epicrispr biotechnologies

Non-Human Primate (NHP) Safety Study of High-Dose EPI-321: A Novel AAV-Delivered Epigenetic Editing Gene Therapy for the Treatment of FSHD

Sid Boregowda, DVM, MS, Ph.D, DABT
Epicrispr Biotechnologies, Inc., South San Francisco, CA, USA

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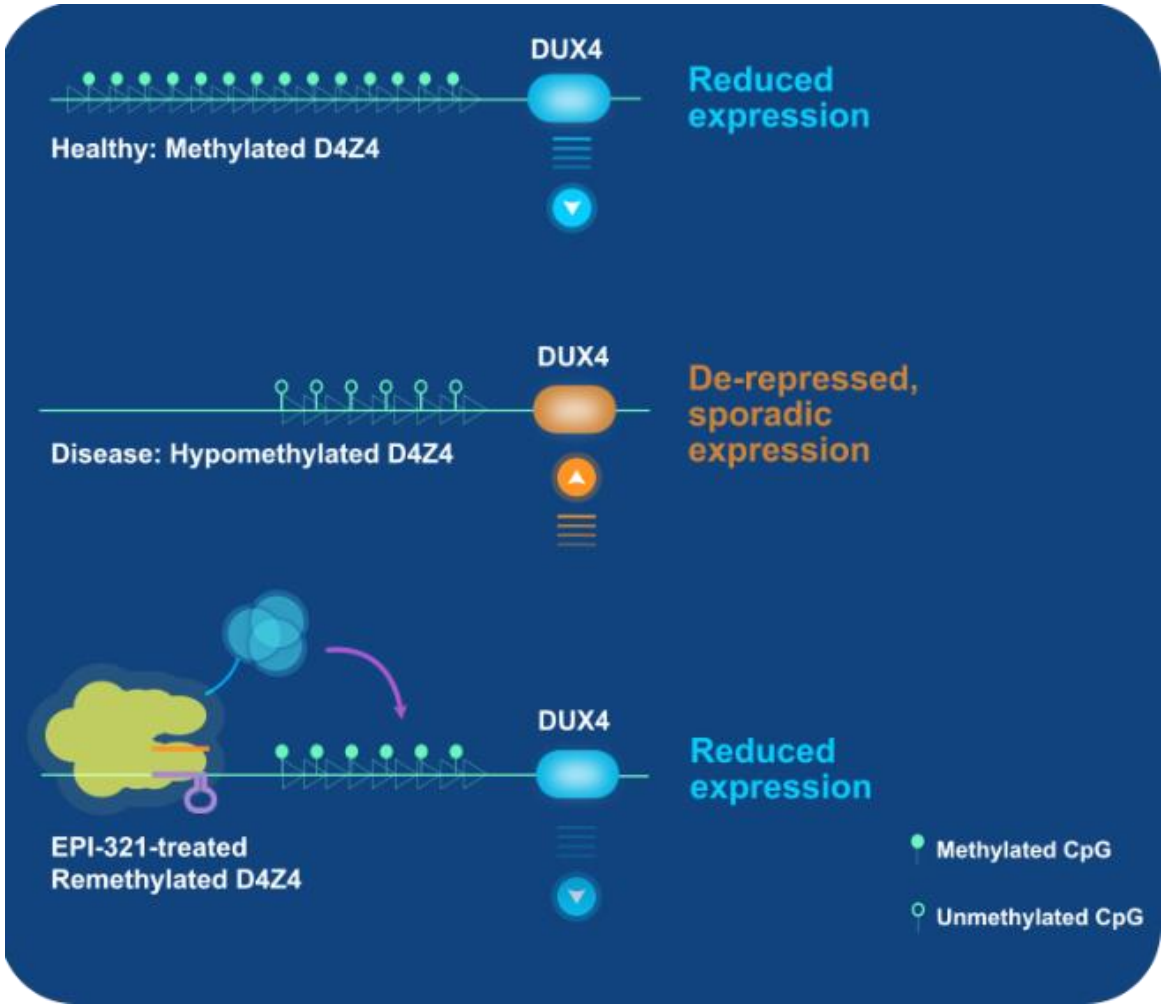
Epicrispr: Company Highlights

