The Chain on the Ladder

The Vacuum.Net Theory and the lysosomal storage diseases, derived from the first distinction

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Summary

A polysaccharide is a word of trits; its degradation is that word read from one end; and a missing step is not a slow step but a carry that never forms. This document derives that statement from the first distinction of the Vacuum.Net Theory and follows it down to the nine enzymes of heparan sulfate catabolism, to the three diseases called Sanfilippo, and to what may and may not be offered to an interrupted chain.

Four results follow from the rules and were not read out of the literature. The glucosamine N-position carries exactly three states, so the sulfation code is a word in balanced ternary. A chain reduced to monosaccharides in exactly five ring-steps holds 3^5 = 243 residues, which is a testable prediction of chain length. A window is three consecutive steps, and the three steps of the window containing the sulfamidase step are exactly the three enzymes missing in MPS IIIA, IIIC and IIIB — which is why those three diseases cannot be told apart clinically. And the unit of therapeutic supply is therefore the window, not the enzyme: the triad should close where the single step does not.

Every number has been recomputed from the hydrogen units. Every external finding is cited with its source and its weaknesses. Nothing here is medical advice.

Part I. The theory from the first distinction

The theory rests on one ground, the trinity, on five axioms N1 to N5, and on theorems derived from them. This part states everything the rest of the document uses, so the reader needs no other text. Theorem numbers refer to The Vacuum.Net Theory: Foundations, version 9.2, and Physics, version 9.0.

1. The first distinction

Spencer-Brown's Laws of Form opens with one instruction: draw a distinction. A mark splits a space into an inside and an outside. Two laws govern marks. Calling twice is calling once. Crossing twice is not crossing. A mark that contains itself cannot settle on marked or unmarked. It alternates. Kauffman reads that alternation as the iterant with a time shift, and shows that it squares to minus one.

The theory states the same act in the language of a strand.

N1 (Strand). There is exactly one strand. Every distinction is a loop: the strand returning to a place it has been.

A place visited at least twice is a node. Everything that exists is a pattern of returns of one strand.

2. Direction and the trinity

N3 (Memory). At every node the passages are ordered. The first passage fixes the direction. Later passages are taken relative to it. The net carries its history as its shape.

The trit rule makes N3 mechanical. A later passage receives +1 if it leaves the node the way the first passage left it, −1 if it leaves the way the first passage came in, and 0 otherwise. The three values sum to zero. This is the trinity.

The trits are digits of balanced ternary and add by the digit rule (T1). A sum s keeps its balanced residue d in the set −1, 0, +1, with d congruent to s modulo 3, at its own scale. The rest, $(s - d)/3$, passes whole to the next scale as carry.

Balanced ternary needs no minus sign. Negation is mirroring. Shifting a word one place multiplies or divides by three: the same word at another depth.

3. The window of three

N2 (Closure). A loop persists if and only if it lies in a closed window. What does not close passes on as tension. Closure is the selection rule. There is no external selector.

A run of equal nonzero trits first leaves no residue at length three. A window is therefore three consecutive trits (T2). It closes when its sum is zero modulo 3. Of the 27 possible windows, 9 close (T3): the 3 whose trits are all equal, and the 6 whose trits are all different (T4). The 18 open windows all have exactly two equal trits.

4. Three elementary closures and what they carry

Every closed trit word reduces to nothing by removing three kinds of piece (T7).

Closure	Form	Digit kept	Carry to the next scale
Standing	0	0	0
Meeting	x, −x	0	0
Ring	x, x, x	0	±1
Open window	two equal, e.g. 1, 1	−1	1

A ring closes at its own scale and becomes one passage of the next scale: 1 + 1 + 1 = 10 in balanced ternary (T7.1). These four lines are the arithmetic of everything that follows.

N5 (Scale). Merged into blocks, the coarse strand obeys N1 to N4 again. What does not close at one scale is the material of the next.

5. What settles, and what does not

A word closes in every window only if its first window closes and it has period three. For every length there are exactly 9 such words (T8). A ring of trits that closes in every window repeats every third trit (T9).

The rewrite of the register sets each trit from its two neighbours. A ring is a fixed point of that rewrite exactly when every window closes (T10).

Recomputed over all rings of length 3 to 10:

Ring length	Already closed	Reach rest	Keep cycling
3	9	0	18 (66.7%)
4	3	24	54 (66.7%)
5	3	0	240 (98.8%)
6	9	0	720 (98.8%)
7	3	0	2,184 (99.9%)
8	3	24	6,534 (99.6%)
9	9	0	19,674 (99.95%)
10	3	0	59,046 (99.99%)

A ring left to its neighbours almost never comes to rest. This single computation decides much of Part IX.

6. Seams

A seam joins a closed window A to a closed window B. The number of open windows at the seam counts only whether the first trits differ and whether the last trits differ. The middle of a closed window is fixed by those two, being the negative of their sum. The seam closes if and only if B equals A (T11).

Over all 81 ordered pairs, 9 seams close, 36 have one open window and 36 have two. Two different closed configurations cannot be joined without tension.

7. The address

Every integer has exactly one balanced-ternary word (T12). A closed configuration read without a starting point is a rotation class. Identity is membership of a class.

8. Two ladders and the comma

Merging meetings doubles; merging rings triples (T15). The ladders by two and by three never meet exactly, because no power of two equals a power of three other than at zero (T16). Their best near-meetings are the denominators of the convergents of log base 2 of 3, the closure depths:

1, 2, 5, 12, 41, 53, 306, 665, 15601, ...

The miss never vanishes. At depth 12 it is the Pythagorean comma, 1.013643. At depth 53 it is 0.997914, a remainder of 0.2086 per cent.

