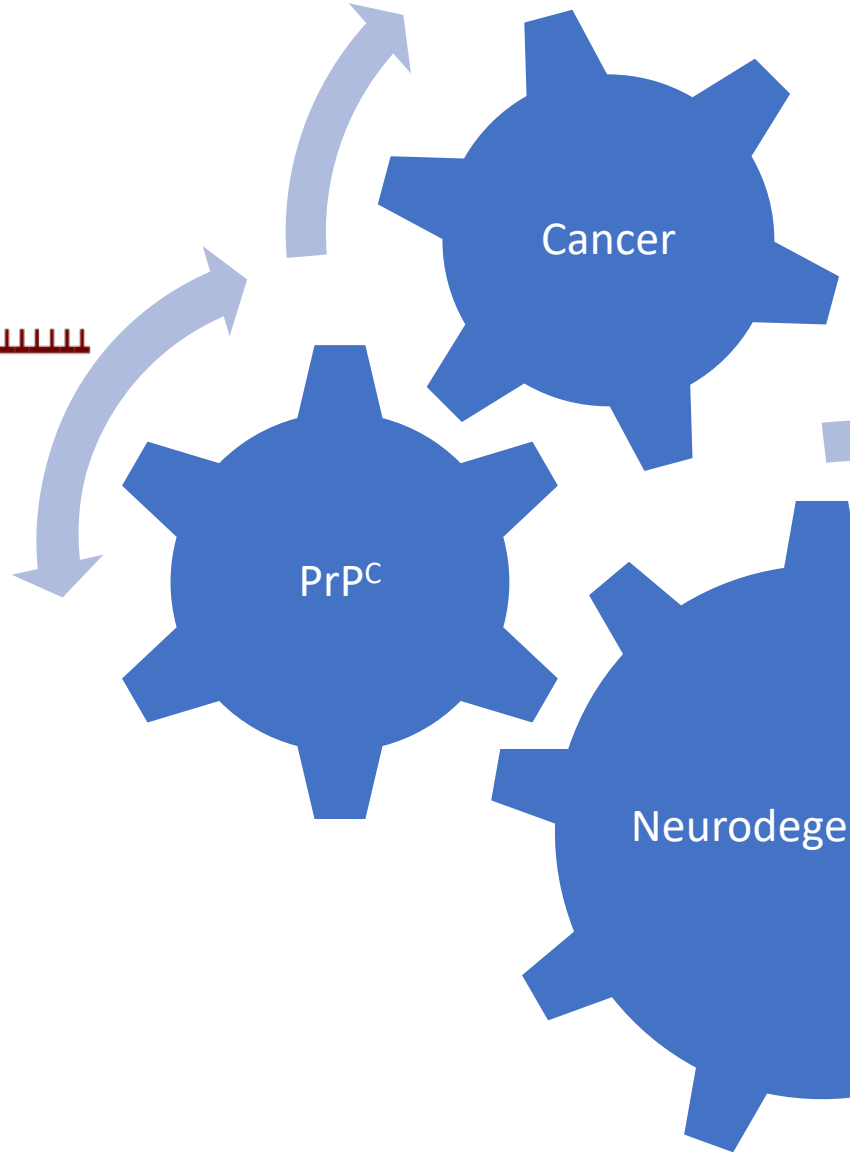
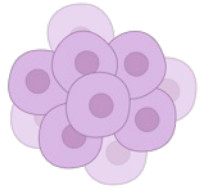
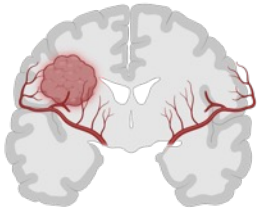
PrP^C : cell death or proliferation









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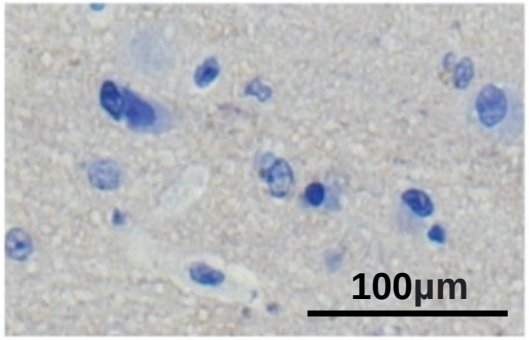
The role of PrP^C in cancer

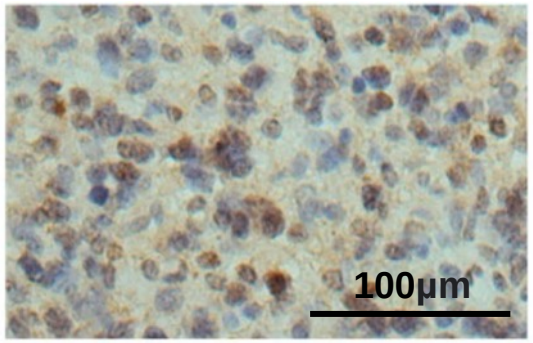
Increased PrP^C expression in cancer:

- Brain (Luo et al., 2020)
- Breast (Dèry et al., 2013)
- Colorectal (Le Corre et al., 2019)
- Gastric (Liang et al., 2006)
- Pancreatic (Bianchini et al., 2021)
- Melanoma (Li et al., 2010)

Control brain



Grade 4 Glioblastoma



PrP^C labelling by immunohistochemistry.
(Luo et al., 2020)

Increased PrP^C expression shown to correlate with:

1. Increased tumour grade

(Luo et al., 2020)

2. Tumour recurrence

(Du et al., 2013)

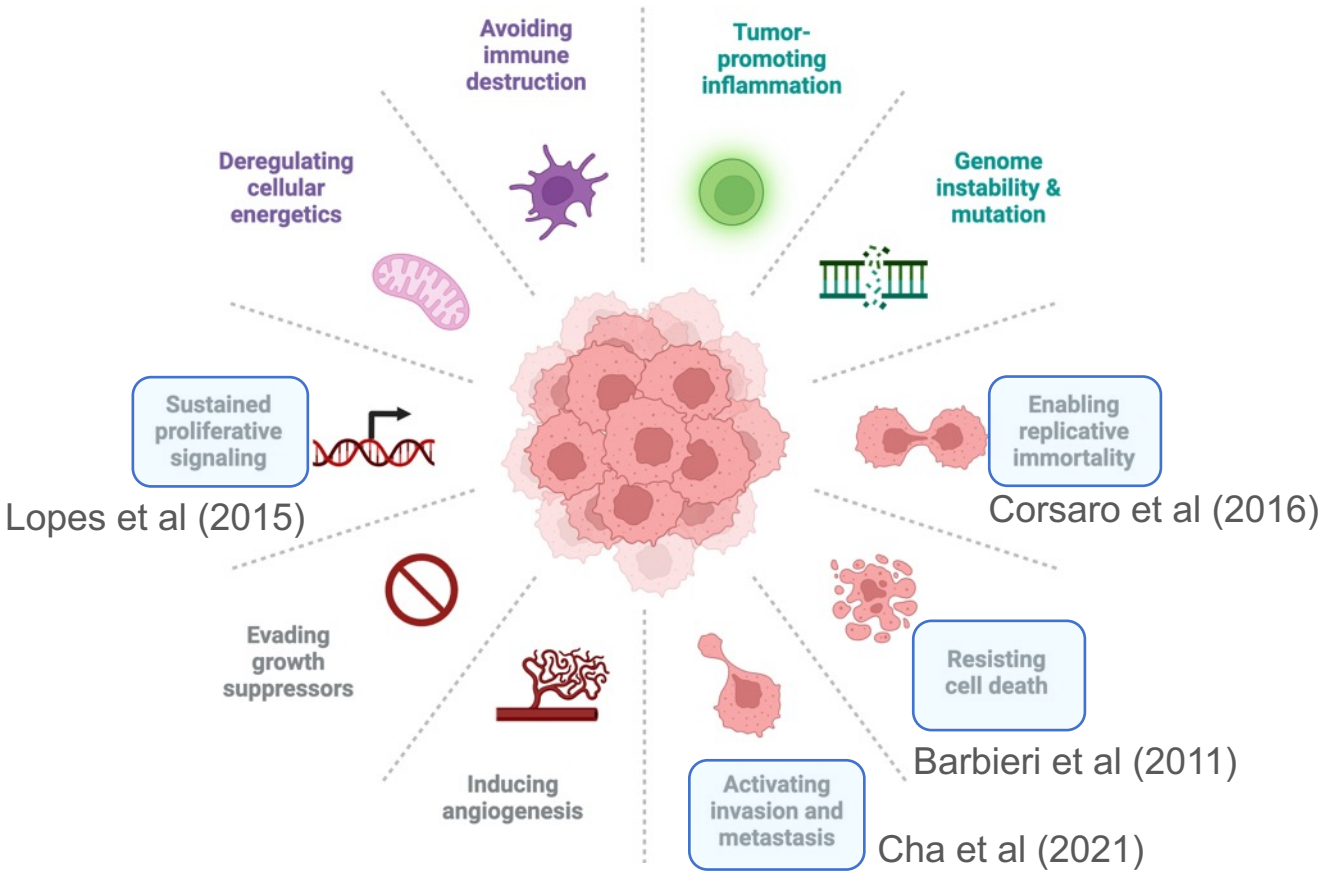
3. Reduced patient survival

(Zhou et al., 2014)

