



Connections: Neuroimmune Medicine and Respiratory Care

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Part 1 • Foundations & Neuroendocrine Integrated Connection • Light Teal Medical Glow

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Part 1 – From Lesion to Network to Action

Shift the model: respiratory disease is not an isolated lung lesion. It is Brain ↔ Gut ↔ Lung ↔ Immune ↔ Endocrine – one orchestrated network. Assessment must capture sensors, rhythm, and defense.

01

REFRAME PARADIGM

Lesion → Network. Chronic cough, asthma, COPD persist because TRP sensors, mast cell MRGPRX2 alarms, and NTS LTP remain sensitized.

Brain-Gut-Lung Axis

02

DECODE CORE LANGUAGE

TRPA1 wasabi, TRPV1 chili, TRPV4 stretch, MRGPRX2 panic button, NK1R Sub P, PAR-2 scissors, sIgA defense, HRV vagal brake SDNN.

Sensors + Processors

03

BEDSIDE TRANSLATION

3 Questions triggers + 1-min HRV SDNN <20 severe loss, sIgA ZRT <30 mg/dL low, saccharin >20 min slow cilia, HARQ LCQ.

Think outside PFTs

1

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What is Neuroimmunology? Telephone Wire → Inflammatory Reflex

Vagus is 100k fibers, 80% afferent listening nerve. Cytokines speak to brain via vagal paraganglia. Brain answers via cholinergic anti-inflammatory pathway – Tracey Nature 2002.

Vagus = sensory: not motor only. NTS in brainstem receives TRP, P2X3, PAR-2 signals. LTP here = chronic cough hypersensitivity.

Inflammatory reflex: efferent arm ↓ TNF, IL-6 via α7 nAChR on macrophages. Resonant breathing 5.5s 0.09 Hz recruits this.

RT access: Auricular branch cymba concha, slow breathing, cold face dive. HRV SDNN is vagal brake biomarker.

Tracey KJ. Nature 2002; Bonaz 2021 VNS; Jarczok HRV



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What is Psychoneuroimmunology? Mind drains the battery

Conditioned immune response: brain learns to suppress sIgA. Chronic stress → low secretory IgA <30 mg/dL, vulnerable mucosa, gut-lung link breaks.

1 Cohen NEJM 1991: psychological stress dose-dependently increases common cold susceptibility – stress ↓ sIgA, NK activity.

2 sIgA is first defense: ZRT <30 mg/dL = high respiratory infection risk. Butyrate from fiber 30g → T-reg → sIgA ↑.

3 Sleep = Immunotherapy: T-cell homing via CXCR4 needs deep sleep. No sleep → IL-6 ↑, sIgA ↓, vaccine response ↓ 50%.

4 RT leverage: Resonant breathing 5.5s ↑ sIgA 45% (Zaccaro 2018) ↓ IL-6 20%. Bright light AM restores CAR.

PNI CORE Reference: Cohen 1991, Zaccaro 2018, Lange Sleep • Sonnenburg Cell 2021 fermented foods ↑ diversity

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MISSING BRIDGE • NEUROENDOCRINE

Hormones are the bridge between brain, gut, lung and immune — not background noise.

Cortisol is the fire extinguisher, CAR is morning alarm, melatonin + GH during sleep drive T-cell homing via CXCR4. Flattened CAR = poor sleep = immune fails to home.

Cortisol = anti-inflammatory brake

CAR restores with bright AM light 30 min

Sleep IS immunotherapy • CXCR4

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Neuroendocrine Integrated Connection – The Missing Bridge

HPA, SAM, PNEC, HPG, Melatonin-GH are not silos. They converge on immune traffic, mast cell tone, and vagal brake. Sleep is immunotherapy via CXCR4 T-cell homing.

HPA AXIS – CAR

Hypothalamus CRH → Pituitary ACTH → Adrenal Cortisol
Morning cortisol spike is CAR. Flat CAR = poor sleep, depression, frequent COPD exacerbations. Bright light AM 30 min restores CAR.

- Flat CAR marker: AM cortisol 8am <10 mcg/dL low – case 3 PHQ9 14
- Sleep loss → GH & melatonin ↓ → CXCR4 T-cell homing fails

Zaccaro 2018, Besedovsky Sleep 2012

SAM

Norepinephrine – Fight Flight
SAM overdrive ↓ HRV SDNN <20 ms, sensitizes TRPV1, mast cell MRGPRX2. POTS +38 bpm standing = SAM.

PNEC

Bombesin – Fibrosis Engine
Pulmonary neuroendocrine cells release bombesin, CGRP, drive fibrosis, SCLC growth. Hamanaka Cell 2022.

HPG + ESTROGEN

Sex Hormones Modulate
Estrogen ↑ TRPV4, mast cell histamine. Explains perimenstrual asthma worsening, case 1 IBS-M overlap.

MELATONIN GH – SLEEP IS IMMUNOTHERAPY

T-cell Homing CXCR4
40°C bath 90 min pre-bed ↑ melatonin, GH. During SWS, T-cells home to lymph nodes via CXCR4. PSQI 13 → 7 = fewer exacerbations.

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Brain–Gut–Lung Axis – Orchestrated Ecosystem

Not three organs. One network, bidirectional. Vagus = 100k fibers, 80% afferent listening nerve. Brain is CEO, gut is factory, lung is shipping dock.

1

Brain CEO – NTS & LTP

100K VAGAL – 80% AFFERENT

Nucleus tractus solitarius receives TRPV1, TRPA1, P2X3, PAR-2. Long-term potentiation here = chronic cough hypersensitivity, scent-triggered bronchospasm.

Tracey 2002 NTS plasticity

2

Gut Factory – sIgA & Butyrate

BUTYRATE → T-REG → sIgA

Fiber 30g → butyrate → T-reg → sIgA. ZRT <30 mg/dL = risk. Budden Nat Microbiol 2019 dysbiosis, Sonnenburg Cell 2021 fermented 4–6x/week restores.

sIgA 22–58 LGG + BB536

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Lung Dock – NO & CBF

NASAL NO +20% – CBF 12–8 HZ

Nasal breathing humidified ↑ NO 20%, PAP, mucociliary clearance. Saccharin >20 min slow, CBF 8 Hz vs 12 Hz normal. Low Vt 6 mL/kg TRPV4 protection.

HRV SDNN 18–38 ETCO2 35–40

● **One Network:** Stress ↓ sIgA 30–50% Cohen NEJM 1991, sleep disruption fails CXCR4 T-cell homing, bright light restores CAR – sleep is immunotherapy.

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Abbreviations A — Sensors & Alarms

The airway listens before it reacts. Four pseudo-allergic sensors drive allergy-negative cough, scent-triggered bronchospasm, and cold-air hyperreactivity — no IgE required.