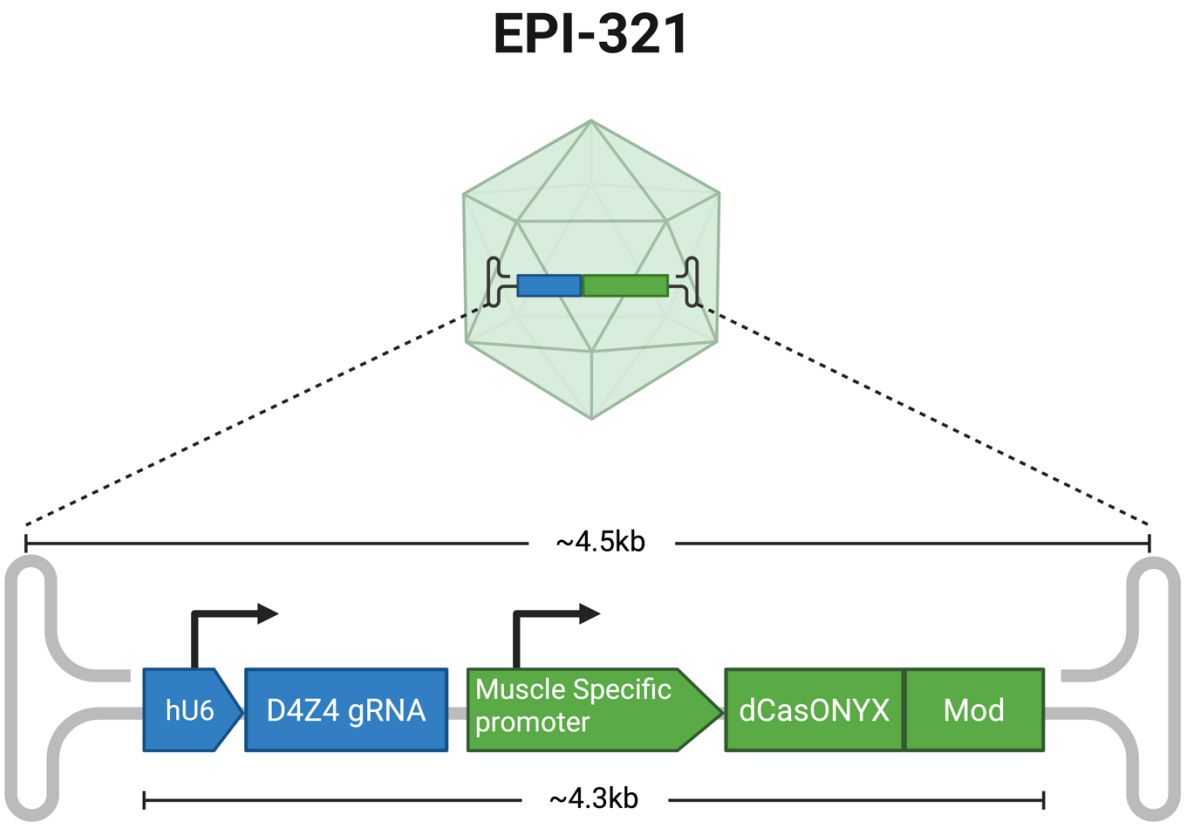
- **Leader in epigenetic editing, initial focus on neuromuscular disease**
- **Differentiated and proprietary platform to persistently suppress or activate any genes of interest, enabling full range of indications across therapeutic areas**
- **EPI-321, a potentially curative therapy for FSHD, received US IND and New Zealand CTA clearance. First-in-human trial set to begin 1H2025**
- **Validating Partnership with Kite Pharma to develop Next-Gen Cancer Cell Therapies**

