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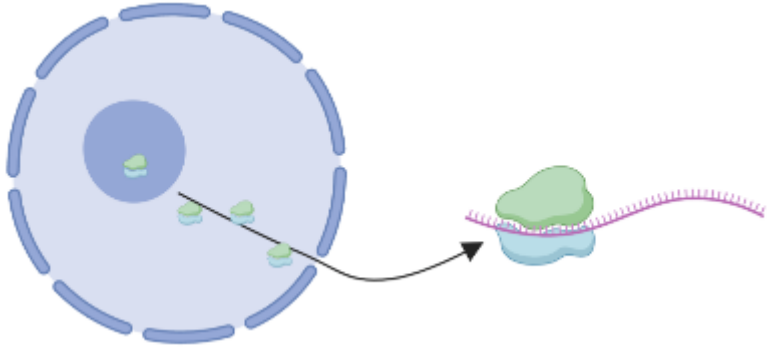
THERAPEUTICS
Innovation and Mechanism

Inhibition of Ribosomal Biogenesis (RiBi) is emerging as an effective treatment option for cancer

- Ribosomes are key to the synthesis of proteins necessary for cellular growth and division
- Ribosomes are manufactured in the nucleolus through a process called ribosomal biogenesis (RiBi)
- Cancer cells require higher levels of ribosomal activity to survive and promote malignancy[1]
- Almost all cancer types display large and/or increased number of nucleoli, promoting greater cancer cell sensitivity to RiBi inhibition[2]
- Therefore, in contrast to healthy cells, cancer cells are much more vulnerable to the inhibition of RiBi[3] – this is supported through PT-112 Phase 1 / 2 safety data
- Inhibition of RiBi with PT-112 promotes Immunogenic Cell Death (ICD)

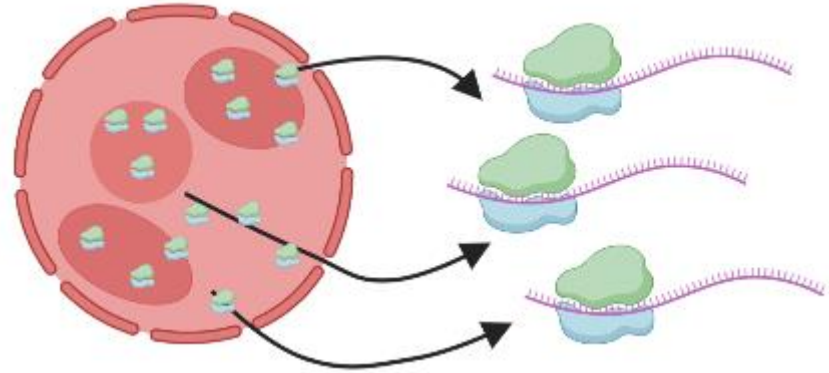
Healthy Cell



RiBi in the nucleolus inside the nucleus

Protein translation in cytosol

Cancer Cell



Larger and more nucleoli promote higher RiBi levels

Aberrant protein translation promoting malignant growth

Sources: 1 – Pecoraro, A. *et al. IJMS* **22**, 5496 (2021). 2 - Quin, J. E. *et al. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* **1842** (2014). 3 - Penzo, M. *et al. Cells* **8**, (2019).

Images created from BioRender.com

PT-112 Induces RiBi Inhibition and Nucleolar Stress
rRNA Binding as Likely Target is Under Validation