4. Increased therapy resistance

(Zhuang et al., 2012)

The role of PrP^C in cancer



Lopes et al (2015)

Corsaro et al (2016)

Barbieri et al (2011)

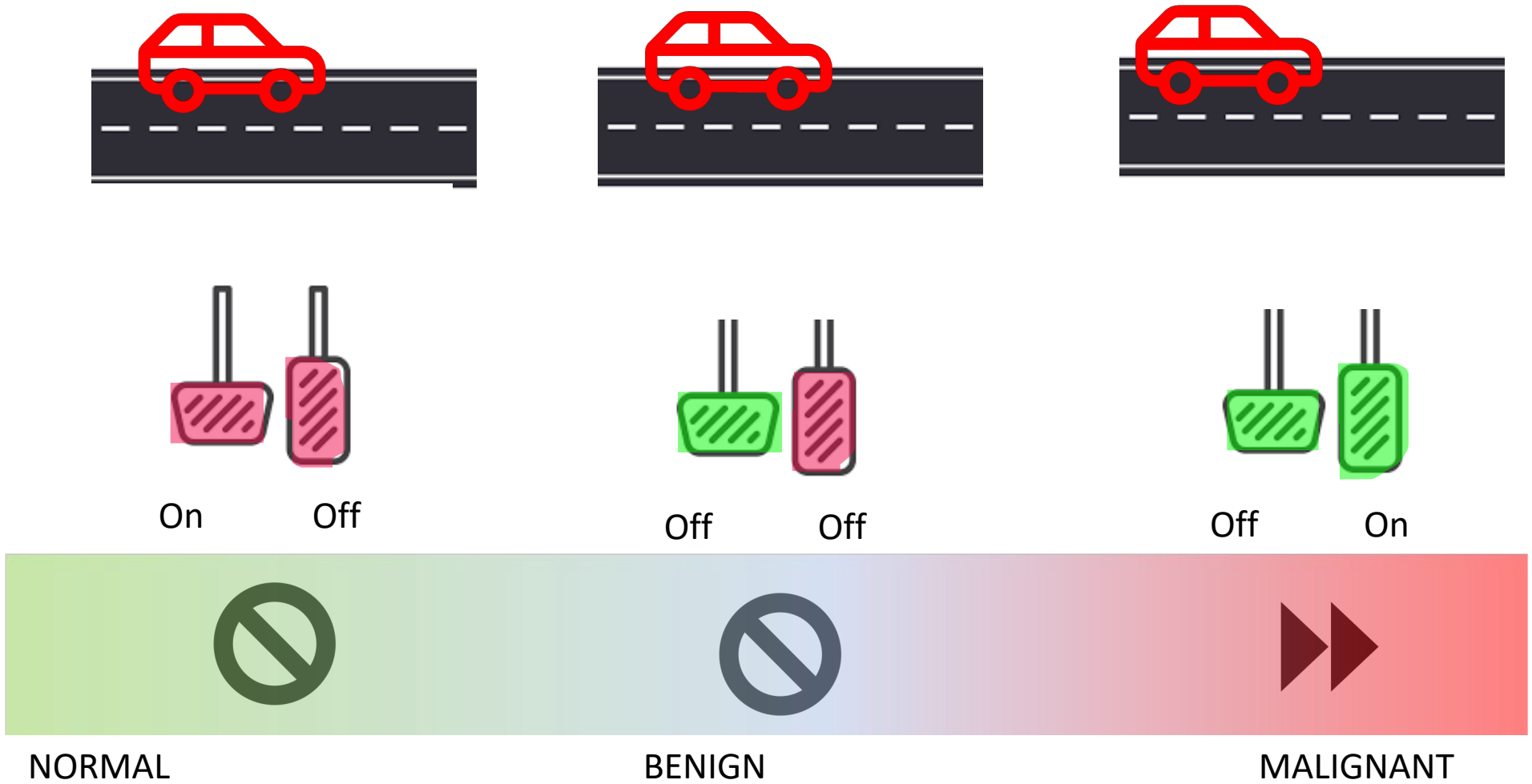
Cha et al (2021)

- Altered PrP^C expression may perturb or exacerbate physiological functions, which have been linked to cancer hallmarks

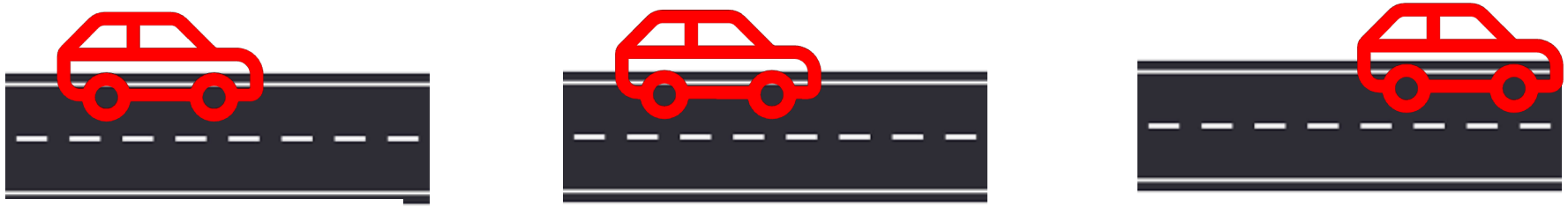
- Interaction between PrP^C and signaling networks may facilitate these roles e.g., Notch1, ERK1/2, PI3K/Akt[1]

[1]Wang et al., 2016; Provenzano et al., 2017; Liang et al., 2009

Cancer progression



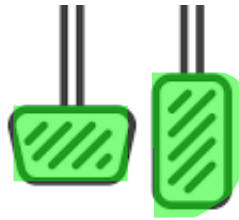
Cancer progression



Tumor suppressor gene

Cancer genes

Oncogene



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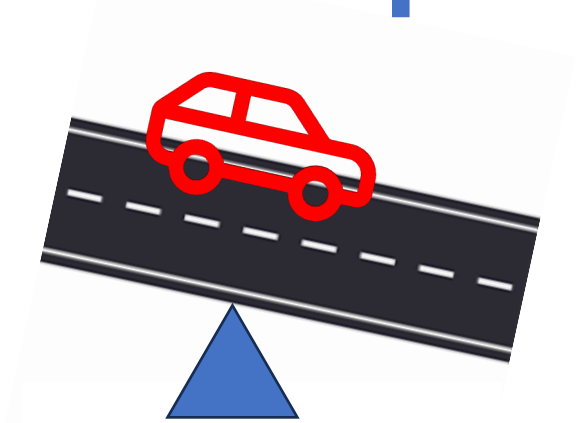
NORMAL BENIGN MALIGNANT

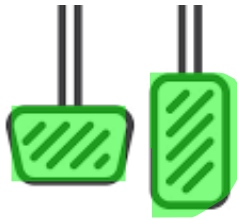
Cancer progression



Cancer genes

On Off

Off Off



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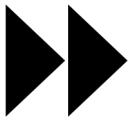
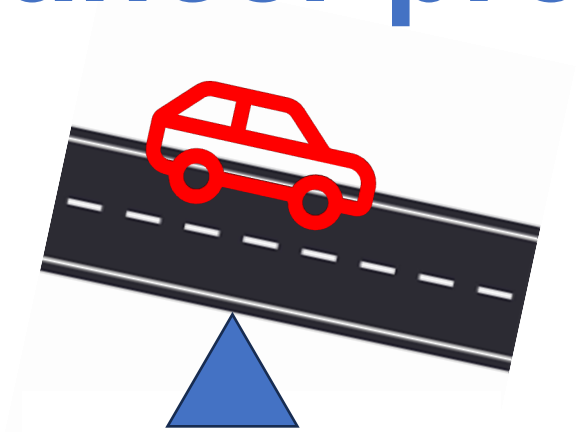
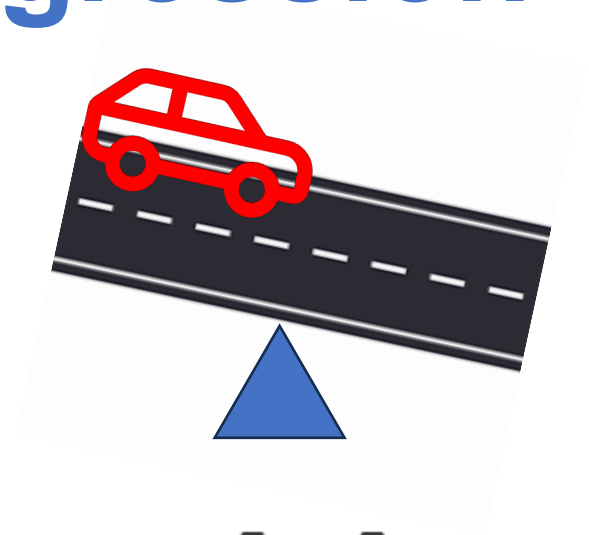


