# MRI-Guided Convection-Enhanced Delivery of an AAV-hIFNβ Vector Achieves Targeted Brain Retention and Durable Transgene Expression in a Large-Animal Model

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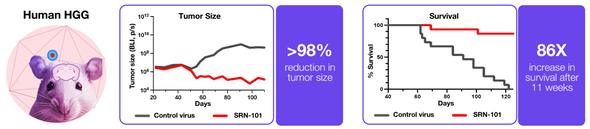
## Introduction

### Challenge: High-grade glioma (HGG)

- Most common and deadliest primary malignant brain cancer
- Median overall survival ~12-16 months[1]
- Profound unmet medical need at recurrence
- Systemic therapies are limited by poor CNS brain penetration and dose-limiting toxicity

### Solution: SRN-101 (AAV-hIFNβ)

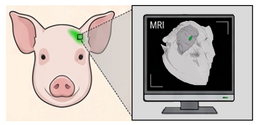
- Human interferon beta (hIFNβ) is a pleiotropic cytokine with potent anti-proliferative and immune-activating properties in solid tumors[2]
- Local delivery to the brain bypasses the blood-brain barrier
- AAV delivery enables sustained expression of hIFNβ at the local site of administration, overcoming the short half-life limitations of systemic recombinant cytokine delivery
- Established efficacy in an orthotopic mouse model of human HGG




## Biodistribution Experimental Design

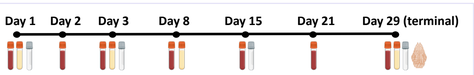
To expand our understanding of the safety and tolerability of SRN-101, the biodistribution of SRN-101 vector genomes (vg) and payload expression (hIFNβ) was assessed in a 28-day non-GLP toxicology study.

**Intraparenchymal administration**

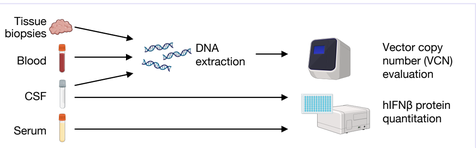



- Healthy Göttingen minipigs
- MRI-guided
- Right parietal lobe infusion
- CED (ClearPoint Neuro SmartFlow® NGS-NC-02)
- 0.5 mL SRN-101 + 2 mM Gadoteridol contrast agent

**In-life + terminal collections**

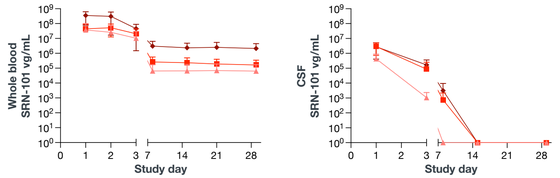



**Biodistribution sample analysis**

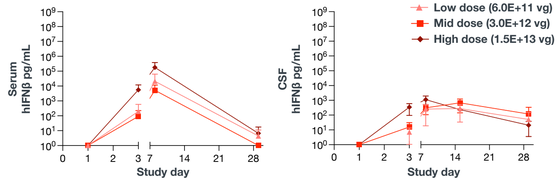



## Longitudinal SRN-101 Biodistribution in Biofluids

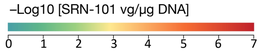
### SRN-101 vector genomes (vg)



