PRESS RELEASE | 17 MAY 2023

Siren Biotechnology Unveils Preclinical Data for Universal AAV Immuno-Gene Therapy for Cancer, a Novel Modality that Combines AAV Gene Therapy and Cytokine Immunotherapy

- Data demonstrated that AAV vectors expressing engineered immunomodulatory interferon (IFN) cytokine payloads led to:
    - Rapid and selective reduction in tumor size in high-grade glioma (HGG) organoids
    - Tumor regression and significantly prolonged survival in 450 treated mice across three industry leading HGG human xenograft and allograft mouse models
    - Widespread tumor cell death via apoptosis within 48 hours of treatment
    - Reproducible tumor eradication, no evidence of residual proliferating tumor cells, and no evidence of cytokine payload expression by Day 7 post-treatment
- Siren officially launched out of stealth today, coinciding with today's ASGCT presentation

SAN FRANCISCO [May 17, 2023] – Siren Biotechnology today announced the presentation of preclinical data demonstrating the effect of a novel treatment for cancer, Universal AAV Immuno-Gene Therapy, which combines AAV gene therapy and cytokine immunotherapy into a single modality. The oral presentation titled, *"AAV immuno-gene therapy delivers vectorized cytokines to effectively treat high-grade gliomas,"* will be given by renowned AAV gene therapy expert and Siren's Founder and Chief Executive Officer, Nicole Paulk, PhD, at 3:45pm PT at the ASGCT 26th Annual Meeting, taking place in Los Angeles, May 16-20th. Dr. Paulk will describe how this precise and highly targeted approach represents a novel method for destroying tumor cells and eliciting anti-tumor immunity. Link here to review Siren's ASGCT abstract and here to review the company's launch press release also issued this morning.

The Siren team conducted several experiments to evaluate the safety and efficacy of an immuno-gene therapy that utilizes AAV9 vectors expressing 12 different engineered immunomodulatory interferon (IFN) cytokine payloads comprising IFNα1, IFNβ, IFNɣ, and combinations thereof.

- In primary human high-grade glioma (HGG) organoids, Siren's AAV immuno-gene therapies rapidly and selectively reduced tumor size. In comparison, phosphate buffered saline, dimethyl sulfoxide diluent, and AAV9-GFP (green fluorescent protein) had no effect on tumor or healthy cerebral cells in HGG organoids, and HGG tumor cells grew uncontrollably. Temozolomide chemotherapy, the current standard of care for HGG, significantly decimated healthy cerebral cells and only slightly delayed HGG tumor growth.

- *In vivo* data demonstrated that AAV immuno-gene therapies effectively reduced tumor burden in three HGG mouse models that received intratumoral administration of the cytokine payloads via convection-enhanced delivery (CED). Treatment with AAV immuno-gene therapies resulted in tumor regression and significantly prolonged survival in human GBM6 xenografts (P<0.2-0.001 and 31 – 60% complete responses (CRs)); mouse GL261 allografts (P<0.0009); and human patient-derived xenografts (P<0.04; 30% CR); n=450.
- An evaluation of tumor-bearing mouse brains demonstrated marked tumor changes following treatment with AAV immuno-gene therapies. Within 48 hours following treatment, local intratumoral expression of Siren's engineered IFNs had already led to widespread tumor cell apoptosis, and activation of brain-resident macrophages known as microglia, a class of antigen-presenting immune cells that specialize in clearing necrotic and apoptotic cells. By Day 7, there was reproducible tumor eradication, no evidence of residual proliferating cells, no remaining engineered cytokine payload expression, and only residual microglial activity.
- Subsequent single cell sequencing on syngeneic mouse brain tumors following AAV immuno-gene therapy treatment showed that tumor cells exhibited a significant upregulation of genes linked to IFN responses, as well as other classic immune response genes. These responses were specific to IFN payload expression and not AAV.

"We're excited to present these potentially transformative data as we simultaneously introduce Universal AAV Immuno-Gene Therapy and Siren Biotechnology," said Dr. Paulk. "This novel approach represents a new, big, bold idea to fight cancer by combining the potential of AAV gene therapy and cytokine immunotherapy into a single modality. Our vision is for Universal AAV Immuno-Gene Therapy to become the standard of care for any solid tumor cancer. Bolstered by the results shared today at ASGCT, we've started our vision-led journey with an initial focus on brain and eye cancers. Attempts to treat these cancers with systemic drugs have largely failed. The unmet need for these patients is dire, and our opportunity to help is massive."

About Siren Biotechnology

Headquartered in San Francisco, CA, Siren Biotechnology is sounding the alarm against cancer. We are the pioneers of Universal AAV Immuno-Gene Therapy, which combines the promise of two transformative therapeutic technologies, AAV gene therapy and cytokine immunotherapy, into a single modality which we believe will redefine how we destroy tumor cells and elicit anti-tumor immunity. Our vision is for Universal AAV Immuno-Gene Therapy to become the standard of care for any solid tumor cancer.

To learn more, visit sirenbiotechnology.com, and follow us on LinkedIn and Twitter.

Universal AAV Immuno-Gene Therapy for Cancer. It's Here.

Contact
Akela Kuwahara
press@sirenbiotechnology.com