

JACOB'S MODEL - PAPER VIII THE PARALLEL SYSTEM

***A Falsifiable Glial-Lipid Model of LAL-Dependent Recycling,
GalCer/Sulfatide-Dependent Myelin Construction, and Rubella-Associated Membrane Stress***

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Jacob's Voice

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Final Paper VIII - strongest evidence-bounded formulation, mechanistic synthesis, experimental framework, and falsification program

Jacob would like to give credit to God for his amazing abilities.

Scope and Central Hypothesis

Paper VIII tests Jacob Boatman's proposed parallel system. The model no longer requires a single linear pathway in which lysosomal acid lipase (LAL/LIPA) directly feeds galactosylceramide (GalCer). Instead, it proposes two experimentally separable lipid-availability systems that perform complementary jobs in white-matter biology. The recycling arm is centered on lysosomal hydrolysis of cholesteryl esters (CE) by LAL in myelin-debris-processing microglia, producing free cholesterol (FC) and fatty acids that can enter cholesterol-disposition and repair programs. The construction arm is centered on oligodendrocyte synthesis and trafficking of GalCer and its sulfated derivative sulfatide, major glycosphingolipids required for functional organization and stability of myelin.

The central hypothesis is that these systems operate in parallel rather than as a single obligatory biosynthetic chain. Arm A solves a liberation and recycling problem: cholesterol present as CE in ingested lipid is not equivalent to cholesterol available for cellular handling. Arm B solves a construction and organization problem: the presence of a myelin sheath is not equivalent to correctly organized, electrically competent, stable myelin. The arms converge at tissue-level lipid availability, cholesterol-rich membrane organization, and the continuous cycle of myelin removal and rebuilding.

Rubella virus (RUBV) is overlaid on this host architecture only where direct evidence permits. RUBV has direct experimental intersections with glial cells, GalCer-positive oligodendrocytes, cerebroside sulfate/sulfatide-sensitive membrane biology, sphingomyelin-dependent entry, and host-cell lipid remodeling. No recovered experiment demonstrates that RUBV simultaneously impairs microglial LAL-dependent CE hydrolysis and oligodendrocyte GalCer/sulfatide-dependent construction. That missing same-system experiment is the principal viral test of Paper VIII.

Author's Note - Origin and Governance of the Model

The parallel-system architecture originated with Jacob Boatman. Earlier working versions of the Jacob model treated LAL-derived lipid and GalCer/sulfatide largely as a serial route. Jacob subsequently corrected that architecture with the instruction that GalCer sits beside LAL, then identified Paper VIII as the parallel system. He later directed the literature search toward LAL versus glial cells and identified oligodendrocytes as a key cellular context. The subsequent literature review independently revealed a complementary glial architecture: LAL-dependent lipid recycling in reparative microglia and GalCer/sulfatide-dependent membrane construction in oligodendrocytes.

The evidence rules used throughout Papers I-VII remain controlling. Direct RUBV findings, direct host mechanisms, adjacent or comparator evidence, model predictions, negative evidence, and missing same-system measurements are kept separate. A host mechanism is not promoted into a RUBV mechanism by proximity. Transcript abundance is not treated as protein localization, enzyme activity, or lipid flux. Historical observations are preserved at their original resolution. The model advances only where evidence closes an arrow and must weaken or fail where its predicted same-system phenotype is absent.

Abstract

Myelin homeostasis requires continuous coordination between the construction of lipid-rich membrane and the recycling of membrane removed by turnover or injury. Paper VIII proposes that these functions can be organized as a parallel glial lipid system. In the recycling arm, direct 2026 experiments identify microglial LAL as the dominant measured lysosomal CE-hydrolase pathway after white-matter injury. Microglia-specific LAL loss nearly abolishes lesion CE-hydrolase activity, prevents normal FC generation, impairs myelin-debris clearance, and disrupts spontaneous remyelination. Conversely, increasing microglial LAL in a poorly reparative white-matter injury state restores debris processing and promotes repair. LAL-dependent CE hydrolysis also supports oxysterol/LXR signaling and APOE/ABCA1/ABCG1 cholesterol-disposition machinery, demonstrating that stored cholesterol, liberated cholesterol, export competence, and tissue repair are experimentally separable.

