

VB-101

Myocardial Regeneration Gene Therapy Discovery Dossier

Virelion Biotech | v0.1 | 2 September 2026

PROGRAM STATUS: DISCOVERY / PRE-EXPERIMENTAL

SCIENTIFIC-STATUS DISCLAIMER

VB-101 is a proposed research program, not a demonstrated gene-therapy product. Virelion has not constructed, produced, administered, or experimentally validated a VB-101 vector. No efficacy, safety, pharmacology, biodistribution, manufacturing, dosing, or clinical claims are made in this dossier.

1. Program Position

VB-101 is Virelion's discovery program for myocardial repair/regeneration after myocardial infarction (MI). The program is framed around controlled activation of endogenous cardiac regenerative biology rather than assuming that a single growth factor or constitutive proliferative signal will be sufficient.

Current lead hypothesis: regulated Hippo/YAP modulation with cardiomyocyte-focused activity and temporal control. This is a proposed hypothesis derived from published literature, not a selected or validated vector.

2. Target Product Profile

Attribute	Target state	Status
Intended use	Post-MI myocardial repair/regeneration	Proposed
Primary biological objective	Transient, productive regenerative state in cardiomyocytes	Proposed
Lead mechanism	Regulated Hippo/YAP modulation	Hypothesis
Target cell	Preferential cardiomyocyte activity	Desired
Expression	Controlled / reversible or otherwise time-limited	Design requirement
Functional outcome	Improved structure and ventricular function after injury	Future endpoint
Key safety requirements	No unacceptable arrhythmia, hypertrophy, fibrosis, vascular leak or systemic toxicity	Unknown
Clinical stage	None	Discovery / pre-experimental

3. Biological Rationale

3.1 Why cardiac regeneration is difficult

Adult mammalian cardiomyocytes have largely exited the proliferative program after maturation. Modern regeneration work therefore treats cell-cycle control, ploidy, sarcomere structure, metabolism, chromatin state and the post-injury microenvironment as a network of constraints rather than a single missing switch.

3.2 Why YAP/Hippo is the lead

YAP is a central downstream effector of Hippo signalling. Published work supports YAP as a regulator of cardiomyocyte proliferation and regeneration. A 2024 Nature Cardiovascular Research study reported that active YAP in adult mouse cardiomyocytes was associated with a renewal-competent cardiomyocyte state and with a multicellular niche involving C3-expressing fibroblasts and C3aR1-expressing macrophages.

A separate large-animal study used AAV9-mediated knockdown of the Hippo-pathway gene Salvador (Sav) in pigs after ischemia/reperfusion MI and reported improved ejection fraction, evidence of cardiomyocyte division and reduced scar size versus control vector. This gives the program a meaningful translational precedent without implying human efficacy.

3.3 Why temporal control is central

Persistent activation of proliferative pathways can become a liability. Recent studies have explored transient or conditional YAP-oriented approaches, including modified RNA and reversible AAV-based strategies, supporting the design principle that regenerative signalling should ideally have a controllable therapeutic window.

4. Candidate Payload Strategy

Candidate	Objective	Strength	Main risk	Program role
Regulated YAP activation	Renewal-state induction	Strong mechanism + recent reversible precedent	Persistent mitogenic activity	Lead hypothesis
Hippo/SAV suppression	Lift endogenous inhibition of YAP	Pig precedent	Pathway/off-target complexity	Lead comparator
Cyclin/CDK axis	Cell-cycle re-entry	Direct proliferation evidence	Incomplete/unproductive proliferation	Secondary
VEGF-family	Vascular support	Human cardiovascular gene-transfer precedent	Leak/oedema; not CM replacement	Secondary comparator
Wnt-family	Developmental/regenerative signalling	Preclinical repair evidence	Complex pathway effects	Exploratory

5. Conceptual Vector Architecture

This section is deliberately conceptual. It does not specify nucleotide sequences, cloning steps, production protocols, vector titres, animal dosing, or administration procedures.

Lead architecture: delivery platform (AAV-family or transient non-viral alternative) -> cardiac-enriched regulatory control -> temporally controlled regenerative signal -> cardiomyocyte state/cell-cycle modulation -> tissue repair -> functional and safety endpoints.