Cancer progression

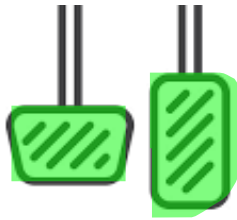




Cancer genes

On Off

Off Off



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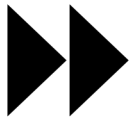
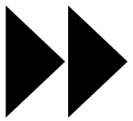
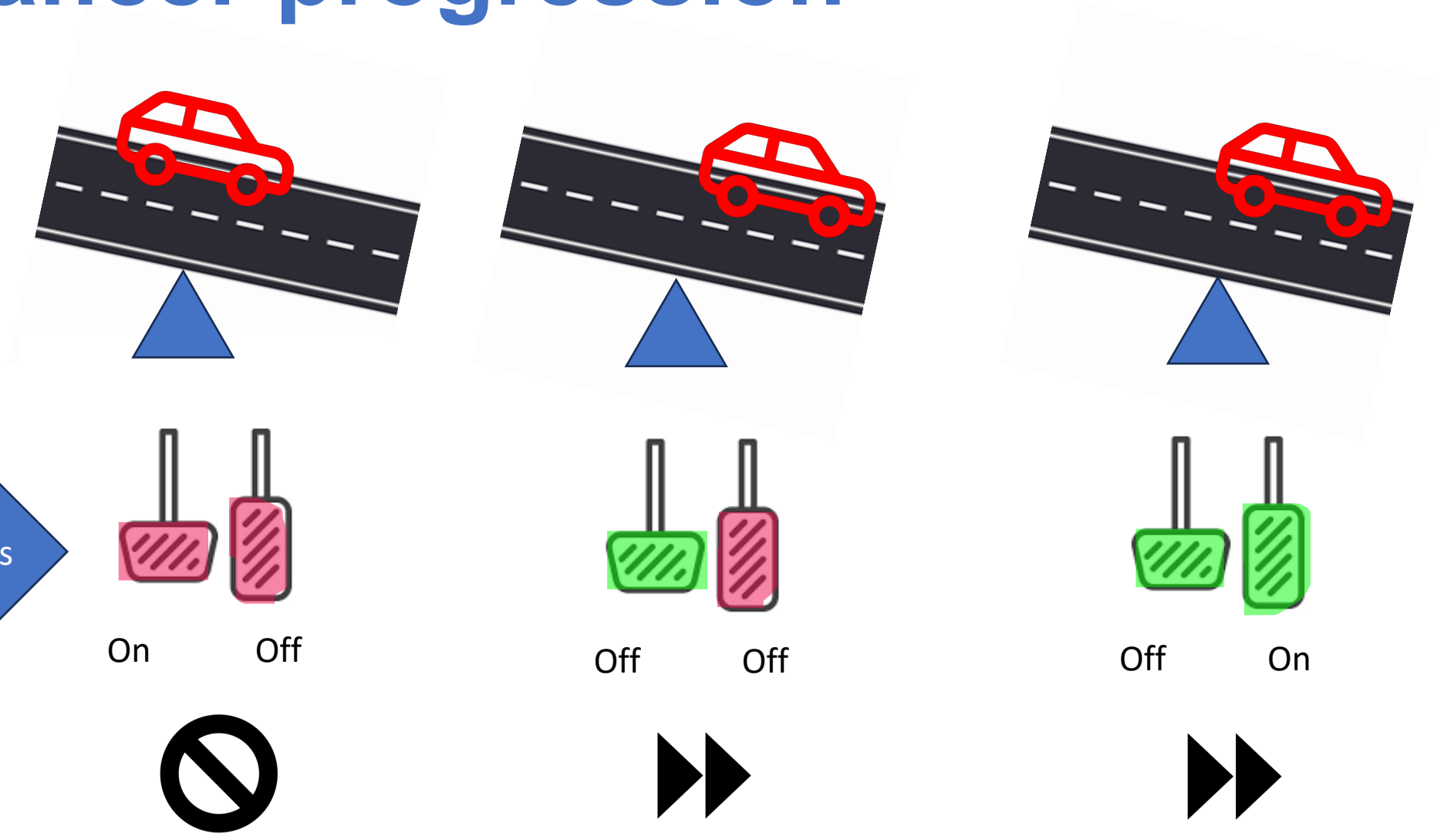
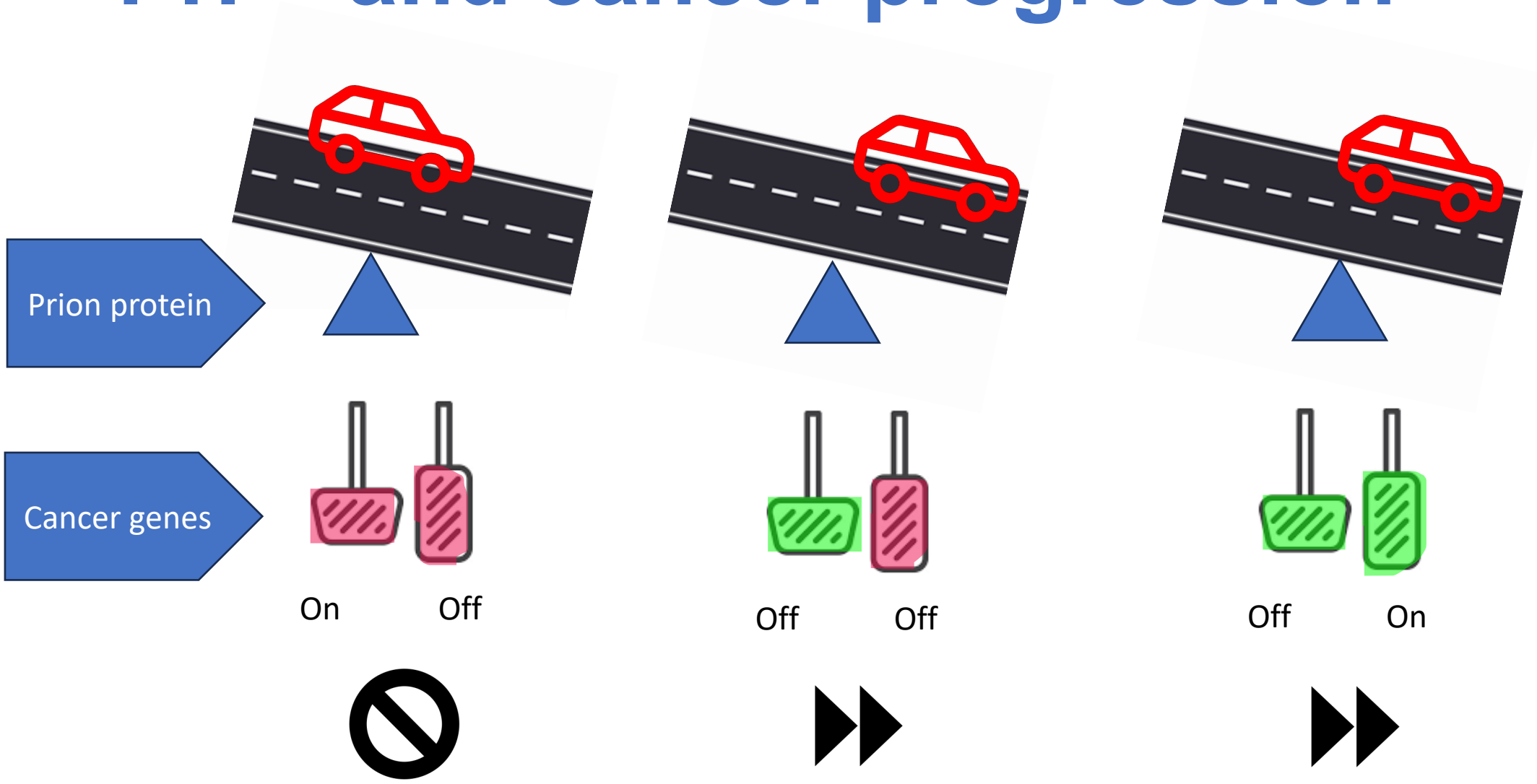