TRPA1 — wasabi sensor

Cold air, ozone, wildfire smoke AQI>100, bleach scent, formaldehyde. Master irritant gate. Explains cold-induced cough.

AIRWAY IRRITANT • COLD + VOC

TRPV1 — chili / capsaicin

Heat >43°C, acid pH, capsaicin C5, inflammatory soup. P2X3 ATP co-sensitizes. Target for speech pathology + LDN.

HEAT / ACID / INFLAMMATION

TRPV4 — stretch mechanosensor

Alveolar stretch. Over-distension → injury. RT pearl: low Vt 6 mL/kg PBW, nasal humidified, pursed-lip 6/min protects.

MECHANICAL • LOW Vt PROTECTION

MRGPRX2 — panic button

Mast cell anaphylatoid via C3a/C5a, drugs, scents. No IgE, normal allergy panel. IgE normal ≠ non-immune.

PSEUDOALLERGY • NON-IgE • ALARM

McNeil 2015 Nature • Belvisi cough hypersensitivity Clinical: scent trigger = MRGPRX2 + TRPA1

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Abbreviations B — Processors & Effectors

Sensors need processors. When processed through NTS plasticity, these effectors convert a transient irritant into chronic cough, mucus, and bronchospasm — the chronicity engine.

**NK1R**
SUBSTANCE P • NEUROGENIC INFLAMMATION

Substance P from C-fibers → plasma extravasation, mucus hypersecretion. COPD GOLD 3 + silica = ↑ bombesin + Sub P.

Block: Aprepitant NK1R antagonist trial rationale, lidocaine 2% nebulized TRP block

**PAR-2**
TRYPTASE SCISSORS → NERVE

Mast cell tryptase cleaves PAR-2 on sensory nerve → NTS long-term potentiation → cough hypersensitivity persists.

Loop: Mast MRGPRX2 → Tryptase → PAR-2 → NTS LTP → Vagal low → repeat

**AhR**
DIOXIN SENSOR • DETOX

Environmental: diesel 1-10, ozone 2-6PM, wildfire, VOCs. AhR senses PAHs → inflammation.

Remove: HEPA bedroom, DIM foods (broccoli), NAC 600-900 BID, VOC scent-free

**P2X3**
ATP • PURINERGIC COUGH • FDA 2024

ATP released from injured epithelium post-viral (Long COVID) → P2X3 → chronic cough. LCQ 11.2 low.

Break: Gefapixant 45 mg BID P2X3 antagonist — FDA 2024 approval, Smith Lancet

Key: Processor = chronicity engine, not just trigger

Recommended Action Plan: AirNow.gov + N95 — no Tucson term

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Abbreviations C — Defense & Rhythm

If sensors are alarms, these are the shields and brakes. Measure them at bedside — they predict exacerbation, infection, and cough hypersensitivity.

**SIGA • MUCOSAL SHIELD**

22 mg/dL → low
ZRT <30 = risk. Case2 22 → 58 after fiber 30g + LGG + fermented 4x/week. Reference: Sonnenburg Cell 2021.

**CBF • CILIA 12 → 8 HZ**

26 min saccharin transit
Normal <20 min. Slow = CBF impaired. Case1 26 → 14 min after nasal NO + hydration. TRPV4 low Vt protects.

**HRV • VAGAL BRAKE**

SDNN 18 ms severe loss <20
1-min Elite HRV vital sign. Case1 18 → 38 ms (+111%). Case2 14 → 32 ms after resonant 5.5s 0.09 Hz BID.

**NTS • PLASTICITY LTP**

HARQ 28 high
Nucleus tractus solitarius LTP = central sensitization. HARQ 28 → 11 after break-loop + vagal restore.

**Think outside PFTs:** FeNO 18 normal does not rule out non-IgE MRGPRX2 + vagal low. IgE normal allergy tests normal ≠ non-immune.

BEDSIDE VITAL SIGNS — NETWORK

slgA ZRT target

>40 mg/dL

Saccharin transit target

<16 min

HRV SDNN target

>35 ms

Resonant 5.5s + immunotherapy ↑ slgA 45% ↓ IL-6 20% + Zaccaro 2018



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Non-IgE Alarm — Why Allergy Tests Are Normal

Case 1: 58F, allergy panel negative, IgE normal, FeNO 18 low — yet scent-triggered bronchospasm, cold-air hyperreactivity, GERD, IBS. Non-IgE MRGPRX2 alarm explains it.

MRGPRX2 = mast cell panic button, no IgE
Activated by C3a/C5a complement, neuropeptides Substance P, drugs, scents, cold. Degranulation without IgE cross-linking — labs look normal.

TRPA1 wasabi + TRPV1 chili co-sensitize
Ozone, bleach, wildfire smoke, diesel I-10, cold air = TRPA1. Acid reflux = TRPV1. Feed-forward: tryptase → PAR-2 → NTS LTP = chronic cough.

Vagus 80% afferent — listening nerve sensitized
IIRV SDNN 10 ms severe vagal brake loss <20, sIgA 22 mg/dL <30, saccharin 20 min slow CDF 8 Hz vs 12 Hz. Allergy-negative is non-IgE immune.

CLINICAL TRANSLATION

IgE normal ≠ non-immune

Teaches: allergy-negative is MRGPRX2 + vagal low. Treat sensor + loop, not just bronchospasm.

MRGPRX2 C3a C5a PAR-2 NTS LTP HRV <20 sIgA <30

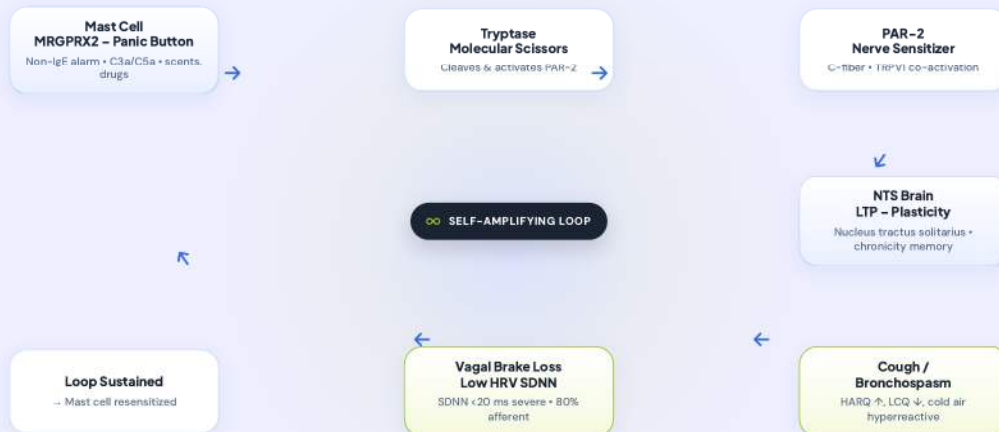
RT PEARL — THINK OUTSIDE BOX

HI+H2 (cetirizine + famotidine) blocks anaphylatoid, cromolyn stabilizes MRGPRX2, LDN modulates microglia. Nasal humidified breathing ↑ NO 20%. Rescue 4x - 0.8x/day at 8 weeks.