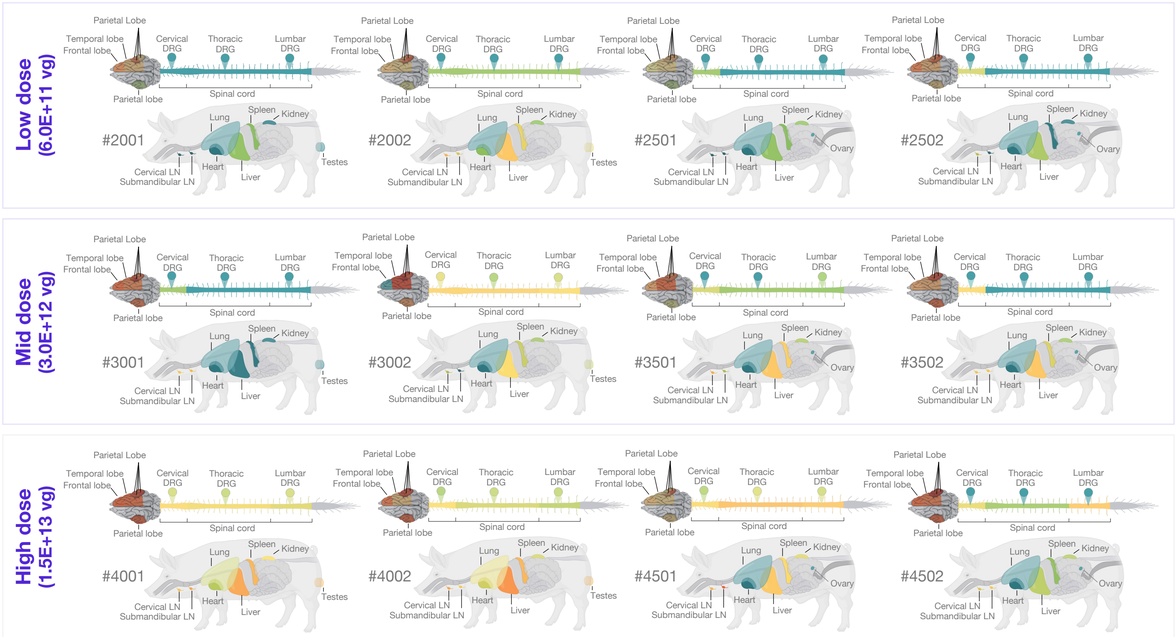

### hIFNβ protein




## Terminal SRN-101 Biodistribution in Tissues

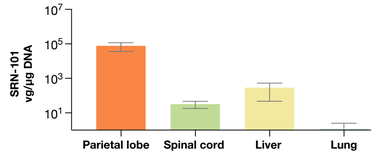



- SRN-101 VCNs are displayed from tissue biopsies from n=4 pigs (2M/2F) per dose level.
- Refer to the color scale for measured SRN-101 vg concentrations in vg/µg DNA.



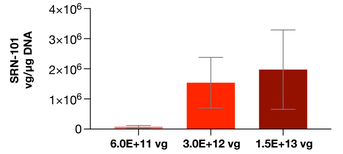

## Key Takeaways

### Local CED resulted in >250X higher SRN-101 concentrations at the site of administration than in off-target tissues




Mean concentration of SRN-101 vg/µg DNA from tissue biopsies of the target site of administration (parietal lobe) and representative off-target tissues following a low dose (6.0E+11vg) of SRN-101 (n=4). Bars = mean ± SEM.

### Tissue concentrations of SRN-101 were dose responsive




Mean concentration of SRN-101 vg/µg DNA from tissue biopsies of the dosed parietal lobe by dose level. Bars = mean ± SEM. n=4 pigs per dose level.

### Biodistribution supports the clinical safety of SRN-101

- 0.5 mL (max feasible) MRI-guided intraparenchymal CED infusion was well-tolerated, and all animals survived to scheduled euthanasia.
- SRN-101 vector genomes were detected in the blood and persisted to Day 28. These did not translate to SRN-101 vector genomes in non-CNS tissues; leakage is anticipated to decrease with lower volumes.
- SRN-101 vector genome concentrations were lower in the CSF and fell below the limit of detection by Day 15.

### SRN-101 effectively and rapidly delivers hIFNβ cytokine

- hIFNβ protein payload was detected within 3 days in both serum and CSF, peaking by Day 8.
- hIFNβ protein payload decreased, likely due to pig immunogenicity to the human IFNβ protein; this is not expected to occur in humans.

### Acknowledgements

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### References

1. Shanker M, Chua B, Bettington C, Foote MC, and Pinkham MB. Re-irradiation for recurrent high-grade gliomas: a systematic review and analysis of treatment technique with respect to survival and risk of radionecrosis. *Neurooncol Pract*. 2019 Mar;6(2):144-155.
2. von Locquenghien M, Rozalén C, and Celià-Terrassa T. Interferons in cancer immunoediting: sculpting metastasis and immunotherapy response. *J Clin Invest* 131, e143296 (2021).