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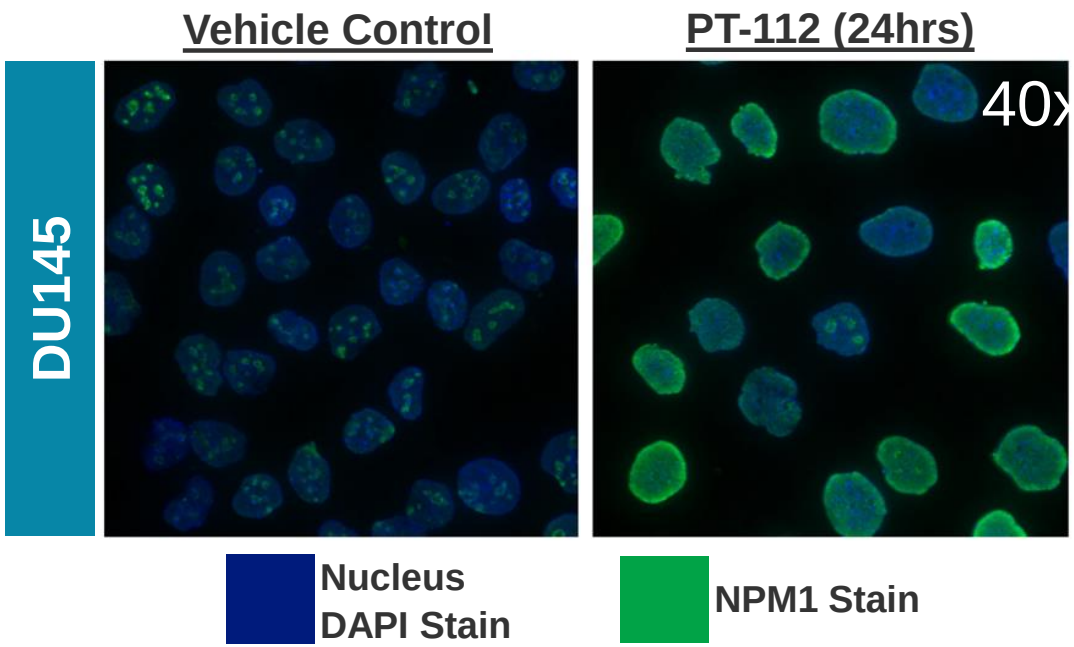
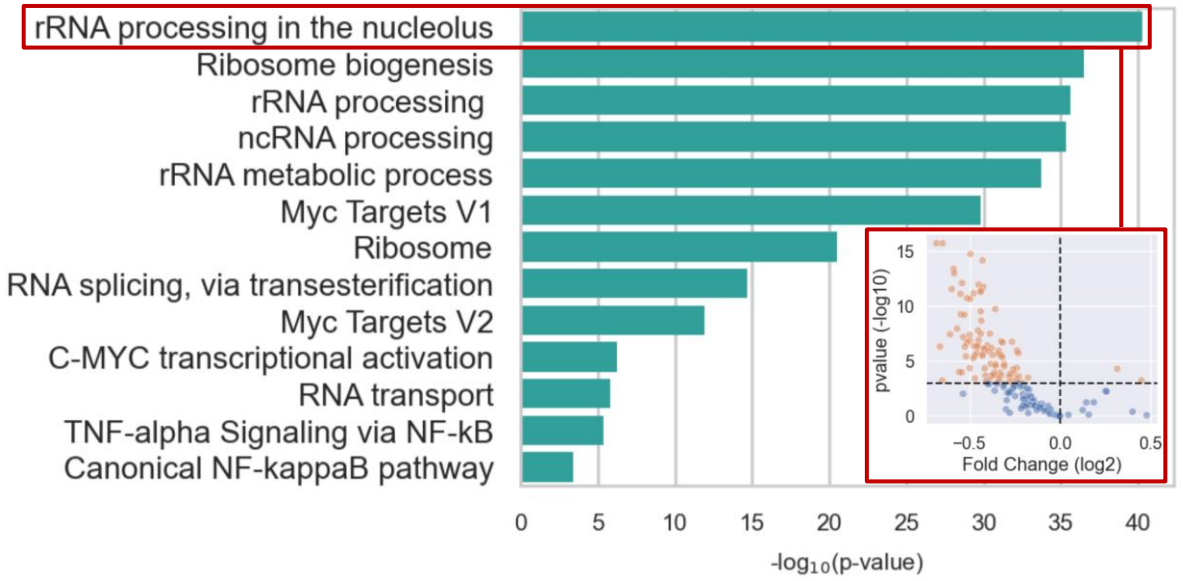
Confocal Microscopy



NPM1 diffusion upon relevant concentration PT-112 in human prostate cancer cells a hallmark sign of nucleolar stress, which directly leads to inhibition of RiBi.[1]