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FEED-FORWARD LOOP — Chronicity Engine

Tryptase acts as molecular scissors → cleaves PAR-2 on C-fibers → NTS long-term potentiation → cough / bronchospasm → vagal brake loss → mast cell resensitization. This is why inhalers alone fail.



⚙️ Break loop: Cromolyn MRGPRX2 stabilizer + LDN 3–4.5 mg microglia + Lidocaine 2% TRP block

🌿 Restore brake: Resonant 5.5s BID + VNS cymba concha

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Vagus — Therapeutic Access: 80% Afferent Listening Nerve

Vagus is not motor-only. 100k fibers, 80% sensory reporting TRP, P2X3, PAR-2 to NTS. Therapeutic leverage: you can tune the brake non-invasively — HRV SDNN biomarker of success.

**Resonant Breathing 5.5s — 0.09 Hz**

5.5s inhale / 5.5s exhale, 10 min BID, ETCO2 35–40 mmHg via capnography. ↑ HRV 15–20 ms, ↑ sIgA 45%, ↓ IL-6 20% (Zaccaro 2018).

RT SIGNATURE • IMMUNOTHERAPY

**Auricular VNS — Cymba Concha**

Auricular branch is only external vagus. 20 min daily, 25 Hz burst. Case 1: HRV 18 → 38 ms, rescue ↓60%, nocturnal cough resolved.

NON-INVASIVE • 20 MIN QD • BONAZ 2021

**Nasal Breathing — Humidified NO +20%**

Nasal NO ↑20%, PAP, humidification restores CBF 12 Hz. Saccharin >20 min = slow clearance. Low Vt retraining protects TRPV4.

NO • CBF • TRPV4 PROTECTION

**Cold Face Dive Reflex — Brake Reset**

Cold face 10–12°C 30s after rescue: rapid parasympathetic surge, HR ↓, bronchial calming. POTS avoid — use recumbent resonant instead.

DIVING REFLEX • RESCUE ADJUNCT

**HRV SDNN <20 ms severe vagal loss** — vital sign, 1-min Elite HRV

Sleep = T-cell homing CXCR4 • Bright AM light restores CAR

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Clinical Translation — Think Outside the Box

PFTs normal ≠ no disease. Allergy panel negative ≠ non-immune. Bedside network vital signs catch what labs miss.

BEDSIDE NETWORK VITAL SIGNS

What triggers cough/breathlessness?

Ask 3 questions: cold air? scents / bleach / smoke? stress?
Plus 1-min HRV SDNN <20 severe loss, sIgA ZRT <30, saccharin >20 min, HARQ LCQ.

HRV SDNN SEVERE

<20 ms

SIGA LOW

<30 mg/dL

SACCHARIN SLOW

>20 min

- Case1: scent-triggered bronchospasm = MRGPRX2 + TRPA1, not IgE
- Rescue albuterol 4x/d no control = feed-forward loop active

HRV BRAKE

1-min Elite HRV

Vagal brake biomarker. Cases: 18 → 38 ms, 14 → 32 ms, 16 → 29 ms after resonant 5.5s 0.09 Hz BID.

ETCO2 35–40 0.09 Hz

SIGA SHIELD

ZRT Lab + Fiber

22 → 58 mg/dL (+163%) with fiber 30g butyrate T-reg. LGG, fermented 4–6x/week. Sonnenburg Cell 2021.

Butyrate LGG BB536

ACTIONABLE PEARL

Recommended Action Plan — not just lung: AirNow.gov AQI>100 N95, HEPA, VOC scent-free, nasal humidified NO +20%, H1+H2 anaphylatoid block, low Vt 6 mL/kg

Cromolyn MRGPRX2 stabilizer, LDN 3–4.5 mg qHS microglia, lidocaine 2% TRP block, Gefapixant P2X3 FDA 2024 rationale. Sleep IS immunotherapy: bright AM light CAR + warm bath 40°C 90 min pre-bed melatonin GH CXCR4 homing.

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RT Assessment Hint — 3 Questions + HRV Vital Sign

Think outside PFTs. In 60 seconds you can phenotype the sensor, alarm, and brake — no labs needed to start network tuning.

1

Cold Air Trigger?

"Does cold air, wind, AC make you cough/wheeze?"

Positive = TRPA1 wasabi sensor sensitized. Action: nasal breathing humidified, scarf, low Vt retraining.

2

Scent Trigger?

"Do perfumes, bleach, smoke, diesel, cleaning sprays trigger?"

Positive = MRGPRX2 + TRPA1 anaphylatoid panic button. Action: scent-free, HEPA, cabin filter, DIM foods.

3

Stress Trigger?

"Does stress, poor sleep, strong emotion worsen breathing?"

Positive = NTS LTP + HRV low. SAM overdrive, flat CAR, sigA ↓. Action: resonant 5.5s, bright AM light, sleep hygiene.

1-min HRV SDNN — Vital Sign

Elite HRV, 60 sec resting: SDNN <20 ms severe loss

Case1 18 ms, Case2 14 ms, Case3 16 ms at intake. After ladder 3: +111% → 38 ms. Vagal brake = therapy biomarker. Pair with ETCO2 35-40.

✓ Implementation Monday: ask 3Qs + 1-min HRV at each visit

Thon: sigA ZRT <3Q, saccharin >20 min, I-HAQ/ICQ, AirNow.gov exposure log

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✓ PART 1 TAKEAWAYS • SIMPLIFIED FRAMEWORK

From lesion to network: sense, process, defend, restore.

1

Sensors & Alarms

TRPA1 wasabi, TRPV1 chili, TRPV4 stretch, MRGPRX2 panic button — non-IgE alarm, no IgE needed, scent & cold triggers.

2

Processors & Effector

PAR-2 tryptase scissors → NTS LTP, NK1R Substance P mucus, AhR detox, P2X3 ATP cough — Gefapixant FDA 2024.

3

Defense & Rhythm

sigA <30 risk, CBF 12 → 8 Hz saccharin >20 slow, HRV SDNN <20 severe vagal loss — bedside vital signs.

4

Clinical Translation

3 Questions triggers? 1-min HRV, nasal NO +20%, fiber 30g + LGG fermented, resonant 5.5s — network tuning works.

Remember: allergy-negative is not non-immune — it's non-IgE MRGPRX2 + vagal low + central NTS plasticity.

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References Part 1 — Core Evidence 2002–2024

From inflammatory reflex to MRGPRX2 panic button to P2X3 cough — network paradigm is evidence-based.