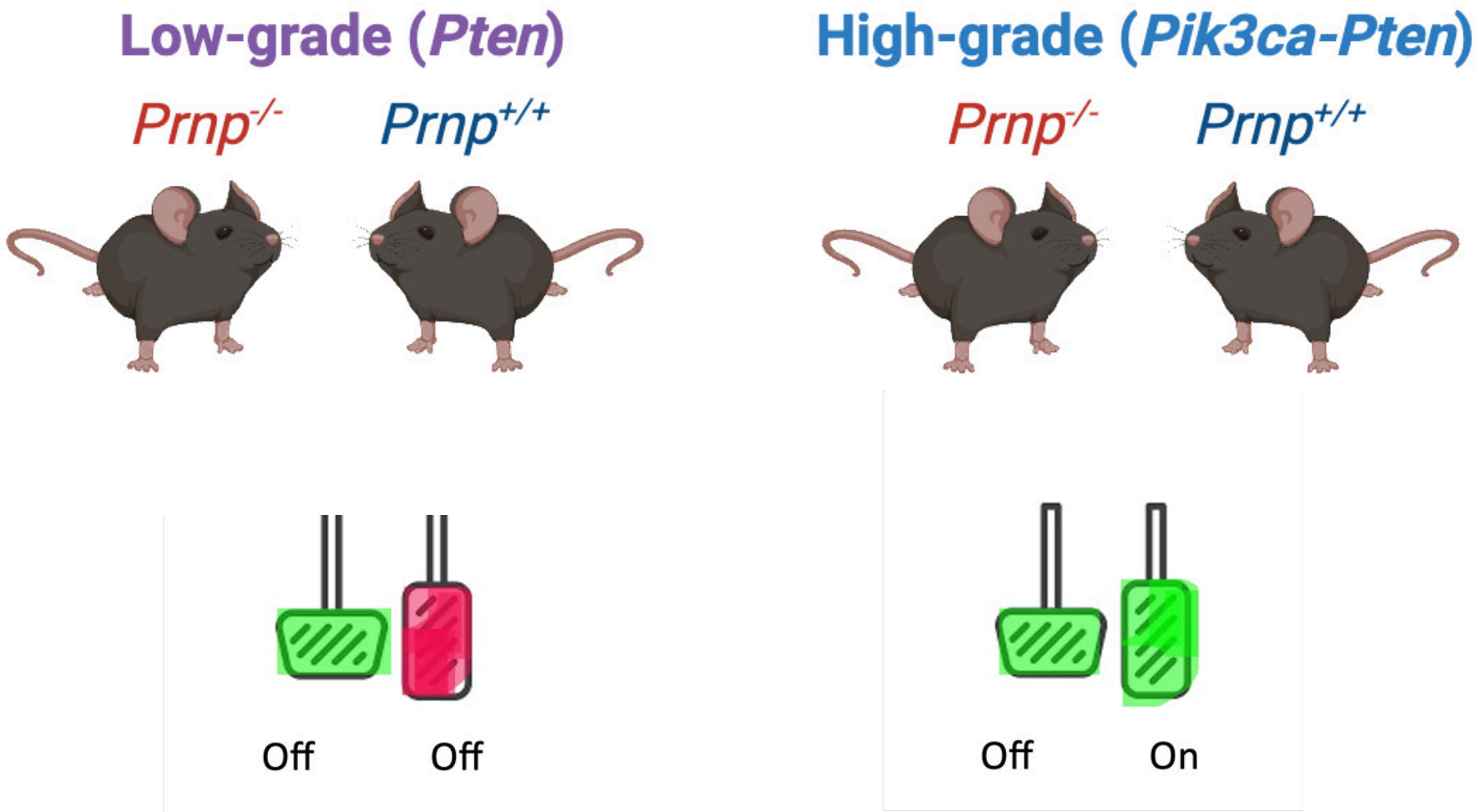
Cancer progression



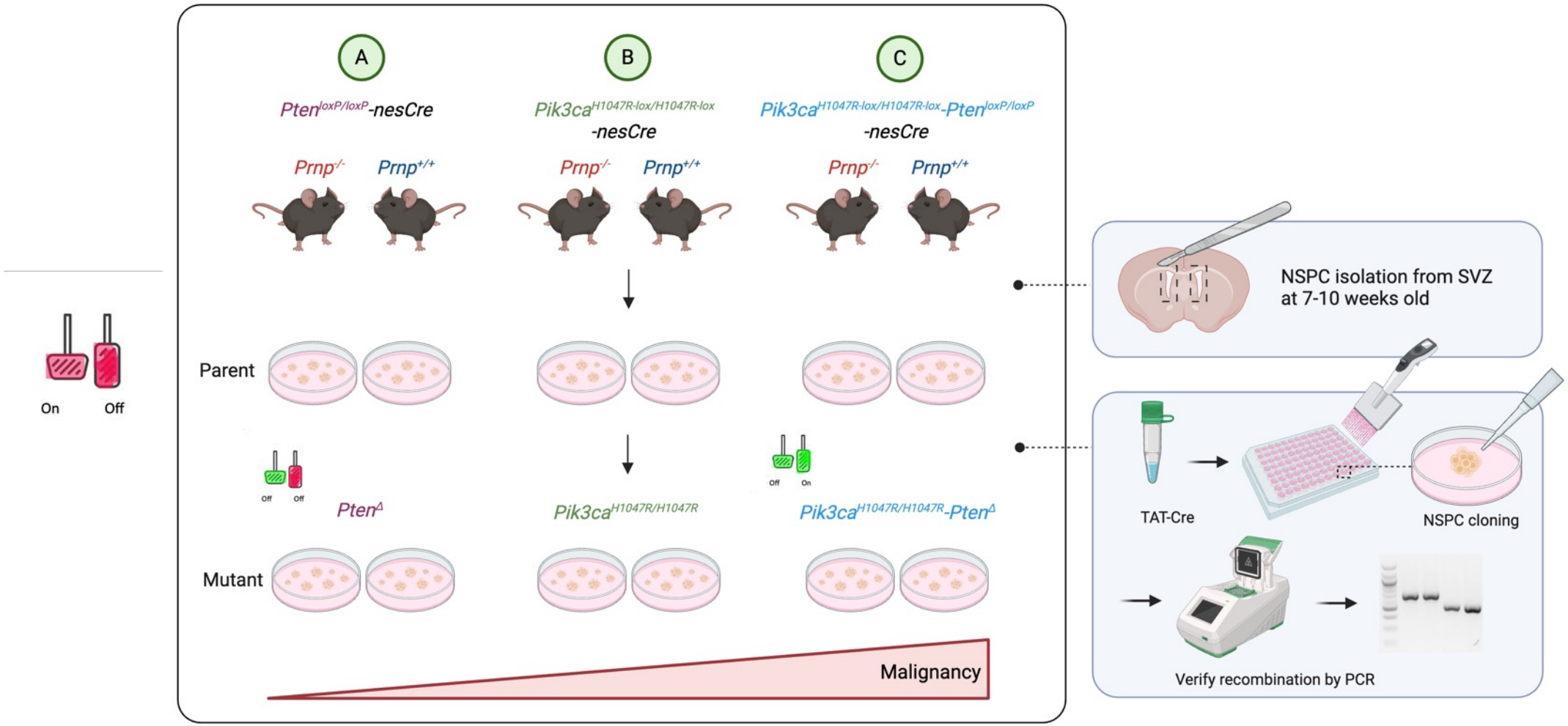
PrP^C and cancer progression



Brain cancer model

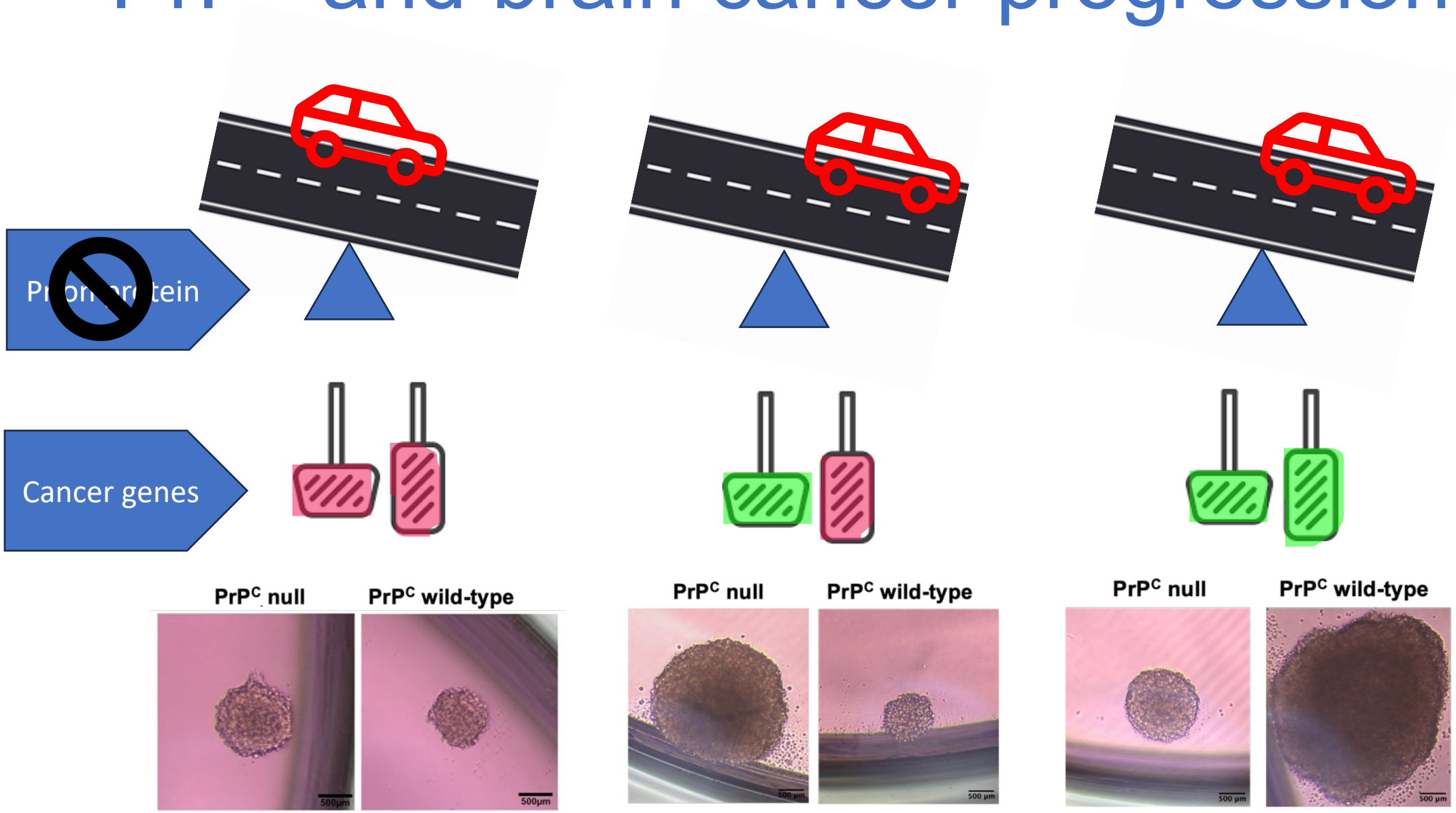


Low- and high-grade cell models of glioma with PrP^C knockout and wild-type expression



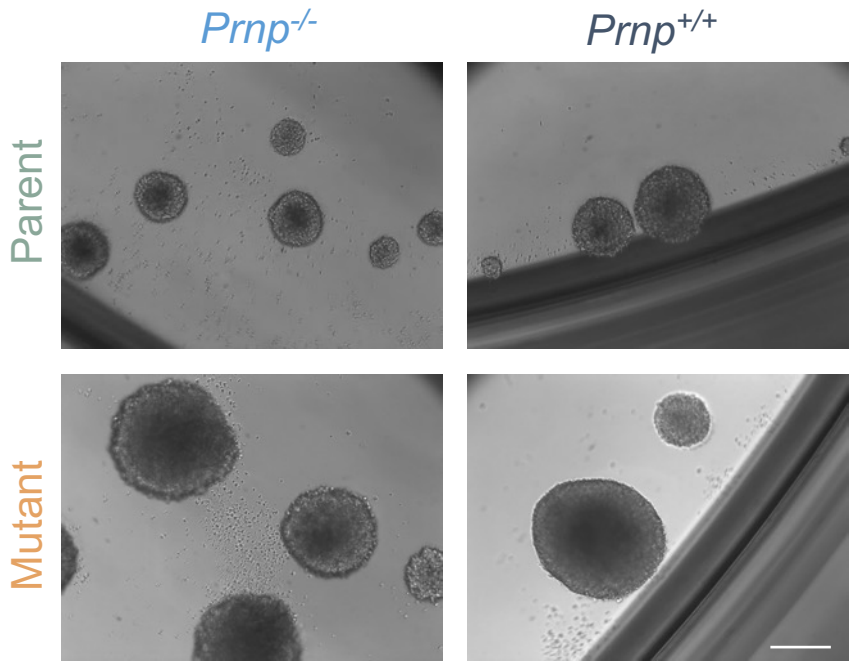