Epicrispr Lead Program: EPI-321 to Treat FSHD



- FSHD is driven by aberrant and toxic expression of DUX4 in Skeletal Muscle.
- No disease-modifying treatments currently approved.
- Nuclease inactive CRISPR-based **Gene Expression Modulation System** (GEMS) can address underlying factors that cause FSHD by epigenetically repressing toxic DUX4 expression

GEMS Platform and EPI-321 Design

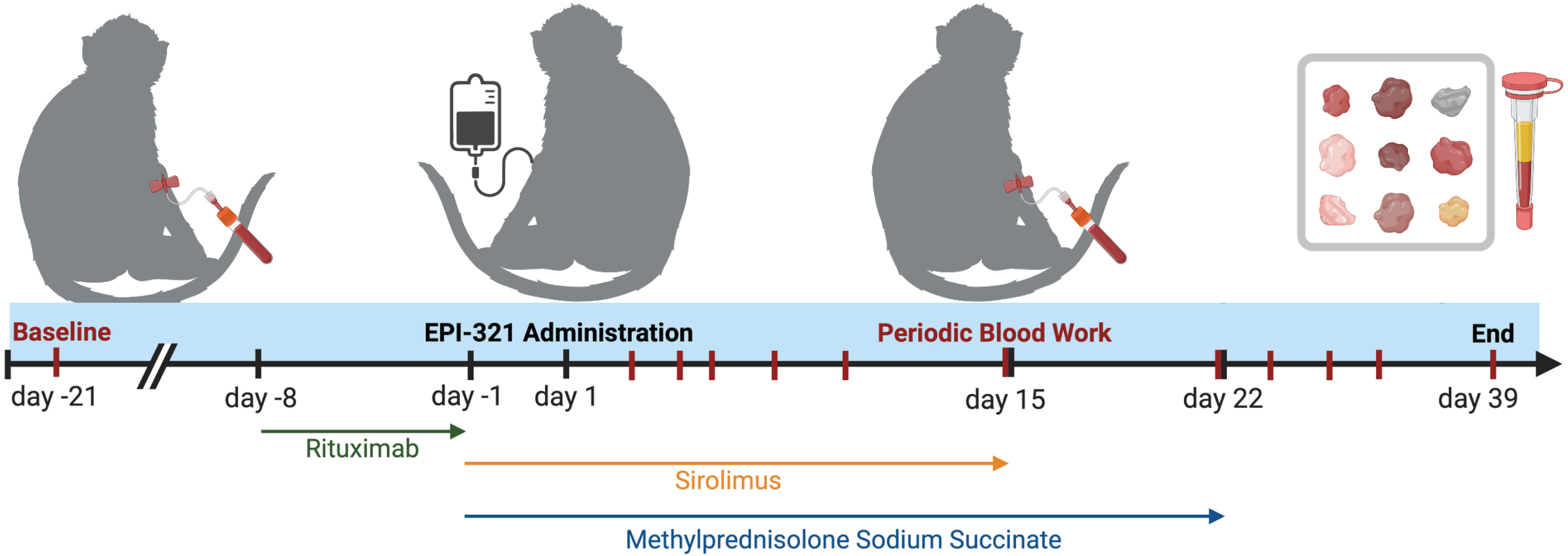


- EPI-321 uses **AAVrh74** to deliver an ultracompact dCas-based epigenetic modulator.
- Target: D4Z4 locus on Chr4 → permanent DUX4 repression achieved via DNA CpG methylation.
- Muscle-specific promoter ensures targeted action.