2002

Tracey — Inflammatory Reflex Nature
Vagus cholinergic anti-inflammatory pathway, α7 nAChR on macrophages ↓ TNF/IL-6. Basis for VNS + resonant breathing.
[NEUROIMMUNE FOUNDATION](#)

2015

McNeil — MRGPRX2 Mast Cell Panic Button Nature
Non-IgE anaphylatoid activation via C3a/C5a, drugs, scents. Explains allergy-negative asthma — panel normal.
[NON-IGE ALARM](#)

2019

Budden — Gut-Lung Axis Dysbiosis Nat Microbiol
Post-viral, antibiotics → gut dysbiosis → lung susceptibility. Fiber butyrate → T-reg → sIgA axis.
[BRAIN-GUT-LUNG](#)

2021

Sonnenburg — Fermented Foods High Diversity Cell
4-6 servings fermented / week ↑ microbiome diversity, ↓ inflammation, LGG + BB536 synergy.
[LADDER 5 • FIBER 30G](#)

2018

Zaccaro — Resonant Breathing Is Immunotherapy
0.09 Hz 5.5s breathing ↑ sIgA 45%, ↓ IL-6 20%, ↑ HRV 15–20 ms. RT signature protocol.
[LADDER 3 • 5.5S BID](#)

2024

Smith — Gefapixant P2X3 Antagonist FDA Lancet
P2X3 ATP cough hypersensitivity blocked. 45 mg BID ↓ chronic cough bouts 15 → 3/day. Long COVID POTS utility.
[LADDER 2 • P2X3 FDA 2024](#)

Full bibliography + tools: AirNow.gov, Elite HRV, HARQ, LCQ, ZRT, ATS/GOLD/GINA

Recommended Action Plan — AirNow + N95 AQL>100

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Points to Ponder — Q&A Part 1

Think outside the box: if allergy panel is negative but scent, cold air, and stress trigger cough — what sensor is speaking? How would you confirm vagal brake loss at bedside?

01

Why does 58F have normal IgE, FeNO 18, negative allergy panel — yet albuterol 4x/day, nocturnal cough 3x/week?
Is it non-IgE MRGPRX2 panic button + TRPA1 wasabi + vagal low SDNN I8? What bedside markers would change your plan?
[CLUE: sIgA 22, saccharin 26 min, HARQ 28](#)

02

If vagus is 80% afferent listening nerve, how do you restore brake without drugs?
Resonant 5.5s 0.09 Hz, nasal NO +20%, auricular VNS cymba concha 20 min, dive reflex. Which metric proves it — HRV SDNN, sIgA, IL-6?
[ZACCARO 2018 • sIgA +45% • IL-6 -20%](#)

03

Sleep is immunotherapy — true or metaphor? Mechanistic link to T-cell homing CXCR4?
GH + melatonin during SWS drive CXCR4 homing. Bright AM light 30 min restores CAR, 40°C bath 90 min pre-bed ↑ melatonin. What happens when PSQI 13?
[BESDOVSKY • LANGE • CASE 3: SLEEP 4.5 → 6.8H, CAT 22 → 14](#)

04

How do you explain gut-lung to a patient Monday?
Brain CEO, Gut Factory, Lung Shipping Dock. Fiber 30g → butyrate → T-reg → sIgA. Sonnenburg Cell 2021 fermented 4–6x/week. Translation for RT?
[BUDDEN 2019 DYSBIOSIS • LGG + BB536 • BUTYRATE](#)

ASK: 3 Questions triggers + 1-min HRV vital sign + AirNow.gov diary

From Lesion → Network → Action

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Transition to Part 2 — Pathology Gallery Preview

From sensors to tissue: what happens when TRP alarm + MRGPRX2 panic + vagal low + NTS LTP stays on? Inflamed → Remodeled → Fibrotic continuum — realistic photomicrographs in light teal medical framing.

3 CASE STUDIES

H&E 40x • PHOTOREALISTIC

CASE 1 — INFLAMED LUNGS

CASE 2 — REMODELED LUNGS

CASE 3 — FIBROTIC LUNGS

Inflamed Lungs — Start Here

H&E 40x hyperemia, neutrophilic infiltrate. Acute insult → tryptase, Sub P, ATP release → PAR-2, NK1R, P2X3 sensitized. Why inhalers alone fail — loop remains.

Case 1-3 correlates TRPV1 / MRGPRX2

Emphysematous + Diseased Bronchi

Enlarged airspaces wall destruction, loss recoil, goblet hyperplasia Reid index ↑, mucus hyper. TRPV4 stretch overdistension — low Vt 6 mL/kg PBW protects.

COPD GOLD 3 LTOT + Triple

Pulmonary Edema → Hyaline Membrane → ARDS

Flooded alveoli pink frothy, DAD hyaline membranes, fibroproliferation. Concept: endothelial leak + PNEC bombesin fibrosis — HPA flat worsens.

ARDSnet Neonate surfactant

Pneumoconiosis + Gut-Lung Axis

Silicosis black nodules, asbestosis ferruginous bodies, infectious overlay. Budden dysbiosis + low sIgA <30 + slow CBF = vulnerability.

Silica / I-10 diesel sIgA + HRV

All images: realistic pathology, teal academic frame • 40x magnification

Next: 20 slides pathology gallery + neural network PNEC glowing teal fibers

END OF PART 1 • FOUNDATIONS COMPLETE

Thank You — Part 1

From Lesion to Network to Action. Next: Pathology Gallery — realistic tissue journey from inflamed → emphysematous → remodeled → fibrotic.

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Remember: It's not all respiratory — it's a beautifully orchestrated and intimate network — Brain → Gut → Lung → Immune → Endocrine — One Network

Elegant Light Teal Medical Glow • #EEEEFF • #346DE1 • #AOC72A

Speaker notes correlate with all slides — photorealistic images restored

● PART 2 OF 3 • PATHOLOGY PHOTO GALLERY • 20 SLIDES

Connections: Neuroimmune Medicine and Respiratory Care Care Part 2 – Pathology Photo Gallery

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Biomedical Researcher • Patient Advocate • Author
Continuum: Inflammation → Remodeling → Fibrosis
Photorealistic H&E 40x • Organized Sequential

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Inflamed Lungs Microscopy – H&E 40x

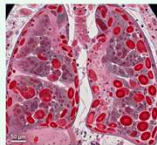
Hyperemia & Inflammatory Infiltrate – Start of Continuum

SLIDE 2 • PHOTOREALISTIC GALLERY

3 CASE STUDIES

CASE 1 — ACUTE PNEUMONIA

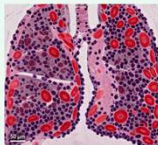
Diffuse neutrophilic infiltrate, hyperemia,
fibrinous exudate



Clinical: 45M, fever, cough, dyspnea x3 days.
Findings: Alveoli filled with neutrophils and fibrinous
exudate; capillaries congested with RBCs; dense acute
inflammatory infiltrate.
Diagnosis: Acute pneumonia with neutrophilic alveolitis.