9. Coupling and context

N4 (Context). The response of the medium is a state function, not a universal constant. Universality is the limiting case in which the state does not vary across the sample.

The stiffness of the medium depends on its local density (T23). The same offering therefore meets a different response in a different state.

Part II. The hydrogen ladder

One length and one time, both fixed by hydrogen, turn every ring of the theory into a measurable depth. Nothing about biology is used to fix them.

1. The units

The model is dimensionless. Its quantities are ratios. For comparison with instruments, Physics 9.0 fixes the conversion by hydrogen with its reduced mass, using CODATA 2018 values.

Unit	Definition	Value
R_H	Rydberg constant corrected for reduced mass	10,967,758.340 per metre
S_0	1 / (2 R_H)	$4.55881671 \times 10^{-8}$ metre
T_0	S_0 / c	$1.52065757 \times 10^{-16}$ second

On the ring ladder the layer at depth *n* has length $3^n \cdot S_0$ and time $3^n \cdot T_0$.

2. The depth rule

The depth of anything with a length L or a period t follows directly: $n = \log_3(L / S_0)$, or $n = \log_3(t / T_0)$.

For electromagnetic waves the two coincide, because T_0 equals S_0 divided by c. For chemical sizes and for bodily rhythms the two are separate: a length gives a space depth, a period gives a time depth.

3. The rings this document uses

All values recomputed from S_0 and T_0.

Ring	Length	What lies there
−5	0.188 nm	a covalent bond
−4	0.563 nm	a pyranose ring, one sugar residue
−3	1.69 nm	
−2	5.06 nm	
−1	15.2 nm	

Ring	Length	What lies there
0	45.6 nm	
1, a closure depth	136.8 nm	a long heparan sulfate chain
2, a closure depth	410.3 nm	the violet edge of vision
3	1,231 nm	
4	3,693 nm	
5, a closure depth	11.08 µm	the cell; the thermal infrared of the body

And in time:

Ring	Period	What lies there
33	0.845 s	heartbeat
35	7.61 s	slow breathing
41, a closure depth	92.4 min	the rest cycle
42	4.62 h	
43.5	1 day	the inner clock
53, a closure depth	93.4 years	a human life

4. Why closure depths matter

At a closure depth the ladders by two and by three come closest. A configuration there closes both as a meeting and as a ring, so closure is strongest and the remainder smallest. Three closure depths fall inside the range of this document: 1, 2 and 5 in space, and 41 in time.

The column that names what lies at each ring is observation. The rings themselves are arithmetic. Every row can be checked with a calculator and the two units above.

Part III. The chain as a word

N1 gives one strand. N3 orders the passages at every node and assigns each later passage one of three values. A polymer is therefore a run of passages at one depth: a word of trits.

For most polymers this is a correspondence. For heparan sulfate it is a count.

1. Three states, not two

Heparan sulfate is built from a repeating pair: a uronic acid and a glucosamine. The backbone repeats. The information sits in the state of each position. At the glucosamine, the nitrogen position carries exactly three states.

State	Notation	Measured share of total glucosamine
N-sulfated	GlcNS	the bulk of the NS domains
N-acetylated	GlcNAc	the bulk of the NA domains
N-unsubstituted	$GlcNH_2$	0.7 to 4 per cent

The third state is real, rare and long overlooked. It is formed by incomplete action of the N-deacetylase and N-sulfotransferase step during synthesis. It is the position that a separate enzyme family, the 3-O-sulfotransferases, singles out for further modification.

2. Where the third state sits

The structural study that located these residues found them preferentially inside the N-acetylated domains, or in the transition sequences between the N-acetylated and N-sulfated domains. Only 20 to 30 per cent of the neighbouring units upstream and downstream were N-sulfated.

In the theory the 0 is neither +1 nor −1 and sits where the two meet. The measured location of $GlcNH_2$ is the boundary between the two substituted domains.

3. What follows

The sulfation code of heparan sulfate is a word in balanced ternary. This is not an assignment and not an analogy. The alphabet has three letters because the position has three states, and the measurement counts them.

Two consequences are taken up below. The word is read from one end, one digit at a time, which makes Part V. And a window of that word is three consecutive positions, which makes Part VII.

One caution belongs here. The O-sulfation positions, at 2-O of the uronic acid and 6-O and 3-O of the glucosamine, are binary: present or absent. The ternary alphabet is the N-position alone. Every derivation below that uses the alphabet uses the N-position.

Part IV. The chain on the ladder

Every depth below is recomputed with the rule of Part II from the measured size. Nothing about the theory is used to obtain the measured sizes.

1. The table

Object	Measured size	Depth	Nearest ring
One sugar residue	0.5 to 0.6 nm	−4.11 to −3.84	ring −4 is 0.563 nm
One disaccharide unit	about 1.0 nm	−3.48	between −4 and −3
A hexasaccharide, three units	about 3.0 nm	−2.48	exactly one ring above the unit
A heparan sulfate chain	50 to 150 nm	0.08 to 1.08	spans one ring, ending on closure depth 1
A lysosome	0.1 to 1.2 µm	0.72 to 2.98	centred on 2.18
A cell	about 10 µm	4.91	next to closure depth 5
Turnover of the chain, half-life 4 to 7 hours	time	41.87 to 42.38	ring 42

2. Two results that were not put in

A hexasaccharide lies exactly one ring above a disaccharide unit. That is T7.1 in matter: three equal steps at ring n are one passage at ring $n + 1$. The theory therefore names the functional unit of heparan sulfate as a hexasaccharide, not a disaccharide and not an arbitrary length. Part VIII tests that against the measured binding length.

The measured chain length spans one ring and ends on closure depth 1. The turnover of the chain lies on ring 42, one ring above the rest cycle at closure depth 41.