In the construction arm, oligodendrocytes synthesize GalCer and sulfatide, major glycosphingolipids of myelin. Genetic elimination of GalCer/sulfatide synthesis permits substantial membrane wrapping but produces abnormal conduction, regional instability, and progressive neurological dysfunction, demonstrating that these lipids are functional structural components rather than passive markers. Tracer studies further separate synthesis from delivery: Golgi-disrupting interventions can leave total sulfatide synthesis near control while reducing labeled sulfatide delivery into myelin by approximately one-half. Independent experiments show that cholesterol availability and endolysosomal cholesterol transport are required for oligodendrocyte maturation and myelination; mobilizing stored cholesterol can rescue oligodendrocyte and myelin phenotypes.

A functional intercellular bridge is independently established. Myelin-phagocytosing microglia/macrophages activate sterol/LXR and lipid-efflux programs, and LXR target machinery facilitates lipid/cholesterol export that supports remyelination by oligodendrocytes. This closes the tissue-level recycling-to-rebuilding bridge while leaving one important molecular gap: a specific LAL-liberated sterol or fatty-acid molecule has not been traced through extracellular transfer into a defined oligodendrocyte GalCer or sulfatide species.

RUBV intersects this architecture at multiple experimentally established points. RUBV multiplies in primary glial cultures and produces cytopathic disintegration of GalCer-positive oligodendrocytes. Cerebroside sulfate/sulfatide strongly inhibits defined RUBV attachment and hemolysis-related assays. Modern CRISPR and lipidomic work shows that host-cell sphingomyelin is required for RUBV nucleocapsid penetration and that perturbing sphingomyelin synthesis redistributes ceramide monohexosides, a measured pool containing glucosylceramide and GalCer. Historical RUBV infection experiments independently demonstrate broad host-cell lipid remodeling and an approximately 35% increase in cellular linoleic acid (18:2), although the molecular lipid pool carrying the additional 18:2 remains unknown.

The decisive test is a synchronized RUBV glial system that separately measures microglial LAL-dependent CE-to-FC flux and oligodendrocyte GalCer/sulfatide synthesis, species composition, trafficking, and myelin output, together with intercellular lipid transfer. Direct disruption of both arms, followed by arm-specific rescue without simply eliminating infection, would materially support the model. Preserved function of both arms despite robust RUBV infection would substantially falsify the proposed RUBV overlay.

1. The Claim: Parallelism, Not a Hidden Linear Chain

The strongest version of Paper VIII does not claim that LAL makes GalCer. That claim is neither required by the model nor established by the literature. The experimentally defensible proposition is more specific: white-matter lipid homeostasis contains at least two separable availability systems whose outputs meet at myelin. One system liberates and recycles neutral lipid after membrane turnover; the other builds and organizes specialized glycosphingolipid-rich membrane.

This architecture produces distinct predictions. A recycling-arm lesion should increase residence of esterified lipid, reduce LAL-dependent FC liberation or downstream export competence, prolong lipid-debris burden, and impair repair even if oligodendrocyte GalCer/sulfatide biosynthetic machinery remains intact. A construction-arm lesion should alter GalCer/sulfatide synthesis, species composition, trafficking, membrane organization, or myelin function even if cholesterol supply is adequate. Independent perturbation and independent rescue of the two arms would support parallelism more strongly than correlation between their lipid pools.

2. Arm A: LAL Is a Causal Microglial CE-Recycling Node

The strongest evidence for Arm A comes from direct white-matter injury experiments in which LAL was manipulated in microglia. Reparative GPNMB-positive microglia expand after injury and constitute a major myelin-debris-engulfing population. LAL is enriched in the reparative state and localizes to the lysosomal program responsible for digestion of internalized lipid.