Mod, Epigenetic Modulator that Induces Suppression via DNA Methylation

Study Rationale and Design

- High-dose AAV is required for effective muscle delivery.
- **Class effects of AAV vectors in NHPs** include early immune-related toxicities such as **complement activation**, **thrombocytopenia**, and **elevated liver enzymes** within the **first week post-dosing**, occasionally necessitating **unscheduled necropsy** *(Hordeaux, J. et al., Molecular Therapy, 2024)*



Group Design and Dosing

- n=4 per group. 2 males, 2 females:
- EPI-321 administered as single IV infusion at high dose: **1.2E14 vg/kg** by dPCR (Equivalent to 3.6E14 vg/kg by qPCR[1])

	Test Article		Immunosuppression Regimen		
Group	Vehicle	EPI-321	*MPSS	Sirolimus	Rituximab
Vehicle	+				
EPI-321		+			
EPI-321 + MPSS		+	+		
EPI-321 + TripleIS		+	+	+	+

[1]Dobnik D, et al. Front. Microbio, 2019. *MPSS, methylprednisolone sodium succinate.

High-Dose EPI-321 is Safe and Well Tolerated in NHPs

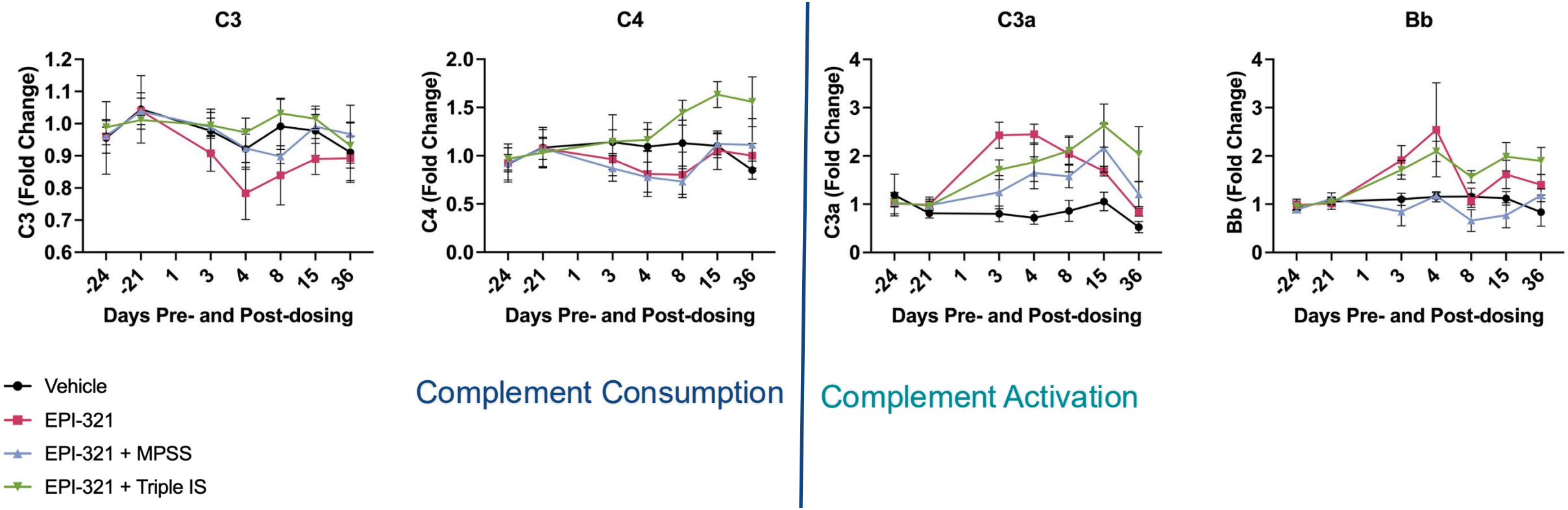
All animals survived to scheduled necropsy

No clinical findings, no anatomic pathology, normal weight, food and water intake

Mild, transient lab findings consistent with known AAV vector class toxicities

High-Dose EPI-321 is Safe and Only Leads to Mild and Reversible Complement Activation