3. The exit is sized at ring −4

The products that leave the lysosome are monosaccharides and sulfate ions, each through its own membrane transporter. Transporters for GlcNAc, for glucuronic acid, for iduronic acid and for sulfate have all been identified.

The exit is therefore gauged at ring −4. What enters at ring 1 must be brought down to ring −4 before it can leave. Nothing between those two sizes has a door.

4. A predicted chain length

The number of ring-steps from the chain to the exit is $1 - (-4.11) = 5.11$. That is next to closure depth 5.

Read the other way: a chain that reduces to monosaccharides in exactly five ring-steps holds $3^5 = 243$ residues. At the measured axial rise of about 0.5 nm per residue that is 121.5 nm, and it sits at ring 0.89, just under closure depth 1.

Measured chains hold 50 to 150 disaccharides, that is 100 to 300 residues. The predicted 243 residues, or 121 disaccharides, falls inside that range and near its middle.

Predicted. The length distribution of heparan sulfate chains peaks at 243 residues, or 121 disaccharides, and is not flat across the range. Refuted if an accurate length distribution is flat, or peaks elsewhere.

This is the one quantity in the document that the ladder fixes and the literature has not measured precisely enough to decide.

Part V. Reading the word

The degradation of heparan sulfate runs from the non-reducing end of the chain, one residue at a time, in a fixed order. In the language of Part I that is a register read from one end, one digit at a time.

1. The carry makes the blockade

In balanced ternary, $1 + 1 + 1 = 10$ (T7.1). The higher digit comes into existence only after the lower one has resolved. A ring closes at its own scale and hands one passage upward. That is a carry chain.

A missing step is therefore not a slow operation. It is a digit rule that is absent, so the carry never forms, and everything above it stands.

This is the derivation of the absolute block. It does not come from biochemistry. It comes from T7.1.

2. What the measurement shows

The prediction of a carry chain is sharp. Once reading starts it should run to completion without leaving intermediates, because each resolved digit immediately enables the next.

That is what is measured. Fragments of about 5 kDa reaching the lysosome are reduced to monosaccharides and sulfate by the series of exohydrolases **without the generation of intermediates**.

And when one rule is missing, the opposite is measured. Partially degraded oligosaccharides accumulate, each carrying the blocked residue at its non-reducing end. In MPS IIIA that terminal residue is glucosamine N-sulfate, which is also how the disorder is diagnosed.

3. The route leaks

The blockade is not total. Those same partially degraded oligosaccharides are excreted in the urine, and their measurement is a standard diagnostic.

The measured levels, in micrograms per milligram of creatinine:

Group	Urinary heparan sulfate
Healthy	0.56 ± 0.9
Attenuated MPS IIIA	4.2
Severe MPS IIIA	117 ± 44.8

Recomputed from those figures: the attenuated case is 7.5 times the healthy level and 27.9 times below the severe level.

So an exit exists for material that is not fully read. It is simply too small relative to the load. Part IX returns to this, because the rule about discharge applies to it directly.

4. The ratio, not the component

N4 states that the response of the medium is a state function. Applied here, the outcome is not set by the presence or absence of the enzyme but by the residual capacity against the load.

The literature records exactly that, within one gene defect. Patients with higher residual activity have an attenuated phenotype, a slower trajectory and a longer lifespan. The standard mouse model carries a missense change leaving about 3 per cent of wild-type activity, and shows a milder phenotype than the knockout models.

The same gene is defective in all these cases. The outcomes differ. Constant gene content cannot explain a variable outcome; a ratio can.

Part VI. The seam

1. Specificity derived

T11 governs the meeting of two closed configurations. The seam closes if and only if the two windows are equal. The count of open windows at the seam turns on two things only: whether the first trits differ, and whether the last trits differ. The middle of a closed window is fixed by those two.

Applied to a reading step: recognition turns on the terminal residue and on the position two places in, not on the position between them.

The measured requirement follows that shape. The sulfamidase step requires a glucosamine at the non-reducing end that is N-sulfated **and** not 6-O-sulfated. That is two positions on one residue, with the intervening uronic acid not part of the requirement.

A second measured case points the same way. Heparanase, the endo step that precedes the exo series, requires N-sulfated glucosamine residues for activity, and 6-O-sulfation of the glucosamine blocks it. Again two positions, again not the one between.

2. Why every step has its own rule

Over all 81 ordered pairs of closed configurations, 9 seams close, 36 carry one open window and 36 carry two. Two different closed configurations cannot be joined without tension.

That is the derived ground for a fact the literature records without explaining it: each step of the sequence has its own rule, and no rule substitutes for another. There is no redundancy in this chain, which is why a single gene defect halts it.

3. The nine steps

The lysosomal degradation of heparan sulfate is carried by nine enzymes acting in sequence.

Step	Acts on	Deficiency gives
Heparanase	internal cleavage, before the exo series	not a named disease
Iduronate-2-sulfatase	2-O-sulfate of iduronic acid	MPS II
Alpha-L-iduronidase	terminal iduronic acid	MPS I
Glucosamine-3-O-sulfatase (ARSG)	3-O-sulfate of glucosamine	MPS IIIE in animals
Sulfamidase (SGSH)	**N-sulfate of glucosamine**	**MPS IIIA**
Acetyl-CoA transferase (HGSNAT)	**acetylates the free amine**	**MPS IIIC**
Alpha-N-acetylglucosaminidase (NAGLU)	**terminal N-acetylglucosamine**	**MPS IIIB**
Glucosamine-6-sulfatase (GNS)	6-O-sulfate of glucosamine	MPS IIID
Beta-glucuronidase (GUSB)	terminal glucuronic acid	MPS VII

The count of nine is the figure given in the recent work that established the order of the sulfatase steps. Other reviews say at least ten exoenzymes, counting the transporters or splitting a step. The count is not fully settled, and nothing below depends on it being exactly nine.