5.1 Platform candidates

Platform	Potential advantages	Major liabilities
AAV-family	Cardiac gene-delivery precedent; durable expression	Off-target/liver exposure; immune barriers; repeat-dose limitations; cargo constraints
Transient non-viral RNA	Naturally time-limited expression; attractive for regenerative pulses	Delivery/distribution and durability limitations
Regional/local delivery	Can increase local exposure	Invasive or technically demanding

5.2 Regulatory element concept

The final program should empirically compare cardiac-enriched regulatory elements rather than assuming that one promoter is universally optimal. Candidate classes include cardiac troponin-associated elements, ventricular

cardiomyocyte regulatory elements and compact cardiac enhancers. Cross-species performance and off-target expression must be measured before selection.

5.3 Delivery concept

Systemic, regional/intracoronary and local myocardial delivery each have different trade-offs between exposure, specificity, invasiveness and translational complexity. Route selection remains an experimental question.

6. Discovery-Phase Project Plan

Aim 1 - Computational target and evidence discovery

- Map Hippo/YAP, cell-cycle, Wnt, angiogenesis and microenvironment literature.
- Re-analyse public cardiac single-cell/single-nucleus and spatial datasets.
- Define regenerative cardiomyocyte signatures and distinguish proliferation from stress/hypertrophy.
- Rank candidate payloads using evidence, specificity and safety considerations.

Aim 2 - Human-cell feasibility

- Use human iPSC-derived cardiomyocytes and, where appropriate, engineered cardiac tissues.
- Measure target engagement, cell-cycle entry, mitosis/cytokinesis, structure, contractility/electrophysiology and stress.
- Assess fibroblast, endothelial and immune off-target responses where relevant.

Aim 3 - Delivery/platform proof of concept

- Compare expression specificity and kinetics across candidate platforms.
- Focus initially on useful specificity and controllability rather than maximum expression.
- Use an institutional vector core or qualified partner for vector work.

Aim 4 - Preclinical cardiac proof of concept

- Move from small-animal mechanism to larger-animal translation only after predefined gates are met.
- Use structural, functional, mechanistic and safety outcomes together.

7. Suggested 12-Month Timeline

Period	Main activity	Evidence target
Months 0-2	Literature + public-data analysis	Mechanism ranked
Months 2-4	Human-cell assay design	Assay-ready
Months 4-6	Mechanism feasibility	Human-cell proof of concept
Months 6-8	Delivery/platform comparison	Lead architecture
Months 8-10	Small-animal proof of concept	Preliminary efficacy/safety
Months 10-12	Replication + translational planning	Large-animal readiness decision

8. Access and Resource Blueprint

Access tier	Requirements
Minimum useful	iPSC-CM culture; fluorescence/confocal imaging; qPCR/protein assays; viability/proliferation assays; contractility/electrophysiology access; institutional vector core
Higher tier	3D cardiac tissue; spatial transcriptomics/multiplex imaging; single-cell sequencing; cardiovascular animal imaging; large-animal infrastructure

Before lab access, Virelion can still complete a substantial discovery package through public-data analysis, evidence synthesis, target ranking, assay design, safety endpoint definition and collaborator-facing planning.

9. Risk and Feasibility

Risk	Impact	Likelihood	Mitigation concept
Persistent YAP activity	High	Medium-High	Temporal control; explicit stopping criteria
Off-target expression	High	High	Regulatory-element comparison; biodistribution assessment
Proliferation without regeneration	High	High	Require mitosis/cytokinesis + tissue/function endpoints
Arrhythmogenic remodelling	High	Medium	Electrical and rhythm assessments
Immune response	High	Medium	Platform/route evaluation; immune monitoring
Inadequate cardiac delivery	High	High	Compare delivery concepts; quantify target exposure
Species translation failure	High	Medium	Human-cell models + large-animal stage
VEGF-related vascular leak	High	Medium	Keep angiogenic approaches as controlled comparators

10. Critical Go/No-Go Logic

VB-101 should not advance solely because a candidate increases a proliferation marker. The evidence chain should progress from target engagement -> cardiomyocyte cell-cycle entry -> evidence of completed mitosis/cytokinesis -> functional new myocardium -> improved ventricular structure/function -> acceptable electrical and systemic safety.