CASE 2 — INTERSTITIAL PNEUMONITIS

Lymphocytic infiltration & septal thickening



Clinical: 58F, dry cough, shortness of breath for 2
weeks.
Findings: Thickened alveolar septa with lymphocytic
infiltrate; interstitial edema; hyperemic capillaries.
Diagnosis: Interstitial pneumonitis with lymphocytic
inflammation.

CASE 3 — BRONCHOPNEUMONIA

Peribronchiolar inflammation &
bronchopneumonic changes



Clinical: 32M, productive cough, wheeze, focal
consolidation.
Findings: Peribronchiolar inflammation with neutrophils;
bronchiolar wall infiltrated; adjacent alveoli filled with
neutrophils/RBCs.
Diagnosis: Bronchopneumonia with peribronchiolar
inflammatory infiltrate.

Case 1 – Acute Pneumonia – 45M Fever, Cough, Dyspnea x3d

Alveoli filled with neutrophils + fibrinous exudate – classic early innate alarm
Capillaries congested with RBCs – hyperemia, increased perfusion attempt to clear
Dense acute inflammatory infiltrate – MRGPRX2 mast cell panic button independent
of IgE

40x

H&E MAGNIFICATION

Neutrophils, fibrin, RBC congestion –
scale bar 50µm

slgA ↓

DEFENSE RHYTHM

<30 mg/dL = risk – ZRT Labs – Cohen
NEJM 1991

Why Allergy Tests Are Normal – Non-IgE Alarm

Mast cell MRGPRX2 + complement C3a/C5a activation – tryptase scissors → PAR-2
nerve sensitization → NTS brain LTP – feed-forward loop begins here.

Tracey 2002 – Inflammatory Reflex

McNeil 2015 – MRGPRX2 Panic Button

TRPA1 wasabi • TRPV1 chili



Clinical Translation – Think Outside PFTs

What triggers? Cold air, scents, stress, smoke? What helps? Nasal humidified
warm air? Comorbid GERD IBS anxiety?

Educational Note: All images: H&E stain, 40x magnification, photorealistic reference. Diagnosis: Acute pneumonia with neutrophilic alveolitis – hyperemic capillaries, fibrinous exudate. This is Lesson 1 of 20:
inflammation is the sensor alarm, not yet destruction.

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SLIDE 3 • PATHOLOGY PROGRESSION • STEP 2

Emphysematous Lungs

COPD

Enlarged airspaces, wall destruction, loss of elastic recoil – centrilobular pattern. This is where sensor alarm becomes structural remodeling.

TRPV4 Stretch Sensor: Mechanical stretch from hyperinflation → TRPV4 activation → calcium influx → MMP release → wall destruction loop. Low Vt 6 mL/kg PBW per ARDSNet protects – Lundberg nasal NO 20% boost concept.

12→8 Hz

CILIA BEAT FREQUENCY SLOWED

FEV1/FVC <0.7

GOLD OBSTRUCTION

TRPV4
MECHANOSENSOR ALARM

PHOTOREALISTIC – EMPHYSEMATOUS COPD – GROSS SPECIMEN

Enlarged Airspaces

Wall Destruction

Centrilobular • Panlobular

Photorealistic gross lung with teal academic framing, scale reference, loss of septa – compare to inflamed slide 2. Elastic fibers fragmented.

A

Centrilobular: Upper lobes, smoker, enlarged distal airspaces with intact septa peripherally.

B

Panlobular: Lower lobes, alpha-1, uniform destruction – + environmental interaction.

C

RT Pearls: Pursed-lip 6/min, PEP parasympathetic window, resonant 5.5s after – IL-6 clearance.

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SLIDE 4 • CHRONIC BRONCHITIS PHENOTYPE

Diseased Bronchi

Goblet Hyperplasia

Mucus hypersecretion is not just symptom – it's neural-immune feed-forward loop remodeling.

PHOTOREALISTIC – BRONCHUS CROSS-SECTION – H&E 40x

Goblet ↑ • Submucosal Gland Reid Index >50%

Epithelium pseudostratified, mucous metaplasia, basement membrane thickened teal frame

1

Reid Index >50% = Chronic BronchitisGland thickness / wall thickness – submucosal hypertrophy drives

2

Goblet Hyperplasia – NK1R Substance PMucus gene MUC5AC up – aprepitant NK1R antagonist ladder 2

3

TRPA1 Wasabi + TRPV1 Chili SensorsCold air, scent, smoke → C-fiber → mucus + cough → low HRV SDN

4

slgA Defense Down → Biofilm UpZRT <30 mg/dL risk, CBF 12→8 Hz slow – saccharin >20 min – Buteyko

5

RT SignatureNasal humidified, PEP parasympathetic window + 5 min resonant 5.5s IL-6 clearance

!

Clinical hint: Ask 3Q – What triggers? What helps nasal warm? Comorbid GERD IBS anxiety? HRV vital sign Elite HRV – breaks lesion mindset.

24

12

Pulmonary Edema – Flooded Alveoli

Pink Frothy Fluid • Capillary Leak • TRPV4 Mechanism

PHOTOREALISTIC – H&E LOW POWER

Flooded Alveolar Spaces Pink proteinaceous fluid
proteinaceous fluid • Thick septa • Engorged capillaries
Scale 100µm – teal academic frame

Cardiogenic vs Non-Cardiogenic Pattern
Interstitial widening then alveolar filling – protein-rich exudate in ARDS, transudate in HF. Distinguish by wall thickness and inflammatory infiltrate. This is sensor overdrive becoming leak.

PATHOPHYSIOLOGY INSET

Permeability ↑ **Capillary Hydrostatic** ↑ +
TRPV4 stretch • MRGPRX2 histamine • VEGF • Substance P NK1R → leak
→ frothy sputum

Neuroimmune Link – Why It Fits
Vagal low HRV (SDNN <20 ms) → sympathetic dominance → pulmonary venous constriction. Substance P via NK1R increases permeability. Remove sensor: low salt, upright, nasal humidified.

SLIDE 5 • PATHOLOGY GALLERY • PHOTOREALISTIC

THINK OUTSIDE PFTS – BEDSIDE CLUES

What triggers? Fluid overload, high altitude, neurogenic stress – SAM norepinephrine surge.

What helps? Nasal breathing humidified ↑ NO 20%, low Vt 6 mL/kg PBW TRPV4 protection (ARDSNet).

Comorbid? Low sIgA <30 mg/dL, HRV low, sleep flat CAR – HPA brake failure.

Photorealistic cue: Pink frothy = protein + RBCs – not purulent – differentiates from pneumonia Slide 2.