NSPC = neural stem progenitor cell
SVZ = sub-ventricular zone

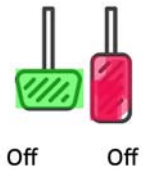
PrP^C and brain cancer progression

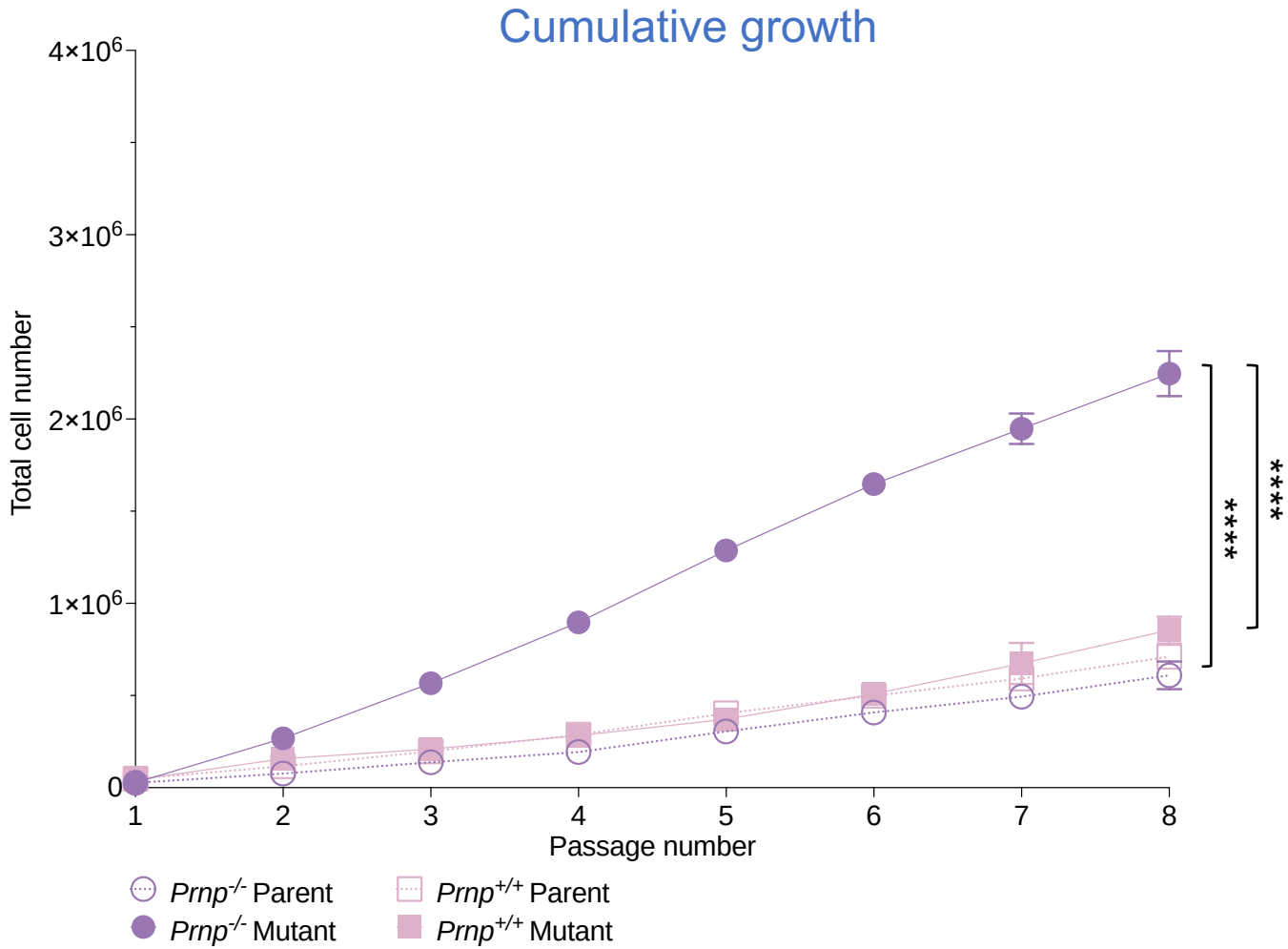


Shana Portelli

Absence of PrP^C increases proliferation in a low-grade brake off/accelerator off *(Pten)* mutant cell model