What the next part does depend on is the three rows in bold, which are consecutive.

Part VII. The window of three

1. The derivation

T2 fixes the window at three consecutive trits. T3 counts 9 closing windows out of 27. Closure does not exist at one position. It exists at three.

Applied to a word being read from one end: the unit of closure is three consecutive steps, not one step.

The window containing the sulfamidase step is this.

Position	What changes at the N-position	Missing in
1	GlcNS becomes $GlcNH_2$	MPS IIIA
2	$GlcNH_2$ becomes GlcNAc	MPS IIIC
3	the N-acetylated glucosamine leaves the end	MPS IIIB

These three are the three commonest forms of Sanfilippo syndrome. They are three different enzymes, on three different chromosomes, with three different modes of failure.

They are also clinically almost indistinguishable. The literature states this plainly and treats it as a feature to be noted rather than explained: the four subtypes present the same picture, and subtype cannot be assigned on clinical grounds.

In the ordinary account this is a puzzle. Three distinct molecular lesions should not converge on one phenotype with such precision.

In the theory it is the prediction. **One window, therefore one failure, regardless of which of the three digit rules is absent.** The window either closes or it does not, and a window is not a position.

This is a retrodiction from the rules. It was not read out of the literature, and the literature offers no competing derivation of it.

2. Why the window is the three it is

The three steps in the window are not an arbitrary cut of the sequence. They are the three operations on one position of the word: remove the sulfate, set the acetyl, remove the residue. Together they take one glucosamine from GlcNS to absent. That is one digit resolved and handed upward: a ring, with carry 1.

The steps on either side act on the uronic acid or on the O-positions. They belong to neighbouring windows.

3. What follows for treatment

T10, recomputed in Part I, shows that 98.8 to 100 per cent of open rings of length 5 to 10 keep cycling when left to their neighbours. Nothing settles by itself. An open window stays open.

Supplying one digit rule leaves the window open. The window still does not close.

The unit of therapeutic supply is the window, not the enzyme.

Predicted. Sulfamidase, acetyl-CoA transferase and alpha-N-acetylglucosaminidase supplied together close the path at a lower level of each than sulfamidase alone reaches at any level.

Measurement. A tri-cistronic vector, or three vectors combined, against the single vector at equal total dose, in MPS IIIA cells and mice. Read heparan sulfate in brain tissue, not in cerebrospinal fluid alone, and read it at two or more time points.

Refuted if the triad at equal total dose does not close better than the single rule.

4. The reach of the prediction

One product for the window would serve MPS IIIA, IIIB and IIIC together. At present there is one approved product, for IIIA alone, and none for IIIB, IIIC or IIID.

That is the practical consequence of reading the chain as a path rather than as a set of components. A component needs one product per gene. A window needs one product per window.

Part VIII. The second register

Everything so far treats the chain as cargo. It is also a working part.

1. Two readings of one closure

T16 states that the ladders by two and by three never meet exactly. Maxwell's quaternion equations carry two registers in one product, read in the theory as two readings of one closure.

Heparan sulfate stands in two registers. In the first it is a word being read toward its exit. In the second it is a structural element of a closed configuration with the growth factor FGF2 and its receptor.

2. The hexasaccharide

Part IV placed the hexasaccharide exactly one ring above the disaccharide unit. The theory therefore names it as the functional unit.

The measured minimal length for FGF2 is contested, and the honest statement has three parts.

- The canonical crystal structures of FGF2 with heparin are a tetrasaccharide and a **hexasaccharide** (PDB 1BFB and 1BFC).
- By size exclusion, the hexasaccharide binds FGF2 in stable one-to-one complexes, while an octasaccharide and longer form two-to-one complexes.
- For receptor dimerisation, several groups give an **octasaccharide** as the minimum, and others report signalling with shorter fragments through a symmetrical complex.

The prediction is confirmed for the binding seam and is silent about dimerisation. A hexasaccharide is the unit that closes with FGF2. Eight is not a ring number, and the theory derives no number for dimerisation, which is a second closure between two already closed units.

This is stated as a partial confirmation, not a full one.

3. What the fragments do to the second seam

T11 again: a seam closes only if the windows are equal, and only the first and last positions count.

The fragments that accumulate when reading is blocked have the wrong length and the wrong terminal position. They should occupy the site without closing the seam.

That is what is measured. Heparan sulfate from MPS IIIA cells binds FGF2 with an affinity similar to heparin, and does **not** support signalling. Adding those fragments to the medium of healthy neural progenitor cells reproduces the defect. The authors' model is competition between the soluble fragments and the cell-surface chains for FGF2.

Two independent results restore part of the function without touching the stored material. Doubling FGF2 partly restores proliferation of MPS IIIA progenitor cells. Adding wild-type heparan sulfate to a CRISPR MPS IIIA cell line reduces the aberrant dopaminergic proliferation, dose-dependently.

4. Why a remainder stays

In mouse and cell models, the altered function of heparan sulfate during embryogenesis produces an increased proliferation of mesencephalic dopamine neurons. The authors state explicitly that this is **not** due to lysosomal dysfunction but to altered heparan sulfate function. The resulting behaviour is corrected by a D1-like receptor antagonist, with the storage untouched.

Three consequences follow, and they are the limits of what any treatment of this class can reach.

Part of the damage is laid down before birth. N3 fixes the direction at the first passage, and identity changes only by a jump of class. What was laid in the embryonic phase is not retrieved by acting on the reading chain.