Gene Expression



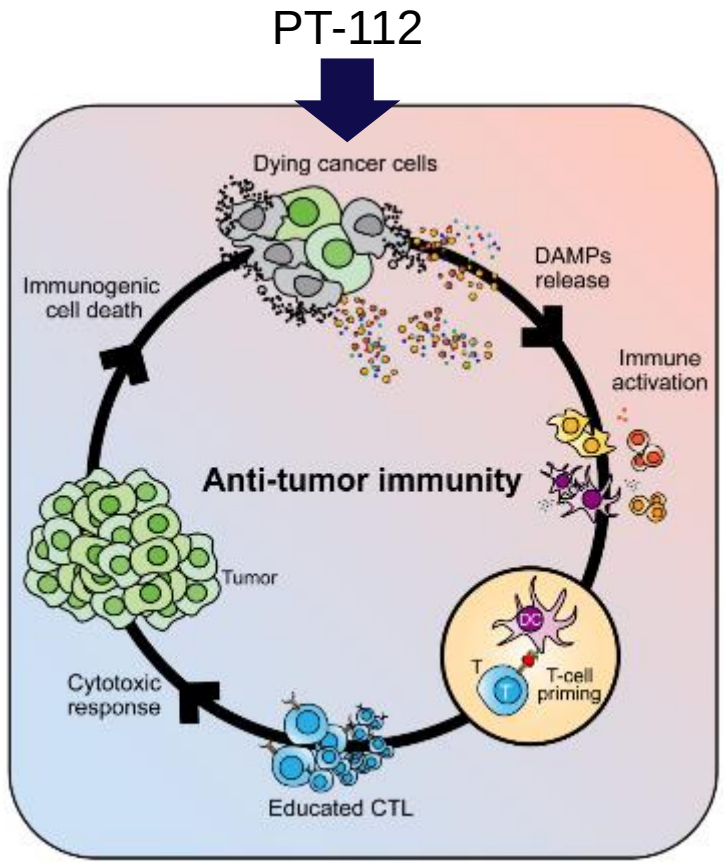
Gene expression changes induced by PT-112 in cancer cells (via nascent RNAseq) shows repression of ribosome-related pathways, including rRNA, corroborating RiBi inhibition.

RiBi inhibition by PT-112 is likely based upon targeting of rRNA in the nucleolus currently under validation

Sources: Data on file, Promontory Therapeutics; 1 – Pfister, A. S. *Front. Cell. Neurosci.* 13, (2019)

Immunogenic Cell Death (ICD) leads to an anti-cancer immune response

- Inhibition of RiBi in the nucleolus with PT-112 leads to organelle stresses (ER and mitochondria) that release specific Damage Associated Molecular Patterns (DAMPs)[1-4]
- DAMPs are the hallmark of ICD, a unique form of cancer cell death that leads to activation of the immune response[5]
  - By contrast, apoptosis is generally tolerogenic and does not lead to an immune response[5]
  - DAMPs bind to specific Pattern Recognition Receptors (PRRs) on dendritic cells, leading to the presentation of tumor specific antigens and activation of effector T-cells[5]
- In addition to the adaptive immune response, PT-112 also activates the innate immune response via engagement of NK cells[6,7]
- This cascade of immune activation results in a robust and potentially durable immune response



Adapted from Choi, M. *et al.* Immunogenic cell death in cancer immunotherapy. *BMB Reports* (2023) doi:10.5483/BMBRep.2023-0024.

Sources: 1 – Yamazaki, T. *et al. OncoImmunology* 9, 1721810 (2020). 2 - Yamazaki, T. *et al*. *J Immunother Cancer* 10, (2022). 3 - Soler-Agesta, R. *et al. Cancers (Basel)* 14, 3851 (2022). 4 - Soler-Agesta, R. *et al. Cancer Research* 82, 1115 (2022). 5 - Kroemer, G. *et al*. *Nat Immunol* 23, 487–500 (2022). 6 – Data on file, Promontory Therapeutics / NCI; 7 – Santara, S., *et al. Nature* 616, 348-356 (2023)

PT-112: Best-in-Class ICD Inducer
Monotherapy Immune Responses and I-O Combination Synergy