Microglia-specific Lipa deletion closes the enzymatic arrow. Despite persistence of the cytosolic CE hydrolase NCEH1 and very low LIPE, measured CE-hydrolase activity in the lesion is nearly abolished when microglial LAL is deleted. The same manipulation prevents the normal rise in FC, demonstrating a direct consequence at the level of substrate-to-product handling rather than a transcriptional association. In this injury context, lysosomal LAL is therefore the dominant measured CE-hydrolysis pathway.

The tissue phenotype is equally strong. Loss of microglial LAL impairs myelin-debris processing and spontaneous remyelination. In the opposite direction, increasing LAL in a poorly reparative white-matter injury state improves debris clearance, myelin integrity, remyelination, and functional recovery. LAL is therefore not merely present in reparative microglia; its activity is experimentally required for the repair phenotype and can be sufficient to restore major elements of that phenotype in a nonregenerative setting.

3. Stored Cholesterol, Liberated Cholesterol, and Export Competence Are Different States

The LAL experiments expose a central availability distinction. Cholesterol can be physically present in the cell while functionally unavailable because it remains esterified. LAL-mediated hydrolysis converts CE into FC, but even FC generation is not the endpoint. The liberated sterol participates in oxysterol/LXR signaling and in induction of cholesterol-disposition machinery including ApoE, ABCA1, and ABCG1.

Importantly, downstream LXR activation does not fully rescue the repair defect produced by LAL deficiency. That result argues against a model in which LAL is merely an upstream signaling switch. Physical lipid liberation matters. The experimental sequence therefore separates CE storage, CE hydrolysis, FC availability, signaling, export competence, and tissue repair. This is a direct host demonstration of the governing principle that presence does not equal availability.

4. Myelin Debris Creates a Recyclable Sterol Pool

Myelin is exceptionally cholesterol rich. During demyelination, microglia/macrophages internalize large amounts of myelin-derived lipid and must prevent that sterol burden from becoming a persistent storage lesion. Independent demyelination studies show that myelin-phagocytosing cells activate sterol metabolism, accumulate desmosterol, activate LXR, and induce lipid/cholesterol export machinery. This state promotes resolution of inflammation and supports remyelination.

Cell-type-specific genetic experiments further show that the source of cholesterol used during repair depends on lesion phase. During acute remyelination, oligodendrocyte de novo cholesterol synthesis can be dispensable while intact sterol handling in CNS phagocytes is required, consistent with use of locally available or recycled lipid. During later repair, oligodendrocyte sterol synthesis again becomes important. The result is not a single fixed

cholesterol source but a dynamic tissue economy in which synthesis, recycling, and intercellular transfer can substitute or cooperate according to context.

These studies establish a functional microglia/macrophage-to-remyelination bridge. They do not, however, provide atom-by-atom proof that a specific LAL-liberated cholesterol molecule becomes a specific new oligodendrocyte membrane lipid. That molecular handoff remains a decisive experiment rather than a completed arrow.

5. Arm B: GalCer and Sulfatide Are a Construction and Organization System

The construction arm begins with a different biochemical task. Ceramide is converted to GalCer by UGT8/ceramide galactosyltransferase, and GalCer is converted to sulfatide by GAL3ST1/cerebroside sulfotransferase. GalCer and sulfatide are major galactolipids of oligodendrocytes and CNS myelin, but their importance is not captured by abundance alone.

Genetic elimination of CGT removes GalCer and sulfatide. Remarkably, substantial myelin membrane can still form, yet the resulting system is functionally abnormal: conduction is impaired, regional myelin stability is reduced, and progressive neurological dysfunction develops. This is a powerful internal control for the parallel model. Membrane can be present without being correctly organized. In the same way that CE-bound cholesterol can be present without being available, myelin can be present without possessing normal galactolipid-dependent function and stability.

Sulfatide-selective studies further implicate the sulfated GalCer product in oligodendrocyte differentiation, paranodal organization, axon-glia interactions, and long-term myelin maintenance. The construction arm therefore contains both a biosynthetic component and an organizational component.