The two registers cannot both be closed exactly. T16 forbids it. A remainder stays, as a remainder of 0.21 per cent stays at closure depth 53.

There is a branch that no treatment of the reading chain touches, and it is addressable on its own: restoring the second seam. Two groups have shown partial restoration there, in cells and in mice, without clearing any storage. No clinical programme is pursuing it.

Part IX. What the derivation prescribes

Six rules follow from Part I. They are the same six that govern acting on any structure in this theory, here applied to a reading chain rather than to a vibration window.

Rule	From	In practice here
Read the state first	N4	Residual activity and the person's own sulfation pattern. The response of the medium is a state function, which is what the attenuated to severe spectrum is.

Rule	From	In practice here
Same window	T11	What is offered must match the window of the chain end: the terminal position and the one two places in.
Three nested	T2, T7.1	Three consecutive digit rules together, not one. A window of three at one ring is one passage at the ring above.
Offer the whole window at once	T10, recomputed	One rule leaves the window open, and open windows keep cycling in 98.8 to 100 per cent of cases.
Throughflow	N2, N5	The exit at ring −4 must be open. Supplying rules without transport capacity lays nothing again.
Silence after	Part I, 5	Drift is repaired where nothing flows. Turnover lies on ring 42, one ring above the rest cycle at closure depth 41.

1. The five places a path can be acted on

The path has five places and no others, because a path has no other places.

Place	What it does to the ratio
Lower the load upstream	reduces the numerator
Supply the missing rule	raises the capacity at the blocked step

Place	What it does to the ratio
Route around the step	raises capacity by another path
Enlarge the exit that already exists	lets material leave before full reading
Empty what has accumulated	clears the registering compartment

2. Continuity

The load is continuous: synthesis, delivery and internalisation run without interruption, and the turnover half-life is 4 to 7 hours.

A capacity that is present for part of the cycle restores the ratio for part of the cycle. Closure is a property of a whole path, not of a point on it, and a level measured at a sampling point is not a closure measure. Closure requires at least two measurements over time.

Derived. A rule supplied in pulses can lower the level without restoring the return, at any dose per pulse.

Part X shows that this is what the two clinical programmes did.

3. Magnitude

From preclinical gene therapy work across MPS IIIA, IIIB and IIIC, the groups involved state that a reduction of 50 to 70 per cent of brain heparan sulfate is needed for neurocognitive effect.

Taken with Part I, 5, that figure is what it should be. An open window does not settle, so a partial shift of the ratio leaves the window open; only a shift past a threshold closes it.

The two conditions together, which every candidate must meet:

- **Continuity.** The restored capacity is present through the whole cycle.
- **Magnitude.** The reduction passes about 50 per cent, measured in tissue and not only in the sampled compartment.

Part X. The clinical record read through the rules

Five classes of intervention have been tried. The rules of Part IX retrodict every outcome.

1. The record

Intervention	Place on the path	What was measured	Outcome
Genistein, 160 mg/kg/day, 12 months, phase III, double blind	lower the load	urinary glycosaminoglycan 32.1 per cent below placebo (p = 0.0495); **no** reduction in cerebrospinal fluid	no clinical benefit
Miglustat, randomised	lower the load	no ganglioside reduction	no benefit
Intrathecal recombinant sulfamidase, 10, 45 and 90 mg monthly	supply the rule, in pulses	consistent decline of heparan sulfate in cerebrospinal fluid in **all** treated patients, sustained for years	**no** slowing of cognitive decline; terminated early
Haematopoietic or cord blood transplantation	supply the rule, from donor cells	in attenuated MPS IIIB, cerebrospinal fluid heparan sulfate stayed in the untreated range	no benefit
AAV9 gene therapy, single dose	supply the rule, continuously, in situ	median 63.98 per cent reduction in cerebrospinal fluid within one month, sustained; at least 50 per cent in 81.5 per cent of patients	23.2-point treatment effect on cognitive raw score; approved September 2026

Intervention	Place on the path	What was measured	Outcome
TFEB, raising lysosomal exocytosis	enlarge the exit	clearance of glycosaminoglycans in MPS IIIA neural stem cells and in multiple sulfatase deficiency models	preclinical only; never taken to the clinic

2. The discriminating pair

Two interventions supply the same missing rule. Both lower the same measure in the same compartment. One closes the path and the other does not.

	Intrathecal enzyme	AAV9 gene therapy
Reduction in cerebrospinal fluid	yes, in all patients	yes, median 64 per cent
Where the rule sits	outside the cell, delivered into the fluid	inside cells, through the tissue
Through the cycle	monthly pulse	uninterrupted
Clinical effect	none	yes

This is the sharpest available test of the claim that a level is not a closure measure. The level fell in both cases. The return was restored in one.

Raising the pulse dose to 90 mg changed nothing, which is consistent: more per pulse does not change the ratio averaged over the cycle.

3. Where the record falls short

A second explanation of the enzyme failure exists: insufficient penetration from the cerebrospinal fluid into the tissue. Both explanations predict the same clinical failure, and the published data do not separate them.

One measurement separates them. Measure heparan sulfate in tissue, or a parenchymal proxy, immediately before and immediately after a dose. On a penetration account the

tissue level stays high in both. On a duty-cycle account it falls after the dose and rises before the next.

That measurement has never been made. Until it is, the continuity rule of Part IX is consistent with the record but not established by it.

4. Why the load-lowering class failed, quantitatively

The threshold is 50 to 70 per cent of brain heparan sulfate. Genistein reached 32.1 per cent in urine and nothing in cerebrospinal fluid. The approved therapy reaches 64 per cent, inside the band.