A candidate should be redesigned or stopped if it produces hypertrophy/arrhythmia without meaningful regeneration, requires impractically nonspecific exposure, fails in human cardiac models, or shows no structural/functional consequence despite target engagement.

11. Honest Current Status

Area	Current status
Disease rationale	Established literature
Regeneration biology	Strong but incomplete literature
Lead mechanism	Strong preclinical rationale; not validated by Virelion
Exact payload	Not selected
Promoter/enhancer	Not selected
Capsid/platform	Not selected
Delivery route	Not selected
Virelion human-cell efficacy	Not tested
Virelion animal efficacy	Not tested
Safety	Not tested
Manufacturing	Not established
Clinical feasibility	Concept only

12. Website-Ready Description

VB-101 - Myocardial Regeneration Gene Therapy | Discovery

VB-101 is Virelion's discovery program exploring gene-transfer strategies to promote myocardial repair after myocardial infarction. The program is focused on controlled activation of endogenous cardiac regenerative biology, with current work centred on the Hippo/YAP pathway and cardiomyocyte state regulation.

Our design framework evaluates therapeutic payloads, cardiac-enriched expression strategies and delivery platforms with an emphasis on temporal control, cardiomyocyte specificity and translational safety. The program is currently at the literature and computational discovery stage; no VB-101 vector has been manufactured or experimentally validated by Virelion.

13. Key References

1. Bois A, Grandela C, Gallant J, Mummery C, Menasché P, et al. Revitalizing the heart: strategies and tools for cardiomyocyte regeneration post-myocardial infarction. *npj Regenerative Medicine*. 2025;10:6. DOI: 10.1038/s41536-025-00394-2.
2. Koopmans T, van Rooij E. Molecular gatekeepers of endogenous adult mammalian cardiomyocyte proliferation. *Nature Reviews Cardiology*. 2025;22:857-882. DOI: 10.1038/s41569-025-01145-y.
3. Li RG, Li X, Morikawa Y, et al. YAP induces a neonatal-like pro-renewal niche in the adult heart. *Nature Cardiovascular Research*. 2024;3:283-300. DOI: 10.1038/s44161-024-00428-w.
4. Dar GM. YAP at the heart of cardiac regeneration. *Nature Reviews Cardiology*. 2026. DOI: 10.1038/s41569-026-01328-1.
5. Gene therapy knockdown of Hippo signaling induces cardiomyocyte renewal in pigs after myocardial infarction. PMID: 34193613.
6. Reversible gene therapy for cardiac repair and protection. *Nature Cardiovascular Research*. 2025;4:1596-1597. DOI: 10.1038/s44161-025-00747-6.
7. Cardiomyocyte-Specific Overexpression of Activated Yes-Associated Protein Modified-RNA Promotes Cardiomyocyte Proliferation and Myocardial Regeneration. PMID: 39470057.
8. Kim Y, Landstrom AP, Shah SV, Wu JC, Seidman CE. Gene Therapy in Cardiovascular Disease: Recent Advances and Future Directions in Science: A Science Advisory From the American Heart Association. *Circulation*. 2024;150:e471-e480. DOI: 10.1161/CIR.0000000000001296.
9. Chamberlain K, Riyad JM, Weber T. Cardiac gene therapy with adeno-associated virus-based vectors. PMID: 28169951.
10. Losordo DW, et al. Gene therapy for myocardial angiogenesis: initial clinical results with direct myocardial injection of phVEGF165 as sole therapy for myocardial ischemia. *Circulation*. 1998;98:2800-2804. PMID: 9860779.
11. Rosengart TK, et al. Angiogenesis gene therapy: phase I assessment of direct intramyocardial administration of an adenovirus vector expressing VEGF121 cDNA. PMID: 10430759.
12. Vascular endothelial growth factor gene transfer therapy for coronary artery disease: a systematic review and meta-analysis. PMID: 30035366.

14. Evidence Classification Policy

Published = directly supported by external literature. Inferred = reasoned interpretation of multiple sources. Proposed = Virelion design hypothesis not experimentally tested. Unknown = requires new data. This classification should be retained in future revisions so that the dossier never implies experimental progress that has not occurred.