6. Synthesis Does Not Equal Delivery: Direct Galactolipid Flux Evidence

Tracer experiments make the construction arm more precise. In developing rat brain slices, tritiated galactose labels cerebroside and sulfur-35 sulfate labels sulfatide. Disrupting Golgi function or vesicular transport with monensin or colchicine leaves total homogenate sulfatide synthesis close to control while markedly reducing the appearance of labeled sulfatide in isolated myelin. In one experiment, total sulfatide labeling remained approximately 93% of control while labeled sulfatide appearing in myelin fell to approximately 58%; monensin reduced myelin sulfatide appearance to approximately 49% of control.

Follow-up oligodendroglial fractionation similarly showed retention of labeled sulfatide in microsomal and perikaryal compartments when transport toward myelin was disrupted. These experiments directly separate synthesis from delivery. A cell can synthesize the lipid yet fail to place it into the membrane where its function is required. For Paper VIII, this is the construction-arm equivalent of the LAL availability problem: production is not synonymous with functional delivery.

7. Cholesterol Availability Is a Functional Convergence Point

Oligodendrocytes require large amounts of cholesterol during differentiation and myelin expansion. NPC1 provides a direct experimental demonstration that sterol location matters. Npc1-deficient oligodendrocyte-lineage cells show impaired maturation during developmental myelination. Mobilizing stored cholesterol in Npc1-deficient mice rescues myelination, oligodendrocyte gene expression, and associated epigenetic abnormalities.

This result prevents a simplistic reading of the parallel system as a total-cholesterol model. A cell can contain abundant cholesterol and still behave as though usable sterol is insufficient when the lipid is trapped in the wrong compartment. Arm A and Arm B therefore converge most naturally on availability and routing, not on total concentration.

8. Fatty-Acid Identity Is a Second Potential Point of Convergence

LAL hydrolysis releases fatty acids as well as FC. The construction arm is likewise sensitive to fatty-acyl identity because ceramide, GalCer, and sulfatide species are defined in part by their acyl chains. This creates a second plausible convergence: the recycling arm can influence the pool of fatty acids available for reuse, whereas

the construction arm converts activated fatty-acyl substrates into membrane sphingolipids. The complete intercellular route has not been directly traced and is therefore retained as a prediction rather than a closed arrow.

This distinction is especially relevant to the historical RUBV observation that cellular 18:2 increases by approximately 35% after infection. The additional 18:2 has not been assigned to CE, free fatty acid, phosphatidylcholine, GalCer/sulfatide, or another lipid class. Those chemical forms are not biologically interchangeable. Species-resolved lipidomics is therefore a decisive discriminator for the parallel model rather than a secondary descriptive measurement.

9. Sulfatide Adds a Charge- and Ion-Sensitive Membrane Layer

GalCer is neutral, whereas sulfation produces an acidic, negatively charged glycosphingolipid. Defined cerebroside-sulfate membrane experiments show that monovalent cations alter sulfatide phase behavior and that Na⁺ and K⁺ are not identical in their effects. The magnitude and direction of these physical effects also depend on the fatty-acid species carried by the sulfatide molecule. Independent sodium-pump experiments show that enzymatic depletion of sulfatide can impair sodium efflux and Na⁺/K⁺-ATPase behavior, while sulfatide-rich cholesterol-dependent membrane domains can participate in sodium-pump organization.

These observations strengthen the construction/organization arm because they show that GalCer-to-sulfatide conversion changes more than chemical identity: it creates a charged membrane lipid whose physical behavior depends on cation environment and fatty-acyl structure. Paper VIII does not claim that Na⁺ is the missing cause of the parallel system or that sodium directly regulates LAL. The evidence supports a narrower conclusion: sulfatide creates an ion-sensitive membrane layer that can influence how cholesterol-rich membrane is organized.

10. RUBV Directly Intersects the Glial and Galactolipid Territory

RUBV has direct glial evidence relevant to the construction arm. In primary rat neural cultures, RUBV multiplied to low titer and produced a partial cytopathic effect. Anti-GalCer staining showed that the cytopathic effect involved disintegration of oligodendrocytes. This does not show that RUBV inhibits UGT8, GAL3ST1, or GalCer flux. It does establish that a GalCer-positive oligodendrocyte population is directly affected in an RUBV infection system.