The trial authors drew the same conclusion from their own data: given the reductions their preclinical work indicates are needed, it seems unlikely that any substrate reduction product could lower glycosaminoglycan enough to improve neurocognition in this disease.

5. A predicted hazard of the exit route

Raising lysosomal exocytosis moves the fragments out of the cell. Outside the cell, those fragments are the species that occupy the FGF2 site without closing the seam (Part VIII).

Derived, and not found in the literature. Enlarging the exit may close the first register at the cost of the second.

Measurement. In a TFEB model, read FGF2-dependent proliferation alongside the glycosaminoglycan reduction. Nobody has read both.

Part XI. Research programme

Six tests decide the claims of this document. Each states its prediction, its measurement and what would refute it. Every test is pre-registered: thresholds and decision rules fixed before data are seen.

1. The tests

Test	Prediction	Measurement	Refuted if
T-A. The window	Sulfamidase, acetyl-CoA transferase and N-acetylglucosaminidase supplied together close at a lower level of each than sulfamidase alone at any level	Tri-cistronic vector against single vector at equal total dose, MPS IIIA cells then mice; brain heparan sulfate at two or more time points	The triad at equal total dose does not close better than the single rule
T-B. Continuity	The failure of the pulsed enzyme is a duty-cycle failure, not a penetration failure	Tissue heparan sulfate immediately before and immediately after a dose, in the MPS IIIA mouse	The tissue level stays high in both readings, which would make it penetration
T-C. Chain length	The length distribution of heparan sulfate chains peaks at 243 residues	Accurate length distribution by mass spectrometry on native chains from several tissues	The distribution is flat, or peaks elsewhere
T-D. The subtypes	Matched MPS IIIA, IIIB and IIIC patients are indistinguishable on quantitative neurocognitive trajectory, not merely on clinical description	Pooled natural history data, trajectory slopes compared between subtypes	A reproducible difference in slope between subtypes at matched residual activity

Test	Prediction	Measurement	Refuted if
T-E. The second register	Restoring the FGF2 seam improves function without clearing storage	Competent heparan sulfate, or a receptor-level agent, in MPS IIIA mice; read behaviour and storage separately	Function does not improve when storage is unchanged
T-F. The exit hazard	Raising lysosomal exocytosis closes the first register at the cost of the second	In a TFEB model, read FGF2-dependent proliferation alongside glycosaminoglycan reduction	Proliferation is unaffected while storage falls

2. Who is placed to run them

The names are those of authors whose published work is cited here. Their participation is not implied.

Group	Why	Fits
Brian Bigger and colleagues, Manchester	Ran the phase III substrate reduction trial and the preclinical gene therapy work across IIIA, IIIB and IIIC that produced the 50 to 70 per cent figure	T-A, T-C
Kim Hemsley and the Adelaide group	The MPS IIIA iPSC and FGF2 work; the murine oligosaccharide distribution work	T-C, T-E

Group	Why	Fits
Alessandro Fraldi and the Naples group	The developmental heparan sulfate and dopamine work in MPS IIIA	T-E
Andrea Ballabio and the TIGEM group	TFEB and lysosomal exocytosis	T-F
Jeffrey Esko, San Diego	Heparan sulfate catabolism, chain structure and turnover	T-B, T-C
Ultragenyx and Nationwide Children's	Hold the Transpher A cohort and the only approved vector	T-A, T-B, T-D

3. What would count as strong evidence

T-A, replicated by an independent group under pre-registration, would be the strongest result this document can ask for. It is predicted by the window rule alone, it has not been tried, and it is within reach of existing vector technology.

The agreements already found, which are the hexasaccharide unit, the three N-states and the indistinguishability of the three subtypes, were found after the fact. They can support the reading. They cannot prove it.

Status ledger

Every statement carries one of five statuses. A summary of this document may not change them.

Statement	Status
Digit rule, window of three, 9 of 27, elementary closures and carry, seam rule, unique address, closure depths, the comma (Foundations T1 to T18)	Proved or conditionally proved, recomputed
98.8 to 100 per cent of open rings of length 5 to 10 keep cycling	Computed, exhaustive

Statement	Status
Hydrogen units, and the depth of every measured size and period in Part IV	Computed from CODATA 2018 inputs
The glucosamine N-position carries exactly three states	Measured by others; the count is exact
N-unsubstituted glucosamine sits preferentially at the boundary between the substituted domains	Measured; placement on the 0 is a correspondence
A heparan sulfate chain spans one ring and ends on closure depth 1	Computed agreement; correspondence
A hexasaccharide is one ring above the disaccharide unit	Computed
The hexasaccharide is the FGF2 binding unit	Confirmed for binding; contested, and the dimerisation number is not derived
Turnover lies on ring 42, one ring above closure depth 41	Computed from a measured half-life range
Chain length peaks at 243 residues	**Predicted, untested**
A missing step is a blockade because the carry never forms	Derived (T7.1)
Reading leaves no intermediates	Derived prediction; measured
Specificity turns on the terminal position and the one two places in	Derived (T11); agrees with the measured sulfamidase and heparanase requirements
Nine enzymes in the sequence	Reported; the count is not fully settled between nine and ten
MPS IIIA, IIIB and IIIC are one window, therefore one picture	**Derived retrodiction**; the clinical indistinguishability is measured
The unit of therapeutic supply is the window, not the enzyme	Derived (T2, T3, T10)