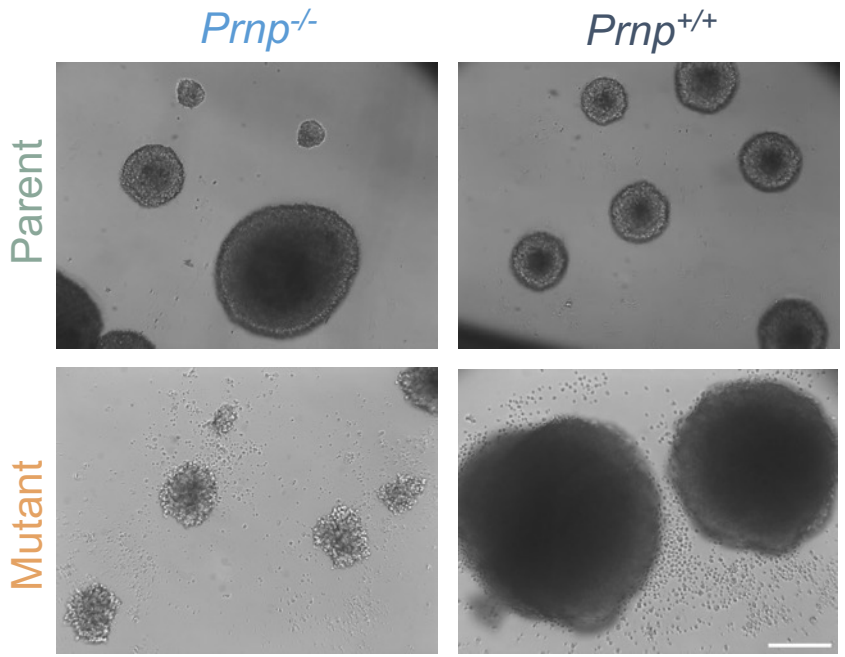


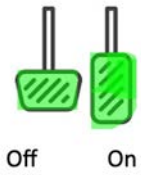


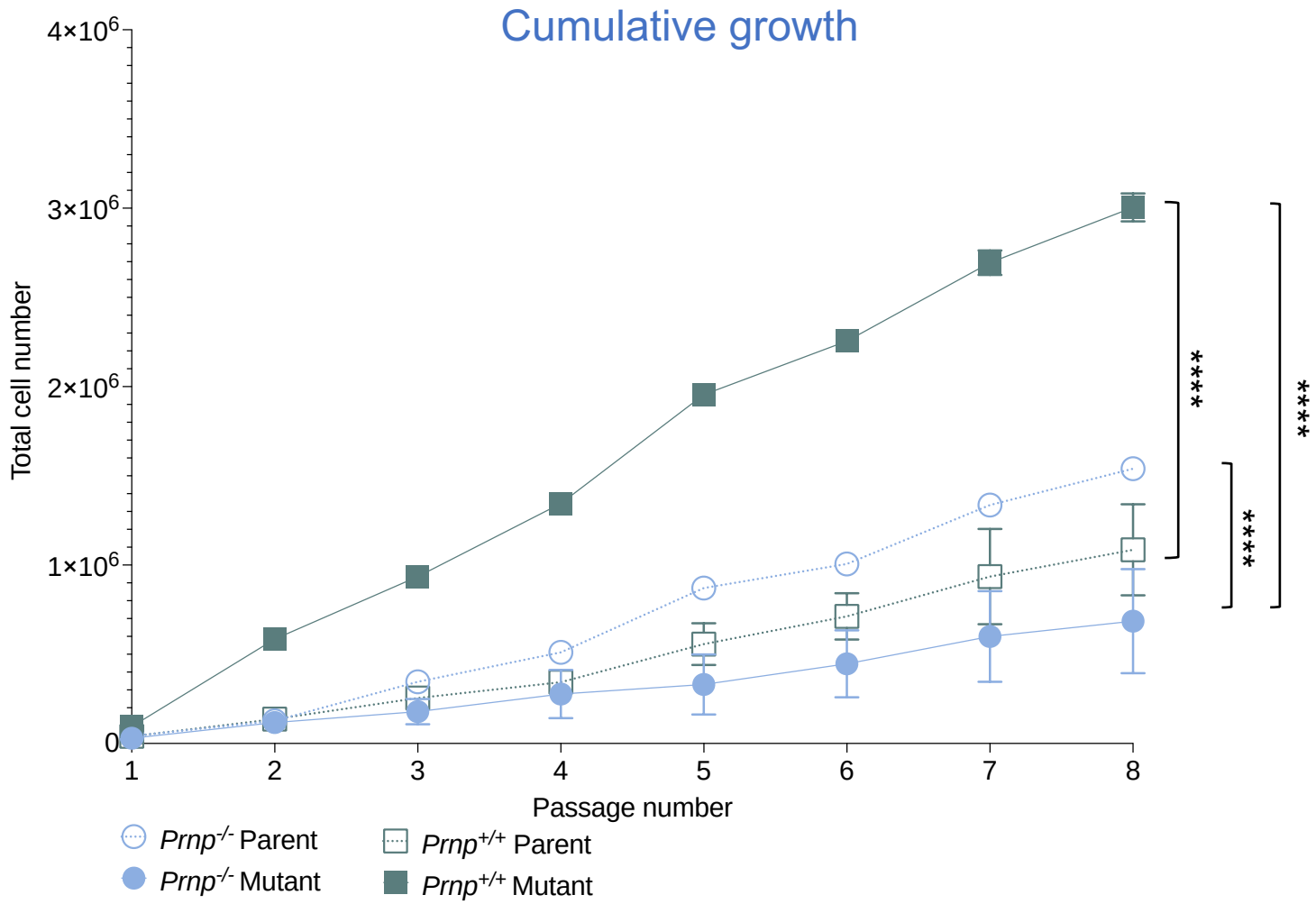


Cell counts performed in duplicate from separate wells
Two-way ANOVA, followed by Tukey's multiple comparisons test; ****$P < 0.0001$
Scale bar = 500µm

Absence of PrP^{C} reduces proliferation in a high-grade brake off/ accelerator on (*Pik3ca/Pten)* mutant cell model

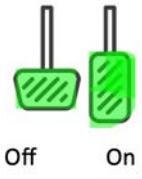






Cell counts performed in duplicate from separate wells
Two-way ANOVA, followed by Tukey's multiple comparisons test; ****$P < 0.0001$
Scale bar = 500μm

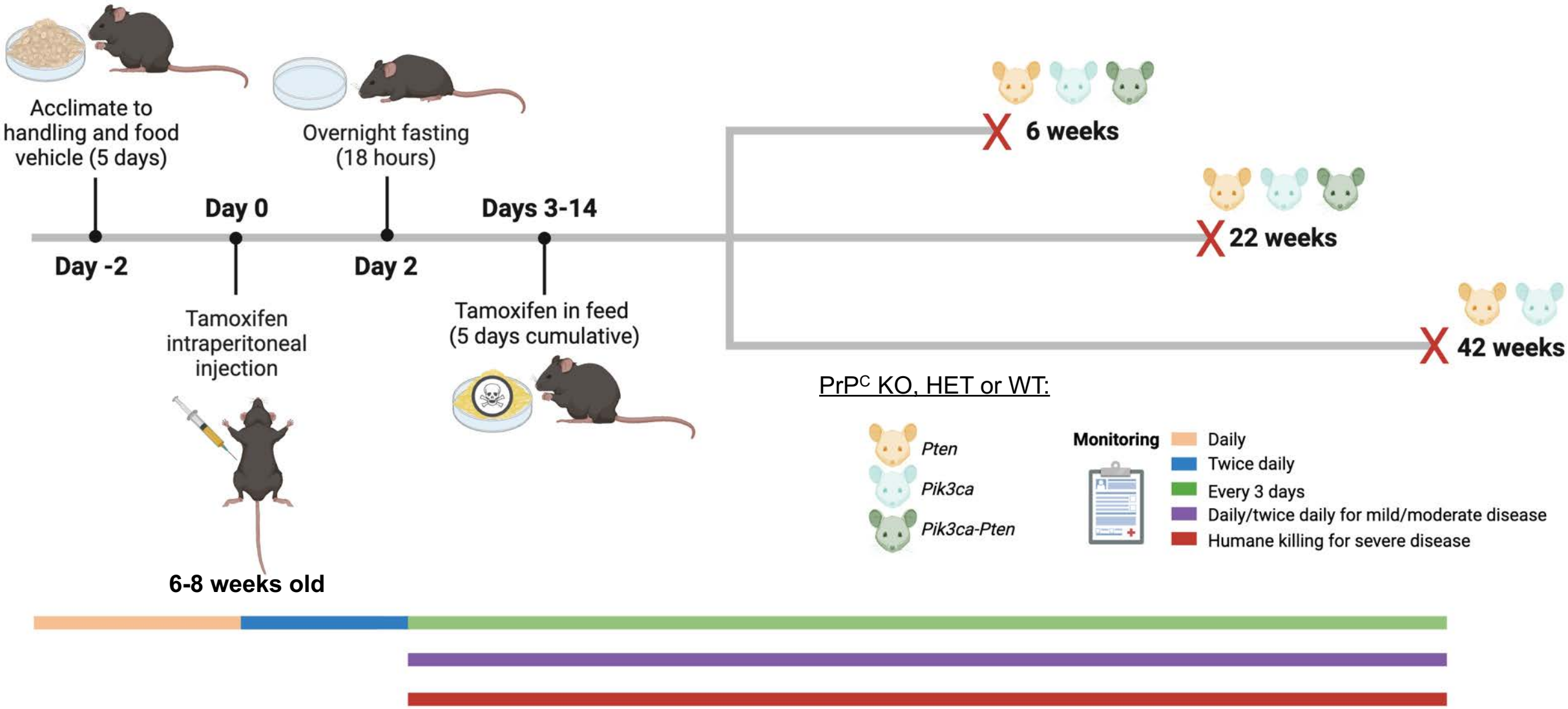
Absence of PrP^C has differing effects on low- and high-grade cell models of glioma