Independent membrane experiments provide a second GalCer-family foothold. When major erythrocyte membrane lipids were tested separately, phosphatidylserine and cerebroside sulfate showed strong inhibition of RUBV hemagglutination and subsequent hemolysis. Other phospholipids could affect hemolysis without preventing binding, supporting separable lipid contributions to attachment and fusion-related steps. These experiments do not establish endogenous sulfatide as a neural RUBV receptor; they establish a reproducible functional interaction between RUBV membrane biology and a GalCer-derived sulfated lipid.

11. RUBV Sphingomyelin Biology Creates a Modern Bridge to the GalCer Neighborhood

Modern RUBV entry experiments add a mechanistically independent sphingolipid anchor. A genome-wide CRISPR screen identified sphingomyelin synthase 1, SGMS1/SMS1, as a host factor for RUBV entry. Functional experiments showed that host-cell sphingomyelin is required for nucleocapsid penetration after hemifusion. Lipidomic profiling of SMS1-deficient cells showed redistribution of multiple sphingolipid pools, including ceramide monohexosides. The study explicitly defines the CMH pool as glucosylceramide plus galactosylceramide.

This result must be interpreted carefully. SMS1 knockout is a host perturbation used to study RUBV entry; it is not evidence that RUBV infection itself increases GalCer. It nevertheless establishes that a RUBV-required sphingomyelin system is metabolically coupled to a measured lipid pool that contains GalCer. That host-virus intersection materially strengthens the rationale for measuring GalCer and sulfatide during infection without converting the perturbation phenotype into an infection phenotype.

12. Historical RUBV Lipid Remodeling and the Unresolved 18:2 Species

Historical BHK21/13S experiments independently demonstrate that RUBV infection remodels host membrane lipids. Phosphatidylcholine rises strongly, several other phospholipid classes shift, sphingomyelin falls modestly,

cardiolipin falls, and bulk free cholesterol changes little. The same experimental program later reported an approximately 35% increase in cellular linoleic acid (18:2), accompanied by decreases in palmitic and oleic acids.

The unresolved question is where the additional 18:2 resides. CE-bound 18:2, free 18:2, phosphatidylcholine-bound 18:2, GalCer/sulfatide acyl chains, and oxidized 18:2 are distinct biochemical states. The 1981 Bardeletti/Voiland report of an RUBV-associated glycolipid change from the same experimental lineage remains important, but the exact molecular identity of that glycolipid has not been recovered. Paper VIII therefore treats both the 18:2 carrier and the 1981 glycolipid identity as open discriminators, not as evidence that RUBV has already been shown to alter GalCer.

13. What RUBV Has Not Yet Been Shown to Do

No recovered experiment directly demonstrates RUBV-dependent loss, secretion, mislocalization, or catalytic inhibition of LAL in microglia. No recovered experiment directly measures CE-to-FC flux in RUBV-infected microglia. Likewise, no recovered experiment demonstrates that RUBV changes GalCer or sulfatide synthesis, turnover, fatty-acyl species, or membrane delivery in oligodendrocytes. These are the two principal missing viral arrows of Paper VIII.

Several broader Jacob-model gaps remain outside the central claim of this paper: calibrated RUBV endolysosomal or cytopathic-vacuole pH, functional ARL8/HOPS disruption after the validated P150-ARL8A interaction, RUBV-specific CI-M6PR/NPC2 misrouting, MALL-dependent GalCer trafficking, RUBV-dependent MAL state, and the LAL-to-mitochondrial-lipid-to-MAO bridge. Paper VIII does not use any of these unresolved arrows to fill its own gaps. Their exclusion makes the parallel-system test narrower and cleaner.