Statement	Status
The triad closes where the single rule does not	**Predicted, untested**
A pulsed supply lowers the level without restoring the return	Derived; consistent with both trial records, not separated from the penetration account
The 50 to 70 per cent threshold	Reported by the trial authors from their own preclinical work; the three underlying papers were not retrieved
Fragments occupy the FGF2 site without closing the seam	Measured
Part of the damage is embryonic and is not retrieved	Derived (N3); supported by the mouse and cell work
Two registers, therefore a remainder that stays	Derived (T16)
Enlarging the exit may close the first register at the cost of the second	**Derived hazard, untested, not in the literature**
Human passages, chains and tissues are trits	Correspondence, except at the N-position, where it is a count
Clinical use of anything in this document	None. Research design only, not medical advice

Limits of this document

Most sources were read as abstracts, excerpts, review passages and patent texts rather than in full. The three preclinical papers behind the 50 to 70 per cent threshold were not retrieved. The reported treatment effect on cognitive raw score appears as 22.7, 23.2 and 23.5 points across three data cut-offs of one study, and those are not three measurements. The mechanism of the secondary ganglioside accumulation is contested, since GM2 and GM3 have been found in separate vesicle populations, which undercuts the usual inhibition account. No measured turnover rate for heparan sulfate in human brain was found, so the load in Part IX remains a direction and not a number.

Annotated references

Each source is listed with what it contributes and how much weight it can bear.

The theory

- **Konstapel, J. (2026a).** *The Vacuum.Net Theory: Foundations*, version 9.2, Ninth Edition, 27 October 2026. constable.blog. The ground, the axioms N1 to N5 and theorems T1 to T24, each with proof and a record of checks. *Why read it: every statement in Part I cites a theorem here, and it can be checked with pencil, paper and a short program.*
- **Konstapel, J. (2026b).** *The Vacuum.Net Theory: Physics*, version 9.0. constable.blog. The hydrogen units, the nilpotent Dirac operator, Maxwell's two registers. *Why read it: it shows that the units of Part II are fixed by hydrogen and not chosen to fit the subject.*
- **Konstapel, J. (2026c).** *MAZE: The Topology of Life.* constable.blog, 17 August 2026. Life as a closure that lays itself again. *Why read it: the source of the throughflow rule used in Part IX.*
- **Konstapel, J. (2026d).** *Why Some Infections End and Others Do Not.* constable.blog, 1 November 2026. The operational definition of closure and the ratio account, derived for infection. *Why read it: its section 4 builds and then falsifies the rule that a path closes when its discharge has somewhere to go. That rule fails for infection, where the route is intact, and holds here, where the route is cut. The present document is the other half of that domain.*
- **Spencer-Brown, G. (1969).** *Laws of Form.* Allen and Unwin. *Why read it: the ground of the first distinction; short and exact.*
- **Kauffman, L. H. (2005).** EigenForm. *Kybernetes* 34(1/2), 129 to 150. *Why read it: the formal side of N2, and why only what reproduces itself persists.*

The alphabet and the chain

- **Westling, C. and Lindahl, U. (2002).** Location of N-unsubstituted glucosamine residues in heparan sulfate. *Journal of Biological Chemistry* 277, 49247 to 49255. $GlcNH_2$ at 0.7 to 4 per cent of total glucosamine, located within N-acetylated domains and in the transition sequences, with only 20 to 30 per cent of neighbours N-sulfated. *Why read it: this is the third letter of the alphabet and the measurement that makes Part III a count rather than an analogy. Primary structural work; the proportions vary by tissue and preparation.*
- **Liu, J. et al. (1999).** 3-O-sulfotransferase-3A sulfates N-unsubstituted glucosamine residues. *Journal of Biological Chemistry* 274, 38155 to 38162. *Why read it: independent confirmation that the third state exists and is acted on; cited for the state, not for the sulfotransferase biology.*

- **Hopwood, J. J. (2006).** Lysosomal degradation of heparin and heparan sulphate. In *Heparin and Related Polysaccharides.* Internalisation and catabolism with a half-time of 4 to 6 hours in rat granulosa cells; endoglycosidic steps producing 5 kDa fragments; those fragments reduced by exohydrolases to monosaccharides and sulfate **without intermediates**; distinct membrane transporters for the monomeric products. *Why read it: the single most load-bearing source for Parts IV and V. It supplies the turnover time, the carry-chain signature and the size of the exit. A review chapter, so its figures are secondary to the primary studies it cites.*
- **Iozzo, R. V. (1987).** Turnover of heparan sulfate proteoglycan in human colon carcinoma cells. *Journal of Biological Chemistry* 262, 1888 to 1900. Step 1 half-life about 6 hours; chloroquine sensitivity establishing the acidic compartment. *Why read it: a second, independent turnover figure; a different cell type gives a different number, which is why Part IV uses a range.*
- **Owens, R. T. and Wagner, W. D. (1991).** Metabolism and turnover of cell surface proteoglycans in macrophages. *Arteriosclerosis and Thrombosis* 11, 1752 to 1758. Half-life 6.9 hours. *Why read it: a third turnover figure, which brackets the range used on the ladder.*
- **Kowalewski, B. et al. (2021).** Decoding the consecutive lysosomal degradation of 3-O-sulfated heparan sulfate by arylsulfatase G. Nine enzymes acting in concert; exolytic action at the non-reducing end; the sequential order of the sulfatase steps. *Why read it: the source of the count of nine and of the strict order. Other reviews say at least ten, so the count is reported here as unsettled.*
- **Lamanna, W. C. et al.** A defect in exodegradative pathways provides insight into endodegradation. Partially degraded fragments accumulate in lysosomes **and** are excreted in the urine. *Why read it: the evidence that the route leaks, which is what Part IX acts on.*
- **Myette, J. R. et al. (2009).** Heparin and heparan sulfate N-sulfamidase from Flavobacterium heparinum. *Journal of Biological Chemistry* 284, 35177 to 35188. A bacterial N-sulfamidase cleaving the same bond, exolytically, requiring an N-sulfated and 6-O-desulfated glucosamine at the non-reducing end, in a **reversed** order relative to the lysosomal pathway. *Why read it: it fixes the two-position requirement used in Part VI, and it is the only concrete candidate for routing around the step, which would need the bacterial pair in the bacterial order.*
- **Coppa, G. V. et al. (2013).** Mild mental retardation and low urinary heparan sulfate in attenuated MPS IIIA. *Clinical Biochemistry* 46, 688 to 690. Urinary figures of 4.2 against 117 and 0.56 micrograms per milligram of creatinine. *Why read it: the quantitative spectrum used in Part V. A single case against group means, so the ratios are indicative, not a distribution.*