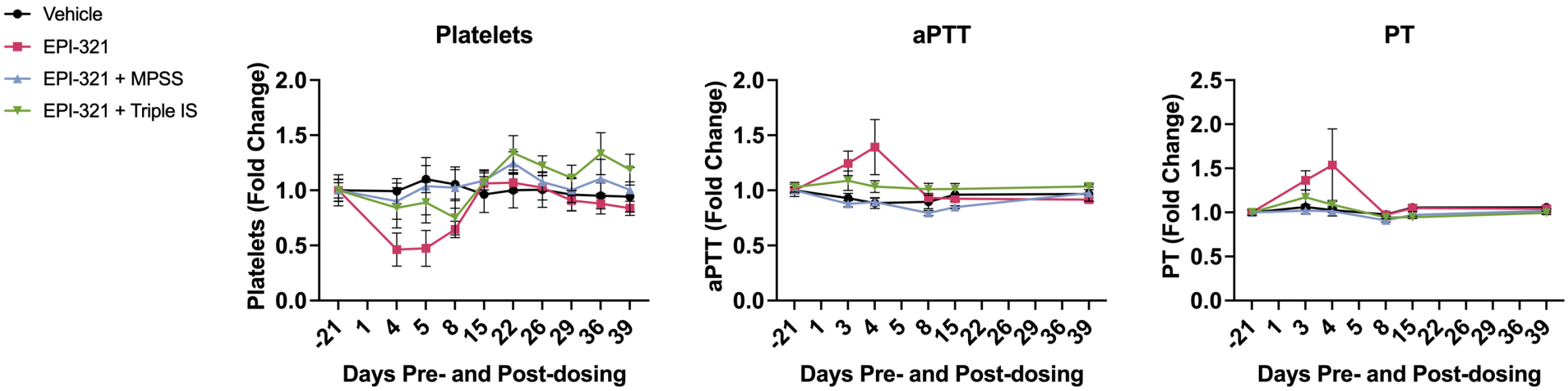
- EPI-321 dosing at day 1



- IS Regimens Attenuate Early and Mild Activation of Components of Complement Pathway Linked to AAV Class Effects

High-Dose EPI-321 is Safe and Only Leads to Mild, Transient, Thrombocytopenia and Coagulopathy

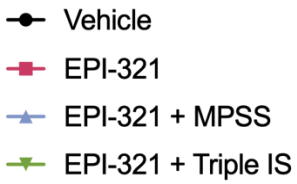
- EPI-321 dosing at Day 1

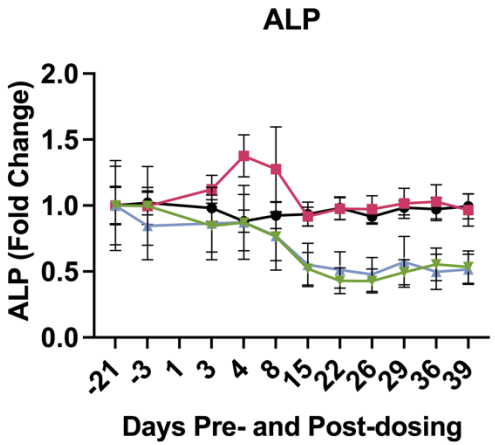


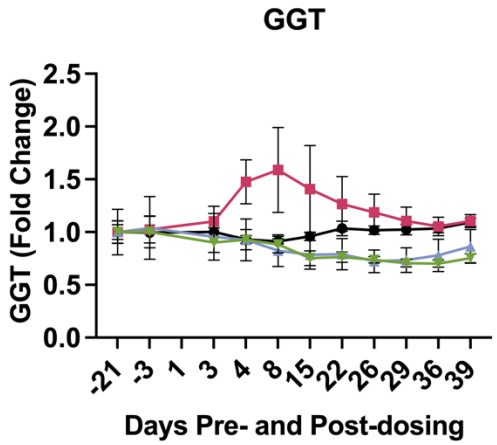
- IS Regimens Prevent Mild, Transient, Thrombocytopenia and Coagulopathy linked to AAV class effects