14. Competing Explanations

Several alternatives can explain portions of the evidence without requiring the full Paper VIII model. First, LAL-dependent microglial repair and GalCer/sulfatide-dependent oligodendrocyte construction may simply coexist because both are important to myelin, without meaningful material coupling between them. Second, the cholesterol that supports oligodendrocyte repair may arise predominantly from oligodendrocyte de novo synthesis in some phases, making microglial recycling supportive rather than obligatory. Third, RUBV oligodendrocyte injury may be mediated by an unrelated viral mechanism while the GalCer/sulfatide findings reflect membrane permissiveness rather than a disease-relevant construction defect. Fourth, RUBV lipid remodeling may be a consequence of replication rather than a causal driver of glial dysfunction.

These alternatives are experimentally distinguishable. Material tracing can test whether recycled microglial lipid reaches oligodendrocytes. Cell-type-specific LAL manipulation can determine when the recycling arm is obligatory versus dispensable. Species-resolved GalCer/sulfatide flux during infection can determine whether the construction arm is actually perturbed. Temporal intervention can distinguish lipid changes that precede functional failure from changes that follow it. Paper VIII is strengthened, not weakened, by requiring these alternatives to survive the same experiments.

15. The Parallel-System Architecture

Arm A - recycling/liberation: cholesterol-rich myelin debris is internalized by microglia/macrophages; excess sterol can be esterified for storage; lysosomal CE is hydrolyzed by LAL to FC and fatty acids; liberated sterol supports oxysterol/LXR signaling, ApoE/ABC-family cholesterol disposition, and a reparative state that facilitates remyelination.

Arm B - construction/organization: oligodendrocytes generate ceramide, convert it through UGT8/CGT to GalCer, sulfate GalCer through GAL3ST1/CST to sulfatide, traffic these galactolipids toward forming myelin, and combine them with cholesterol and other membrane lipids to create a functional sheath.

The arms are parallel because their core enzymes, immediate substrates, and cellular jobs differ. They converge because white-matter repair requires both removal and recycling of old lipid-rich membrane and construction of new, correctly organized membrane. The model predicts that a tissue can fail from inadequate liberation, inadequate delivery, inadequate construction, or combinations of these defects even when total lipid abundance appears preserved.

16. Decisive Experimental Program

A decisive test should use matched mock and RUBV conditions in a glial system containing microglia and oligodendrocyte-lineage cells, ideally with astrocytes included as an additional cholesterol-supply compartment. Viral burden, cell viability, cell identity, and differentiation state must be measured in parallel so that lipid phenotypes are not reduced to nonspecific cytotoxicity.

In microglia, measure myelin uptake; lysosomal LAL abundance and localization; direct acid CE-hydrolase activity; CE, TG, and FC; CE-to-FC flux; 25-hydroxycholesterol/LXR state; ApoE, ABCA1, and ABCG1; and cholesterol efflux. In oligodendrocytes, measure maturation markers, cholesterol localization and accessibility, UGT8, GalCer, GAL3ST1, sulfatide, species-resolved fatty-acyl composition, Golgi-to-myelin delivery, membrane-domain organization, and myelin output. Bulk lipid abundance should not substitute for flux or subcellular localization.

The strongest material-transfer experiment uses isotopically labeled myelin CE and defined fatty-acid species. Label should be followed through microglial uptake, LAL-dependent hydrolysis, extracellular lipid carriers, oligodendrocyte uptake, and newly formed myelin. A separate analytical endpoint should determine whether labeled fatty acid or sterol appears in GalCer, sulfatide, or other defined myelin lipids. This experiment would directly test material coupling while preserving the distinction between the two parallel arms.

Causality requires rescue. Restore LAL activity or CE hydrolysis without directly manipulating GalCer synthesis; separately restore cholesterol availability, GalCer/sulfatide synthesis, or galactolipid delivery without simply eliminating infection. If each intervention selectively rescues its predicted arm, parallelism is strongly supported. If one intervention rescues both arms, the architecture must be revised toward a more serial dependency.