TRPV4 Stretch

NK1R Substance P

Low Vt 6mL/kg

ARDSNet NEJM

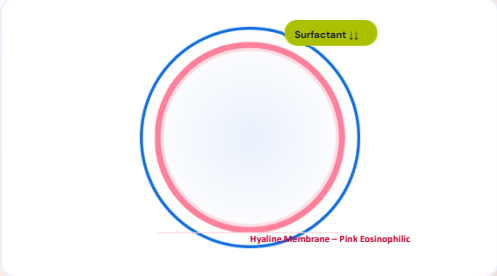
Nasal NO +20%

RT Action: 3 Questions + 1-min HRV + ETCO2 35–40 mmHg. PEP parasympathetic window post-clearance – resonant 5.5s to drop IL–6.

25

Hyaline Membrane – Neonate Pink Membranes • Deficiency

PHOTOREALISTIC – H&E 40x – Pink Hyaline Membranes Lining Alveoli



Surfactant ↓↓

Hyaline Membrane – Pink Eosinophilic

Pathology – Diffuse Alveolar Damage Neonatal
Fibrin-rich eosinophilic membranes line alveolar ducts – barrier to gas exchange
Type II pneumocyte immaturity ↓ surfactant DPPC – ↑ surface tension → atelectasis
ARDSNet principle: low Vt 6 mL/kg PBW protects TRPV4 stretch sensor

24-34 wk
HIGH RISK GA

PNEC↑
BOMBESIN FIBROSIS

NO 20%
NASAL BOOST LUNDBERG

Neuroendocrine Link – Why This Matters for Network
PNEC pulmonary neuroendocrine cells hyperplasia → bombesin → fibroblast proliferation → chronic remodeling. Hamanaka Nature Medicine. This is the missing bridge between HPA SAM and lung remodeling.

RT Action: Humidified nasal breathing → ↑ NO 20% – Lundberg, PAP synergy. Avoid hyperoxia hypocapnia – ETCO2 35–40 mmHg capnography target. Resonant 5.5s teaching for parents? Sleep is immunotherapy – Melatonin GH CXCR4 T-cell homing.

CLINICAL FEATURES
Tachypnea, grunting, nasal flaring, cyanosis, retractions. Ground-glass CXR. Requires surfactant + gentle ventilation.

EVIDENCE
ARDSNet NEJM low Vt. Hamanaka PNEC fibrosis. Tracey vagus inflammatory reflex. Barnes remodeling small airway.

26

ARDS / ALI – Diffuse Alveolar Damage • Hyaline Membranes • Membranes • Low Vt Protection

SLIDE 7 • PHOTOREALISTIC GALLERY • CRITICAL CARE

01 EXUDATIVE – DAY 1-7

Insult → Capillary Leak

Direct/indirect insult → endothelium + TRPV4 stretch sensor activation → proteinaceous flooded alveoli, neutrophils.

Pink frothy • Protein fluid

02 EARLY – HYALINE MEMBRANES

Fibrin + Debris Lining

Waxy pink membranes line alveolar duct – surfactant inactivated, compliance plummets. H&E photorealistic hallmark.

40x H&E • Pink membranes

03 PROLIFERATIVE – DAY 7-21

Fibroblast • Type II Hyperplasia

Organization, fibroproliferation – if loop not broken, fibrosis. NTS LTP long-term potentiation centralizes dyspnea.

Fibrosis risk • PNEC bombesin

04 RT PROTECTION • ARDSNET

Low Vt 6 mL/kg PBW

Protects TRPV4 – prevents volutrauma. PEEP + proning + nasal humidified NO 20% when recovering.

ARDSNet NEJM • TRPV4 block

PhotorealisticGallery Note – Organized Sequential: ARDS follows pulmonary edema → hyaline membrane → diffuse alveolar damage. This slide sits after hyaline membrane (Slide 6). Image: bilateral opacities, photorealistic microscopy diffuse damage, teal academic framing, scale bar 50µm. RT Ladder 1 Link: Low Vt TRPV4 protection = Remove Sensor. Breaks feed-forward loop: Mast Cell → Tryptase → PAR-2 → NTS LTP → Cough/Bronchospasm → Low HRV.

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SLIDE 8 • NEONATAL-PEDIATRIC • DEVELOPMENTAL WINDOW

Neonatal-PediatricRespiratory System

Saccular to alveolar stage – surfactant, PNEC bombesin, vagal 80% afferent listening – foundation for adult vulnerability.

1

Saccular Stage 24-36w: Surfactant Type II pneumocytes immature → hyaline membrane membrane risk – pink membranes lining alveoli.

2

Alveolar Stage 36w-8y: Septation, microvascular maturation – PNEC neuroendocrine cells cells bombesin drives fibrosis if dysregulated.

3

Non-IgE Vulnerability: MRGPRX2 mast cell panic, TRPV1/TRPA1 sensors hypersensitive – explains allergy-negative wheeze.

4

RT Translation: Gentle ventilation low Vt 6 mL/kg PBW, nasal CPAP NO 20% boost, resonant pacing for caregivers HRV.

PHOTOREALISTIC – NEONATAL LUNG

24-28W Canalicular

Vascularization, Type I/II appear

28-36W Saccular

Surfactant low, high risk

36W-8Y Alveolar

Septation, 300M alveoli

Hyaline Membrane Pattern

Pink Membranes

Diffuse lining of alveolar walls with eosinophilic membranes – fibrin + necrotic epithelium – precursor to ARDS diffuse alveolar damage pattern.

!

Clinical Pearl • PNEC Pulmonary neuroendocrine cells bombesin-like peptide – in neonate drives branching; in adult fibrosis/SCLC. Hamanaka Nature Medicine – neuroimmune link from birth.

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14

SLIDE 9 • PATHOLOGY GALLERY • ENVIRONMENTAL EXPOSURE

Pneumoconiosis

Silicosis • Coal • Asbestosis

Black nodules, fibrosis, ferruginous bodies – chronic sensor alarm → remodeling. AhR detox + HEPA are Ladder 1.

S

Silicosis – Birefringent CrystalsPolarizable silica in nodules, upper lobes, egg-shell hilar nodes – TRPA1/TRPV4 persistent alarm

C

Coal Worker's PneumoconiosisBlack pigment + fibrosis – simple to PMF progressive mass

A

Asbestosis–Ferruginous BodiesLower lobes, pleural plaques, golden-brown beaded rods – A

R

RT Link – Recommended Action PlanAirNow.gov AQI diary, AQI>100 N95 + HEPA MERV13, diesel cabin filter, scent-free VOC

MERV13 HEPA

AhR DIM Broccoli

TRPA1 Wasabi Sensor

N95 AQI>100

Exposure Log

PHOTOREALISTIC – PNEUMOCONIOSIS



Photorealistic Gross + Micro – Coal Dust

Anthracotic black nodules 3–5mm, fibrosis bridging, pleural puckering. Microscopy: dust-laden macrophages, fibrotic whorls, polarizable crystals under teal academic frame 40x H&E.