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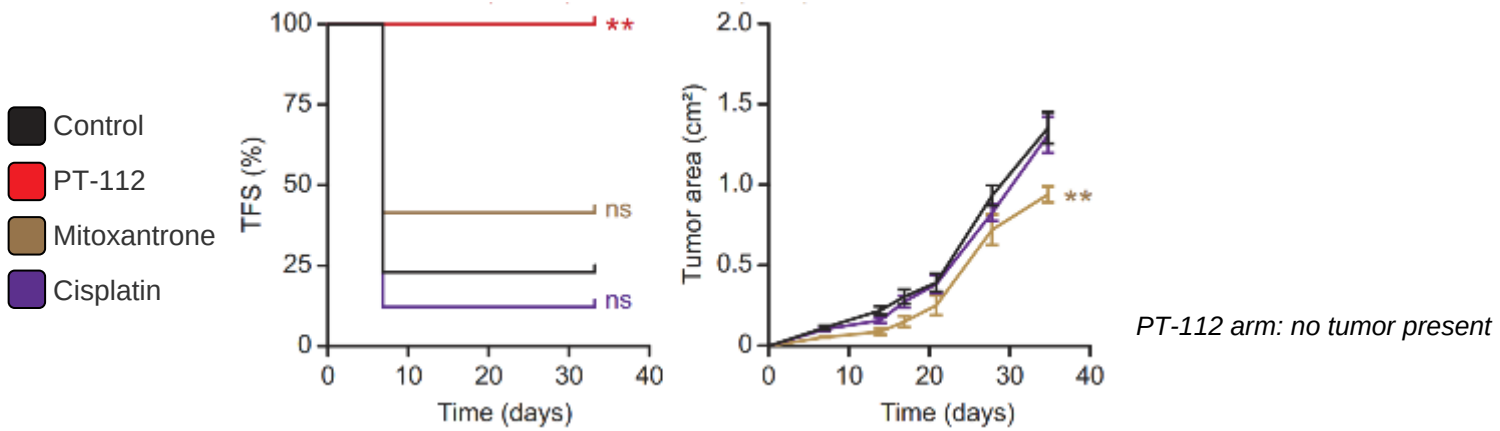
PT-112 induces best-in-class immunogenic cell death (100% tumor-free survival), synergistically combines with checkpoint inhibitors, and causes increases in immunogenic white blood cells and decreases in immunosuppressive cells in the tumor microenvironment (TME), in *in vivo* models.

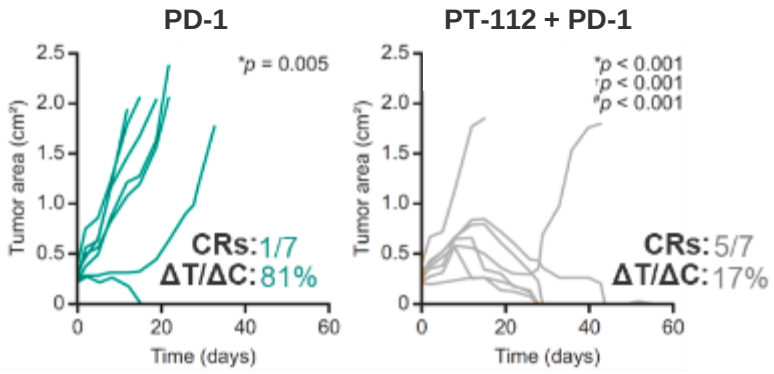
In vivo ICD Validation

(Gold-standard vaccine model)