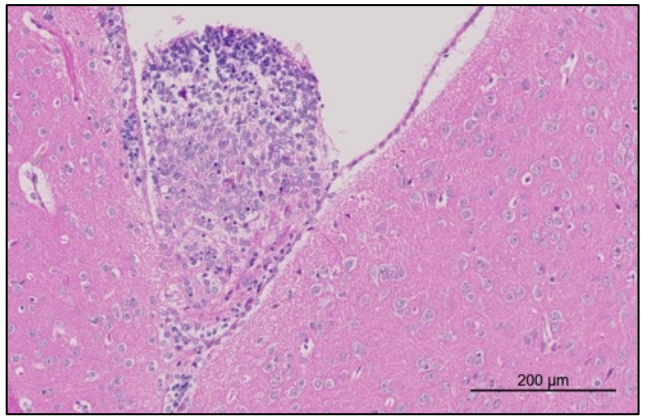
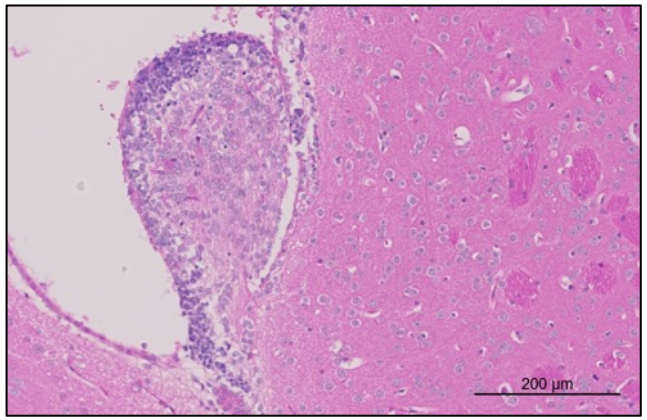
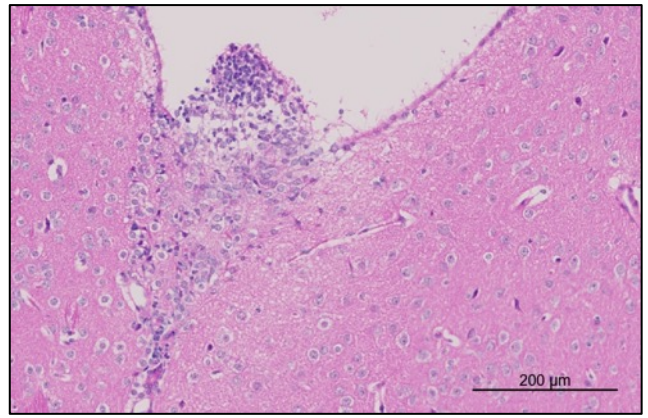
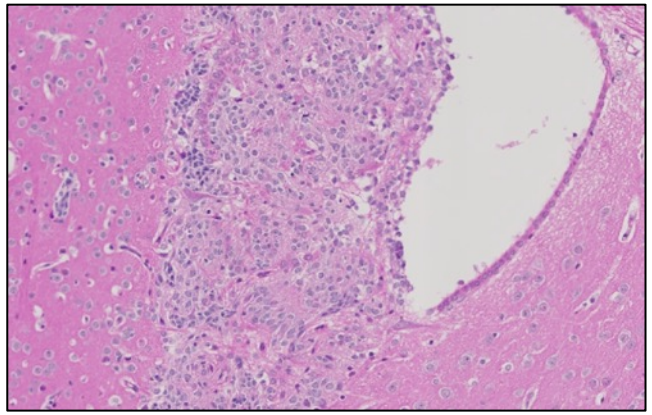
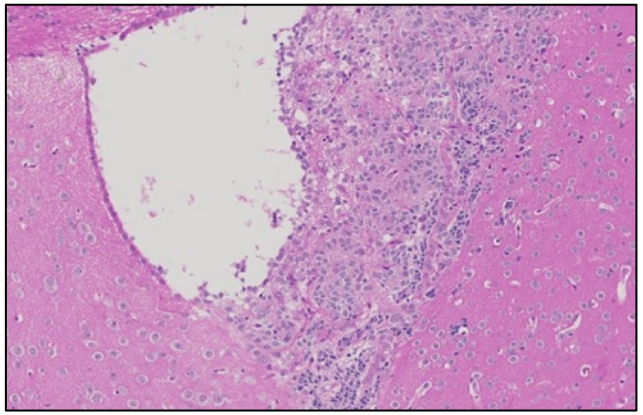
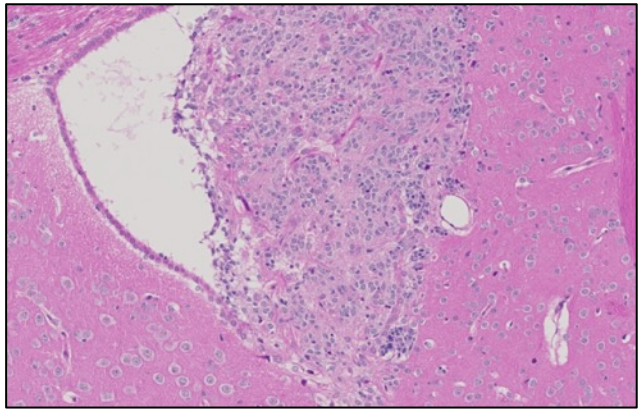
Malignancy

In the absence of PrP^C	*Pten*	*Pik3ca/Pten*
Proliferation	Increased	Reduced
Viability	No effect	Trend to reduced
Sphere forming efficiency	Increased	No effect
Neurosphere size	Increased	Reduced
Neurosphere number	Increased	No effect
Invasion	Increased	Trend to reduced

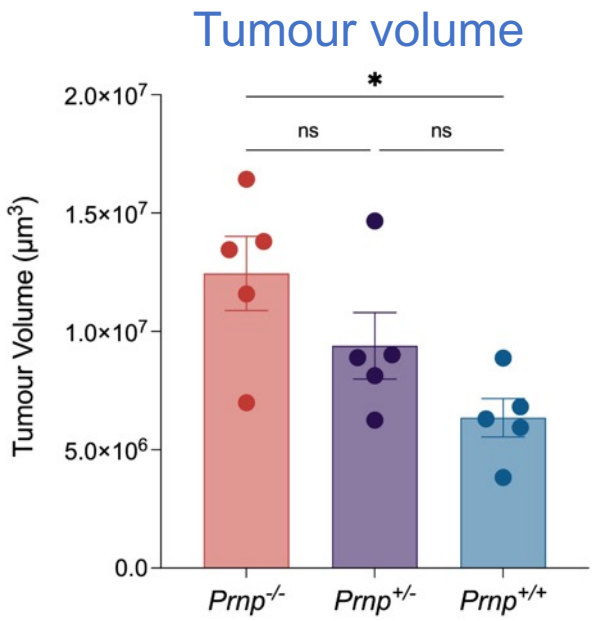
The role of PrP^C in glioma tumour initiation and progression

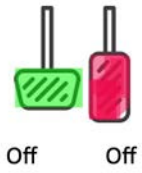


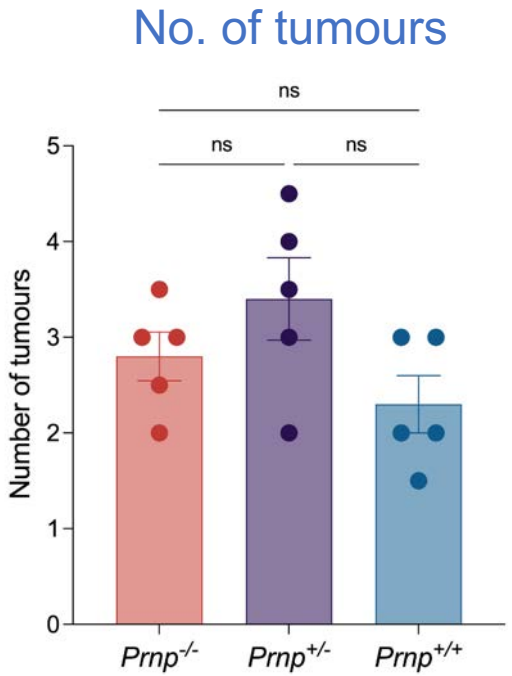
The role of PrP^C in glioma tumour initiation and progression