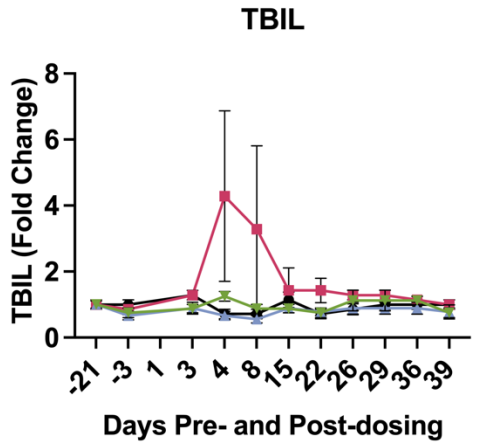
High-Dose EPI-321 is Safe and Only Leads to Transient Hepatobiliary Elevations

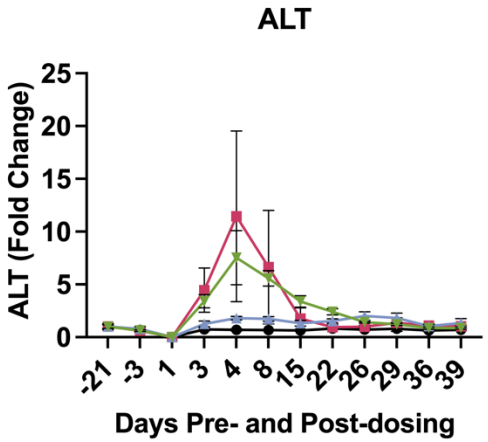
- EPI-321 dosing at day 1
- Serum Chemistry
- Hematology