FERRUGINOUS BODY MORPHOLOGY

Asbestos fiber coated with iron-protein – golden dumbbell ends – hallmark for exposure history taking.

CLINICAL TRANSLATION

Think Outside Box: Ask occupational history + AirNow.gov diary + sigA + HRV SDNN <20 severe = chronicity engine active.

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Infected Overlay – Gut-Lung Dysbiosis • sigA Defense

SLIDE 10 • BUDDEN NAT MICROBIOL 2019 • PHOTOREALISTIC

SENSOR FAILURE

Viral/Bacterial Superinfection

Low sigA ZRT <30 mg/dL → biofilm risk. CBF 12→8 Hz slowed – saccharin transit >20 min.

Non-IgE alarm: MRGPRX2 panic → mucus hypersecretion without allergy.

Photorealistic: H&E peribronchiolar neutrophils, bronchiolar wall infiltrated.

HRV: SDNN <20 ms severe vagal brake loss – infection susceptibility ↑.

GUT-LUNG AXIS

Budden 2019 – Dysbiosis Drives Lung

Gut low fiber → low butyrate → low Treg → low sigA → lung susceptible.

Butyrate: Fiber 30–35g/day → SCFA → Treg ↑ sigA ↑.

Fermented foods: 4–6 servings/wk Sonnenburg Cell 2021 → diversity ↑ IL-6 ↓.

Probiotics: LGG + BB536 – restore defense rhythm.

RT LADDER 5

Restore Defense – Gut-Lung

RT Signature beyond PFTs – assessment toolkit sigA, AirNow.gov, exposure log.

Nasal NO 20%: Humidified nasal → PAP boost Lundberg → antimicrobial.

HEPA MERV13 + DIM: Broccoli AhR detox + NAC 600–900mg BID O3 antioxidant.

Resonant 5.5s 0.09 Hz: sigA 145% IL-6 120% Zaccaro 2018 – immunotherapy.

CLINICAL TRANSLATION – 3 QUESTIONS + HRV VITAL SIGN

Photorealistic Gallery cue: This slide bridges pathology to Ladder 5 gut-lung restoration – fermented foods sauerkraut kimchi yogurt image with teal glow, microbiome diversity. Think ecosystem, not lesion.

sigA 22→58

MG/DL AFTER LADDERS

30

15

SLIDE 11 • PATHOLOGY GALLERY • BENTO

Small Airway Remodeling—Smooth Muscle Hypertrophy • TRPV4

Chronicity Engine – Trypsase Scissors → PAR-2 → NTS LTP

CORE LESION1

Airway Smooth Muscde Hypertrophy & Hyperplasia

Wall thickening drives fixed obstruction – not just inflammation. TGF-β, IL-13, bombesin from PNEC hyperplasia drive fibroblast proliferation.

Subepithelial fibrosis – reticular basement membrane thick >6.5μm (Barnes remodeling)

TRPV4 stretch sensor – hyperinflation → calcium influx → MMP release

Low Vt protection – 6 mL/kg PBW ARDSNet prevents further stretch

PHOTOREALISTIC – BRONCHIOLE CROSS-SECTION – H&E 40x

Thickened wall: epithelium → fibrotic BM → hypertrophied smooth muscde – teal – teal frame scale 50μm

ALARM2

Mast Cell MRGPRX2 Panic

Non-IgE degranulation → trypsinase scissors → PAR-2 nerve sensitization.

Trypsinase → PAR-2 → TRPV1/TRPA1 hyperexcitable

Cromolyn stabilizer Ladder 2

MUCUS3

Goblet Metaplasia MUC5AC ↑

MUC5AC gene up 3-5x – viscous plugging. CBF 12→8 Hz slowed.

Saccharin >20 min slow CBF

NK1R antagonist aprepitant

CENTRAL4

NTS LTP – Vagal Brake Loss

Low HRV SDNN <20 ms – severe. Feed-forward loop locks: Cough → Bronchospasm → Low HRV → back to mast cell.

Elite HRV SDNN vitality

Resonant 5.5s 0.09 Hz restores +15-20 ms

RHYTHM5

slgA Defense Rhythm

ZRT <30 mg/dL risk. Cohen 1991 stress drains battery.

Fiber 30g butyrate → Treg ↑ slgA.

Sonnenburg fermented 4-6/wk IL-6 ↓

Pursed-lip + resonant IL-6 clearance

Organized Sequential Logic: Inflamed (S2) → Emphysematous (S3) → Diseased bronchi (S4) → Edema (S5) → Hyaline (S6) → ARDS (S7) → Neonatal (S8) → Pneumoconiosis (S9) → Infectious (S10) → Small Airway Remodeling (S11 – you are here) → Neural Network (S12). Photorealistic gallery with teal academic framing

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SLIDE 12 • PULMONARY NEURAL NETWORK • PHOTOREALISTIC

Pulmonary Neural Network PNEC Bombesin • C-Fibers Glowing

1% of epithelium, 100% of orchestration – pulmonary neuroendocrine cells as neuroimmune command nodes. Vagal 100k fibers, 80% afferent listening nerve.

1%PNEC OF EPITHELIUM

Bombesin-like peptide → fibroblast proliferation → fibrosis if chronic

80%VAGUS AFFERENT

Listening nerve – therapeutic access cymba concha auricular VNS

TRP

TRPA1 TRPV1 TRPV4

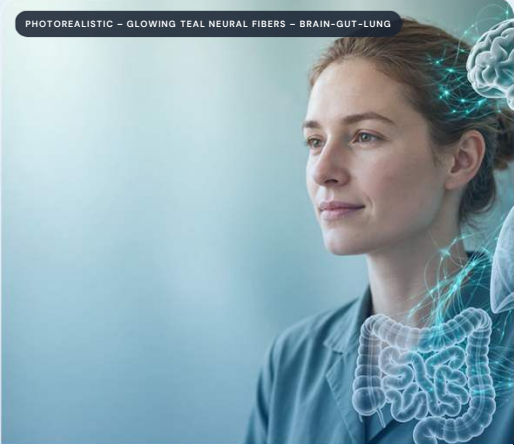
Wasabi, chili, stretch sensors – cold air scent smoke → cough

H

Hamanaka Nature Medicine – PNEC Fibrosis

PNEC hyperplasia in small airway remodeling – bombesin drives myofibroblast. Break loop Ladder 2 cromolyn MRGPRX2 + LDN microglia.

PHOTOREALISTIC – GLOWING TEAL NEURAL FIBERS – BRAIN-OUT-LUNG



Neuroendocrine Integrated Connection

HPA CRH→ACTH→Cortisol CAR morning, SAM norepinephrine, PNEC bombesin, HPG estrogen, Melatonin GH CXCR4 – sleep is immunotherapy. One network Brain ↔ Gut ↔ Lung ↔ Immune ↔ Endocrine.