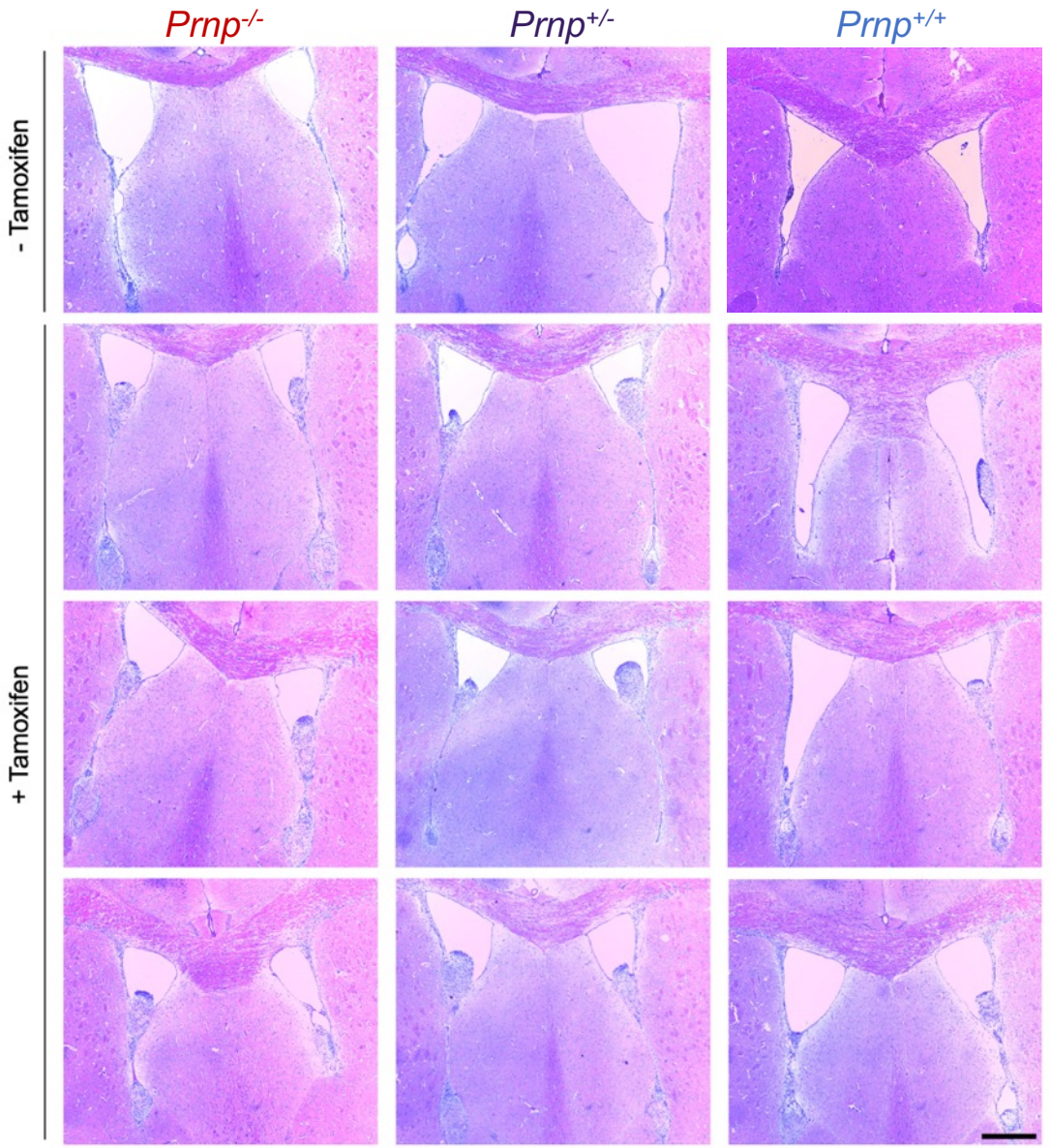
	PrP^C KO	PrP^C HET	PrP^C WT
Pten Off Off			
Pik3ca-Pten Off On			

Absence of PrP^C promotes tumour size in low-grade brake off/accelerator off *(Pten)* mutant mouse model 6-weeks post induction



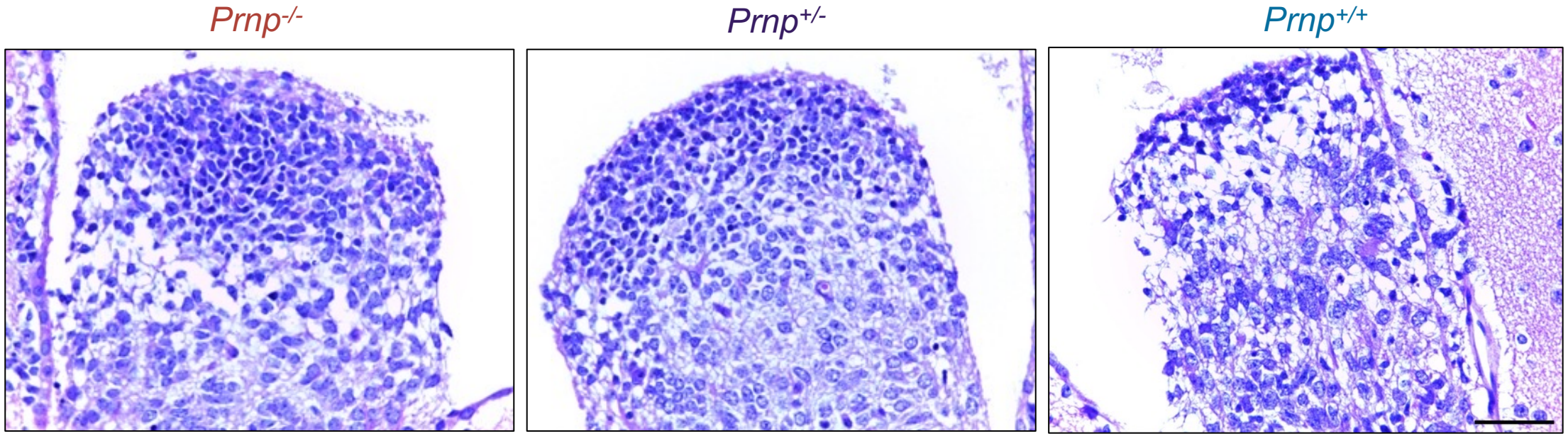


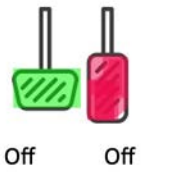




N = 5 each *Prnp* genotype
One-way ANOVA, followed by Tukey's multiple comparisons test; ns = not significant, **P* < 0.05
Scale bar = 200µm

Increased cell density at leading edge of PrP^C knockout low-grade brake off/accelerator off *(Pten)* mutant tumours (6-week t.p.)





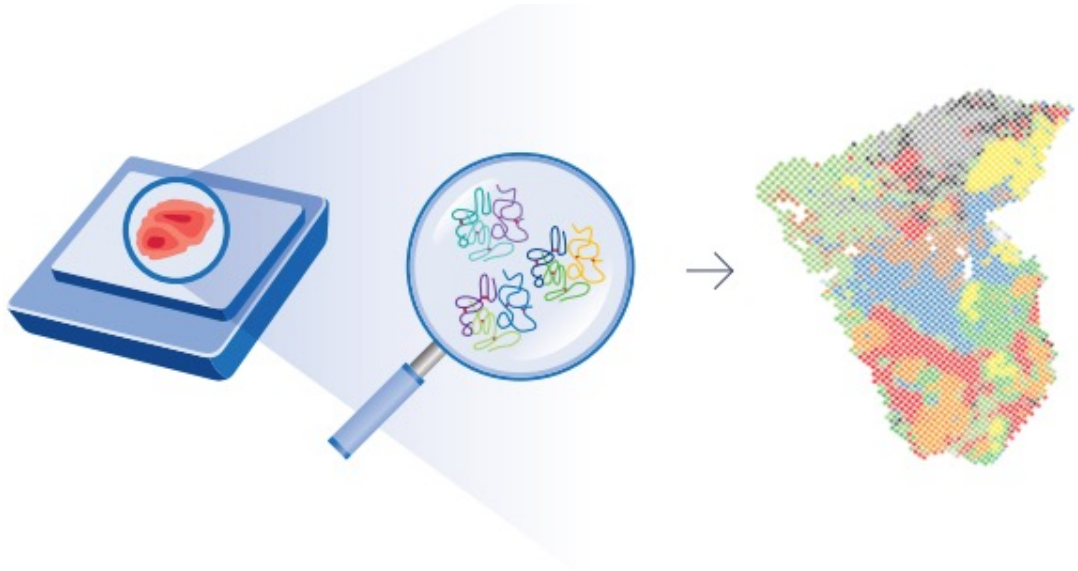
N = 5 each *Prnp* genotype. Scale bar = 50μm

Visium Spatial Gene Expression

6 weeks post induction

PrP^{C} KO, HET or WT

+ Tamoxifen			- Tamoxifen
			
Pten	*Pik3ca*	*Pik3ca-Pten*	Controls



Progress update:

1. Visium sample preparation
2. Visium workflow
3. Generation of Visium libraries
4. Sequencing
5. Analysis

Adapted from 10x Genomics

Acknowledgements

CREUTZFELDT-JAKOB DISEASE FOUNDATION, INC.

Supporting Families Affected by Prion Disease

We are grateful for the support of:

- The Strides for CJD Research Grant
- The CJD Foundation Research Grant