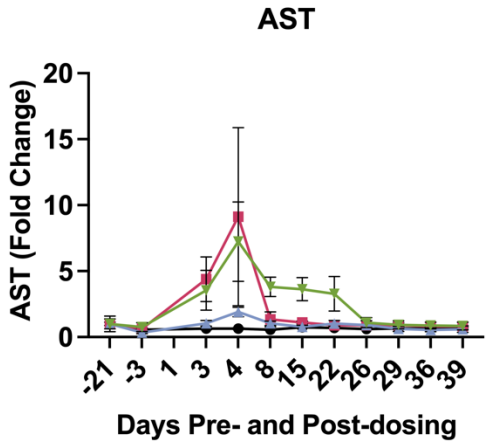


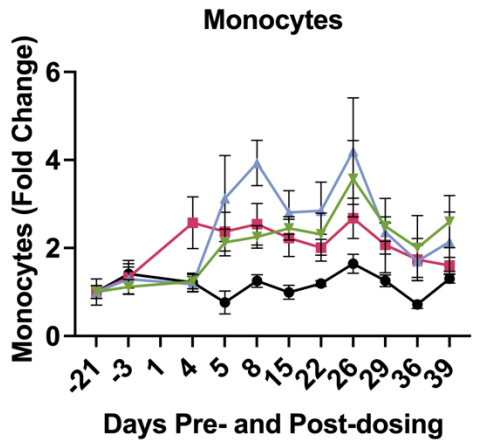








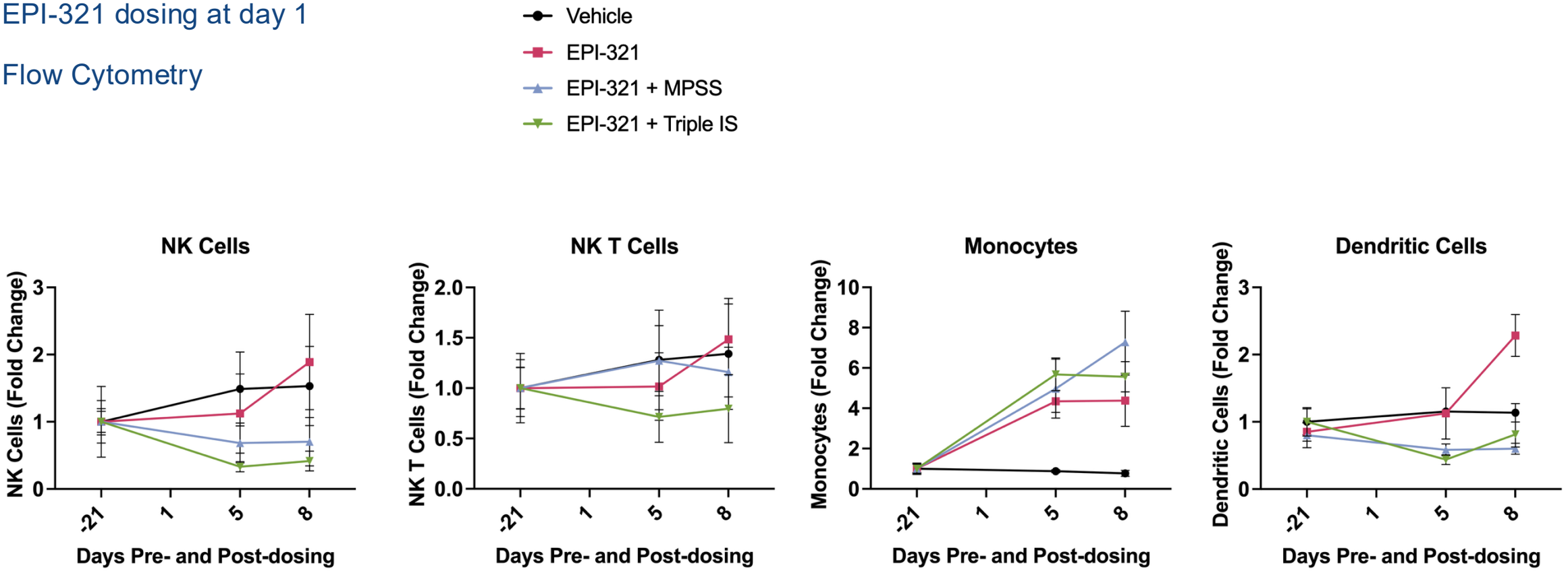




- IS Regimens Mitigate Transient Hepatobiliary Elevations linked to AAV class effect

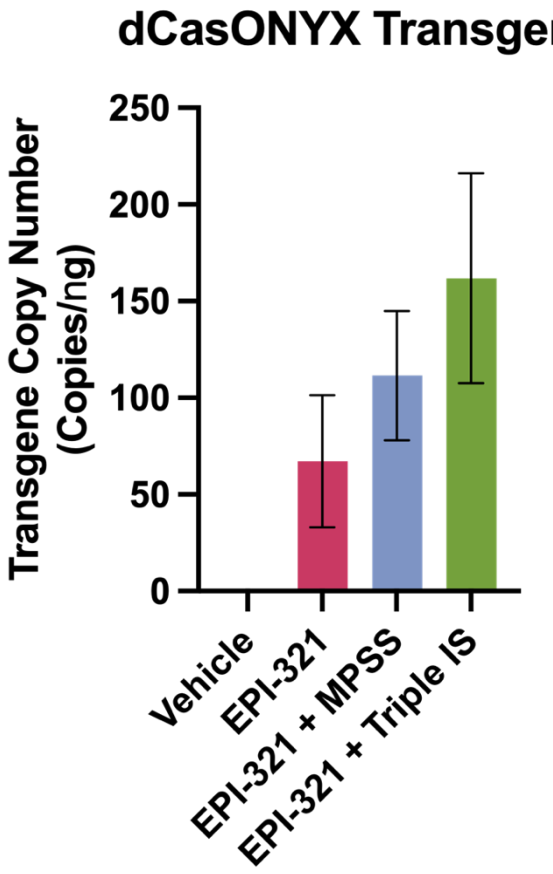
High-Dose EPI-321 is Safe and Only Leads to Mild Innate Immune Cell Activation