- **Lehmann, R. J. et al. (2021).** Impaired neural differentiation of MPS IIIA iPSC-derived neural progenitor cells. *Molecular Genetics and Metabolism Reports.* Reduced proliferation; MPS IIIA fragments bind FGF2 like heparin but inhibit signalling; the defect is reproduced by adding those fragments to control cells; partial rescue by doubling FGF2. *Why read it: the load-bearing source for Part VIII. The authors note the competition model is inferred from binding and function, not demonstrated structurally.*

The second register

- **Pellegrini, L. et al. (2000).** Crystal structure of a ternary FGF-FGFR-heparin complex. *Molecular Cell* 6, 743 to 750. The hexasaccharide forms a one-to-one-to-one ternary complex; the minimal length for dimerisation is disputed. *Why read it: the measured hexasaccharide unit, and the honest statement of the dispute that Part VIII reports.*
- **Faham, S. et al. (1996).** Heparin structure and interactions with basic fibroblast growth factor. *Science* 271, 1116 to 1120. The FGF2 tetrasaccharide and hexasaccharide structures, PDB 1BFB and 1BFC. *Why read it: the canonical structures; cited for the hexasaccharide, not for the tetrasaccharide controversy.*
- **Harmer, N. J. et al.** Differential effects of heparin saccharides on ternary complex formation. An octasaccharide as the minimum for dimerisation, with exceptions by receptor type. *Why read it: the counterweight; it is why Part VIII claims only the binding seam.*
- **De Pasquale, V. et al. (2021).** Altered heparan sulfate metabolism during development triggers dopamine-dependent autistic behaviours. *Nature Communications* 12, 3495. Increased proliferation of mesencephalic dopamine neurons originating in embryogenesis, explicitly **not** from lysosomal dysfunction; correction by a D1-like antagonist; wild-type heparan sulfate reduces the phenotype dose-dependently. *Why read it: the strongest evidence that the second register is separable and separately treatable. Mouse and cell models only.*

The clinical record

- **Ghosh, A. et al. (2021).** High dose genistein in Sanfilippo syndrome: a randomised controlled trial. *Journal of Inherited Metabolic Disease* 44, 1248 to 1262. Urinary glycosaminoglycan 32.1 per cent below placebo; no reduction in cerebrospinal fluid; no neuropsychological benefit; and the authors' own statement that 50 to 70 per cent of brain heparan sulfate reduction appears to be needed. *Why read it: the threshold figure on which Parts IX and X turn. That figure is the authors' reading of their own preclinical work, and those three papers were not retrieved for this document.*

- **Seker Yilmaz, B. et al. (2021).** Novel therapies for mucopolysaccharidosis type III. *Journal of Inherited Metabolic Disease* 44, 54 to 71. The full record of enzyme, substrate reduction, transplantation and gene approaches, including the termination of the intrathecal programme in 2016. *Why read it: the single best overview of what has been tried and what each attempt measured.*
- **Muschol, N. et al. (2021).** Long-term safety and clinical outcomes of intrathecal heparan-N-sulfatase. *Molecular Genetics and Metabolism.* Heparan sulfate in cerebrospinal fluid and urinary glycosaminoglycan reduced in all treated patients; no slowing of cognitive decline; terminated for failure to meet efficacy criteria. *Why read it: half of the discriminating pair in Part X, and the reason a level is not a closure measure.*
- **Jones, S. A. et al. (2016).** A phase 1/2 study of intrathecal heparan-N-sulfatase. Dose escalation to 90 mg, consistent declines in cerebrospinal fluid. *Why read it: it establishes that the pulse dose was raised and that the biomarker followed.*
- **Ultragenyx (17 September 2026).** Approval of FAYUVI, the first approved treatment for MPS IIIA. AAV9 delivering SGSH; indicated for pediatric patients with preserved neurodevelopmental function. *Why read it: the indication wording is the clinical statement of the embryonic limit derived in Part VIII. A company announcement, so the regulatory fact is firm and the framing is not independent.*
- **NeurologyLive (2026).** FDA approves UX111. Median 63.98 per cent reduction in cerebrospinal fluid heparan sulfate; at least 50 per cent in 81.5 per cent of the efficacy population and 88.2 per cent of younger patients; a 23.2-point treatment effect. *Why read it: the figures used in Part X. Secondary reporting of company data; the effect size appears as 22.7, 23.2 and 23.5 across three data cut-offs.*
- **Medina, D. L. et al. (2011).** Transcriptional activation of lysosomal exocytosis promotes cellular clearance. *Developmental Cell* 21, 421 to 430. TFEB clears stored glycosaminoglycans in MPS IIIA and multiple sulfatase deficiency models, through TRPML1-dependent lysosomal exocytosis. *Why read it: the only published work on the exit route, and the basis of test T-F. Cell and mouse models; never taken to the clinic.*
- **Tiesinga, E. et al. (2021).** CODATA recommended values of the fundamental physical constants: 2018. *Reviews of Modern Physics* 93, 025010. *Why read it: the inputs of the hydrogen units.*

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