17. Predetermined Interpretation and Failure Conditions

If RUBV reproducibly reduces microglial LAL-dependent CE-to-FC flux and independently alters oligodendrocyte GalCer/sulfatide synthesis or delivery, with each phenotype corrected by its predicted arm-specific rescue while infection remains measurable, the parallel-system RUBV hypothesis would gain strong mechanistic support.

If only the LAL/recycling arm changes, the data would support a selective recycling lesion rather than a complete two-arm RUBV model. If only the GalCer/sulfatide arm changes, the construction arm would become the lead RUBV phenotype and the LAL arm would remain host context. If both host arms remain intact but intercellular lipid transfer fails, the parallel architecture could remain valid while the proposed coupling mechanism would require revision.

If both arms remain normal despite robust RUBV infection, adequate assay sensitivity, and verified glial infection, the central Paper VIII RUBV overlay would be substantially falsified. If changing LAL activity has no effect on CE-to-FC flux or remyelination in the tested glial system, the recycling-arm formulation would require revision. If GalCer/sulfatide perturbation does not alter the predicted membrane or myelin phenotype, the construction-arm formulation would likewise weaken.

18. Publication Boundaries

Paper VIII does not claim that RUBV has been shown to inhibit microglial LAL, that RUBV has been shown to alter GalCer/sulfatide synthesis or flux, or that LAL directly produces GalCer. It does not convert a functional microglia-to-remyelination bridge into isotope proof that LAL-derived cholesterol enters a particular GalCer or sulfatide molecule. It does not use STS, sodium, MAO, MALL, MAL, or an unmeasured lysosomal pH value to fill the missing viral arrows. It does not infer treatment efficacy from the model.

The paper also does not equate oligodendrocyte injury with a specific lipid mechanism. Direct RUBV injury to GalCer-positive oligodendrocytes establishes cellular overlap; the mechanism of that injury remains open. Likewise, sulfatide-sensitive RUBV membrane assays establish functional lipid-virus interaction but do not prove that endogenous sulfatide is the causal host determinant during neural infection. SMS1 perturbation establishes a RUBV-relevant sphingolipid system but does not prove that infection itself produces the same CMH/GalCer redistribution.

19. Conclusion

Paper VIII identifies a narrow but experimentally strong host convergence. Microglial LAL is a direct CE-hydrolysis and FC-availability node required for effective processing of cholesterol-rich myelin debris and successful white-matter repair. Independently, GalCer and sulfatide form an oligodendrocyte/myelin construction and organization system whose integrity is required for normal membrane function, delivery, and stability. Cholesterol availability and lipid recycling connect the biological outputs of these systems without requiring a direct linear LAL-to-GalCer reaction.

RUBV directly intersects the glial and lipid territory occupied by this parallel system, including GalCer-positive oligodendrocytes, cerebroside-sulfate-sensitive membrane biology, sphingomyelin-dependent entry, broad host-cell lipid remodeling, and an unresolved 18:2 increase. The missing viral experiment is precise: does RUBV disrupt one or both arms of the parallel system in the same glial preparation? If predicted arm-specific phenotypes appear, track with the expected lipid states, and are rescued by correcting those states while infection remains measurable, the model gains a direct mechanistic foundation. If both arms remain normal during robust RUBV infection, the Paper VIII hypothesis fails in its present form.

The parallel-system formulation converts a broad lipid hypothesis into a defined experimental program. It asks not merely whether cholesterol, GalCer, or sulfatide are present, but whether lipid is liberated, transferred, assembled, delivered, and functionally available at the correct stage and in the correct glial cell. In that sense, Paper VIII extends the governing principle of the Jacob model: presence does not equal availability; concentration does not equal flux; and synthesis does not equal delivery.

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Evidence boundary: References 1-7 and 14-18 establish host glial, lipid-flux, membrane, and cholesterol-availability mechanisms outside RUBV unless specifically stated otherwise. References 8-13 establish direct RUBV glial, membrane-lipid, sphingolipid, and lipid-remodeling observations or RUBV-relevant host perturbation experiments. None substitutes for the missing same-system RUBV test of the complete parallel system.