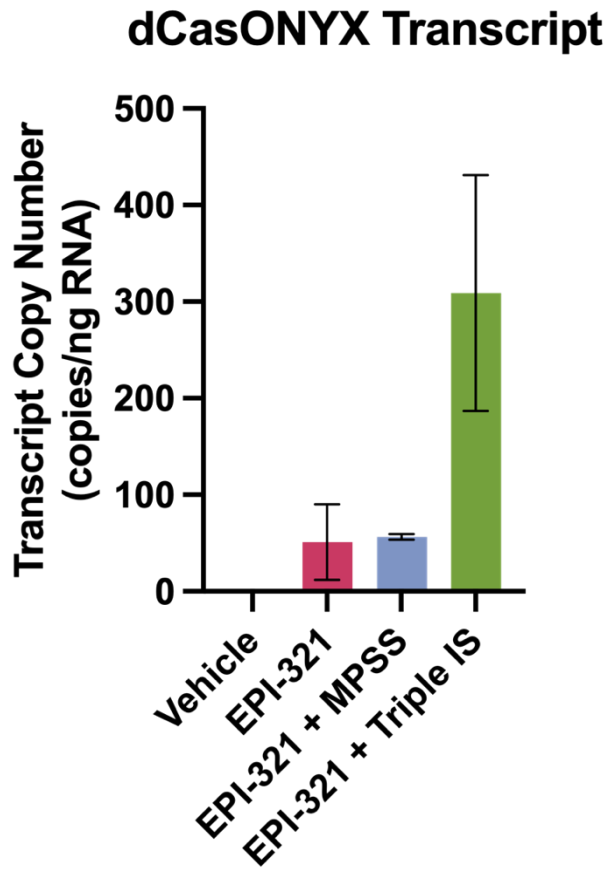
- EPI-321 dosing at day 1
- Flow Cytometry



- IS Regimens Attenuate Innate Immune Cell Activation linked to AAV class effect

IS Regimens Potentially Enhance EPI-321 Biodistribution to the Skeletal Muscles





Conclusion & Clinical Path for EPI-321

EPI-321 is safe and well tolerated. Mild, transient lab findings consistent with known AAV vector class toxicities: NOAEL is 6-times initial clinical dose.

Immunosuppression, specifically MPSS showed clear mitigation of AAV vector-related effects.

-delayed/suppressed components of complement activation.

-Improved platelet counts, stabilized coagulation parameters.

-Mitigated transient hepatobiliary changes.

-Attenuated innate immune cell activation

-Potentially enhanced biodistribution to skeletal muscles

First-in-human trial (EPI-321+Prednisone) beginning in 1H2025.

Other Presentations from **Epicrispr** This Week!

TUE 13th 6:00-7:30 PM	TUE 13th 6:00-7:30 PM	WED 14th 5:30-7:00 PM	THU 15th 5:30-7:00 PM
Courtney Klappenbach, **Poster Number, 617:** Directed evolution and characterization of Cas effectors in mammalian cells for expanded epigenome editing space	James Kim, **Poster Number, 967:** Small Scale AAV Bioreactor Optimization Demonstrates Iterative Titer Gains of rAAVrh74 Serotype EPI-321, a CRISPR-mediated Epigenetic Therapy	Dan Hart, **Poster Number, 1110:** Compact DNA Demethylase-activator combination Modulators for CRISPR Mediated Epigenetic Gene Activation	Surabhi Godbole, **Poster Number, 1939:** EPI-321 Development: Strategies to Establish a Robust and Scalable rAAVrh74 Upstream Manufacturing Process from 0.5 L to 1000 L Scale

Thank You!

7000 Shoreline Court, Suite 100 San Francisco,
CA 94080

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