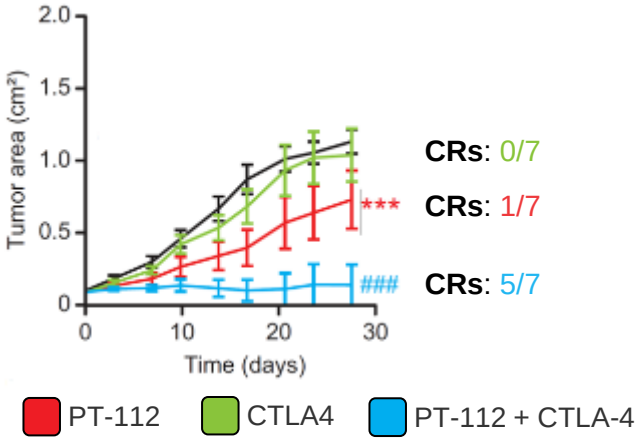


PT-112 arm: no tumor present

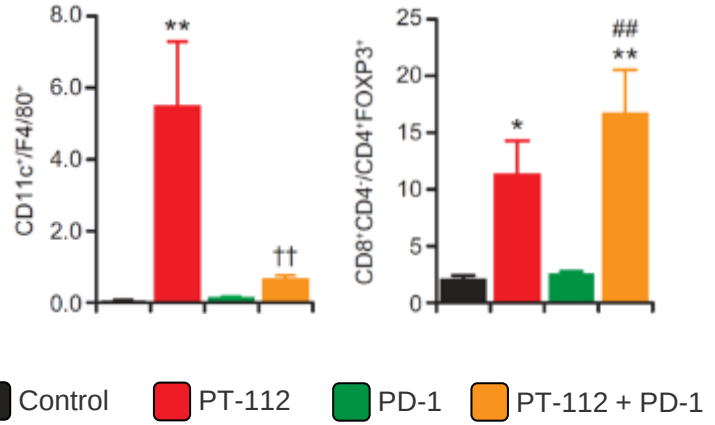
PD(L)-1 Synergy



CTLA-4 Synergy



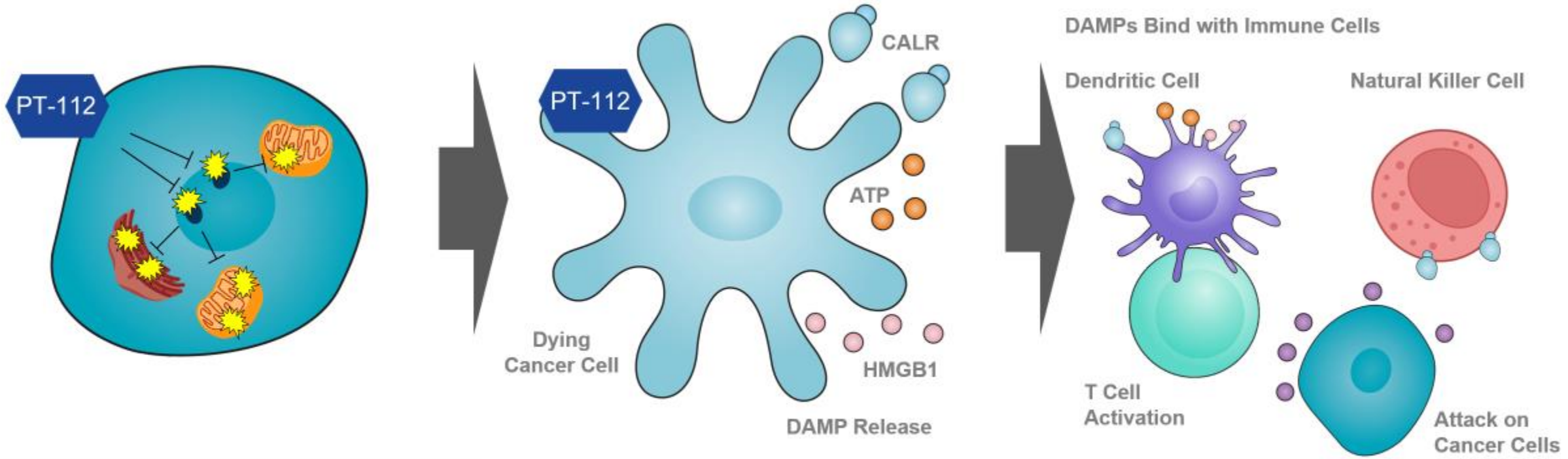
Positive TME Changes



OncoImmunology

Source: Yamazaki et al. (2020) Oncoimmunology, 9:1

Summary of PT-112's Unique Mechanism of Action:
Selective inhibition of RiBi Leads to Immune Activation via ICD



Nucleolar RiBi Inhibition Induces Organelle Stress
Mitochondria, Endoplasmic Reticulum (ER)

Immunogenic Cell Death
Distinct from Apoptosis

Anti-Cancer Immune Response
Adaptive and Innate

Images modified from BioRender.com and *Nat Rev Immunol* 2017; **17**: 97–111