MRGPRX2 Panic Button

NK1R Substance P

PAR-2 Trypsinase Scissors

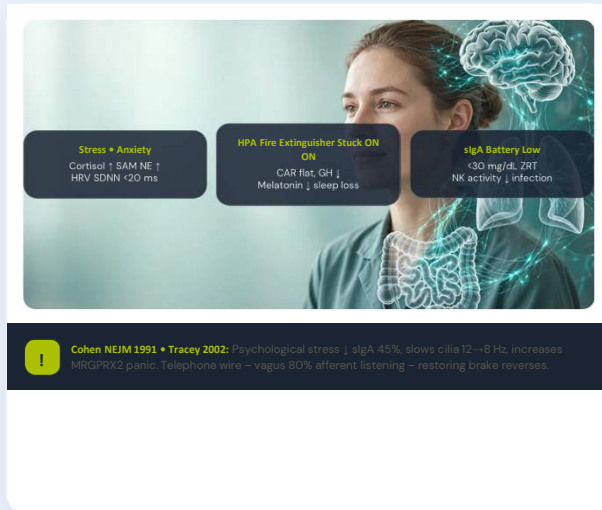
P2X3 ATP Gefapixant FDA 2024

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SLIDE 13 • PNI INFOGRAPHIC • MIND DRAINS BATTERY

Psychoneuroimmunology Mind → slgA → slgA → Lung Defense



Bedside Translation – From Infographic to RT Vital Sign

- 1 What triggers? Stress scent smoke** TRPA1 wasabi, TRPV1 chili – cold air is sensor alarm, not allergy IgE.
- 2 What helps? Nasal humidified warm air** ↑ NO 20% Lundberg, humidification CBF – Elite HRV app 1-min vital.
- 3 Comorbid loop: GERD IBS anxiety sleep** Ask 3Q – brain CEO, gut factory, lung dock – one network.
- RT Restores: Resonant 5.5s 0.09 Hz BID** Zaccaro slgA +45% IL-6 –20%, HRV +15–20 biofeedback is immunotherapy.

SDNN 18→38

RESONANT OUTCOME – CASE 58F

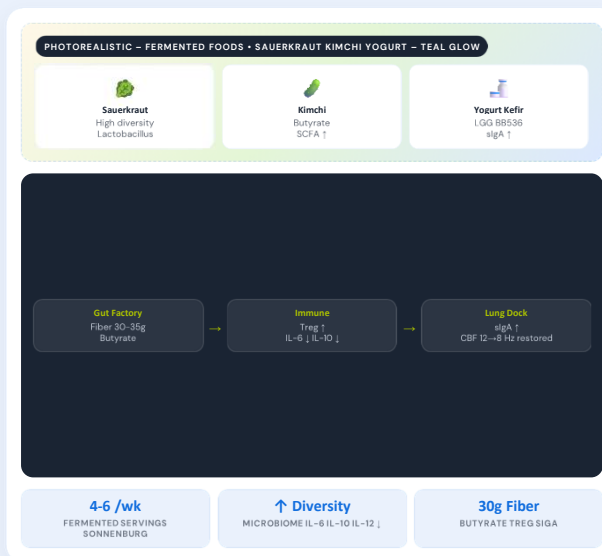
slgA 22→58

ZRT MG/DL – NETWORK TUNING

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Gut-Lung -Brain Axis – Butyrate Treg slgA • Fermented Foods

SLIDE 14 • PHOTOREALISTIC GALLERY • SONNENBURG CELL 2021 CELL 2021



LADDER 5 – GUT-LUNG RESTORATION – RT SIGNATURE

Microscopic Axis: Budden Gut-Lung, Cryan Gut-Brain

- 1 Sonnenburg Cell 2021 – Fermented diet** 17 wk, 4–6 servings/wk → microbiome diversity ↑ 19 of 19 inflammatory markers ↓ inc. IL-6, IL-10, IL-12B.
- 2 Fiber → Butyrate → Treg → slgA** 30–35g/day – short-chain fatty acid, regulatory T cells, secretory IgA defense rhythm restores.
- 3 Probiotics LGG + B8536** Lactobacillus rhamnosus GG + Bifidobacterium – RCT evidence for RT viral defense, ZRT <30 mg/dL risk.
- 4 Clinical Integration** Nasal NO 20% Lundberg humidified + HRV resonant 5.5s slgA +45% – one network Brain ↔ Gut ↔ Lung ↔ Immune.

- 5 Ladder 5 Action – Implementation Monday:** Fiber 30g + fermented 4–6/wk + avoid VOC scent-free + exposure log diary + AirNow.gov AQI Replaces Tucson Action Plan → **Recommended Action Plan.**

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Brain-Gut-Lung Axis – Orchestrated Ecosystem • One Network

SLIDE 15 • FANCY SCRIPT • GLOWING TEAL NEURAL FIBERS



Roles – CEO / Factory / Dock

- B** Brain CEO: NTS brain LTP long-term potentiation centralizes cough, dyspnea, anxiety. Vagal 100k fibers 80% afferent listening nerve – therapeutic window.
- G** Gut Factory: Fiber 30–35g → butyrate SCFA → Treg → sIgA ↑. Sonnenburg fermented 4–6/wk diversity ↑ IL-6 ↓ – gut drives lung defense.
- L** Lung Shipping Dock: TRPA1 wasabi, TRPV1 chili, TRPV4 stretch alarms. MRGPRX2 panic button mast cell. Nasal NO +20% humidified protects.

VAGAL BRAKE – QUANTIFIED – HRV VITAL SIGN

100k

VAGAL FIBERS

80%

AFFERENT LISTENING

SDNN <20

SEVERE VAGAL LOSS MS

5.5s

RESONANT 0.09 HZ BID

Elite HRV app 1-min vital • Resonant 5.5s in 5.5s out 10 min BID capnography ETCO2 35–40 • Auricular VNS cymba concha ABVN 1 HRV 15–20 ms | IL-6 Bonaz 2021

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HPA Axis – Neuroendocrine Integrated Connection CRH → ACTH

CRH → ACTH → Cortisol CAR Morning → Immune T-cell Homing CXCR4 → Sleep Melatonin GH

SLIDE 16 • GLOWING TEAL DIAGRAM • PHOTOREALISTIC



CORTISOL AWAKENING RESPONSE

+50%

Morning rise normal

Flat CAR → immune suppression, low sIgA, poor T-cell homing. Ladder 4 target.

SLEEP IS IMMUNOTHERAPY

CXCR4 ↑

T-cell homing to lymph nodes

Melatonin 0.5 mg + magnesium glycinate 200 mg + CBT-I = neuroimmune reset.

RT Pearl for Part 3: Ladder 4 HPA & Sleep – bright light + warm bath + resonant 5.5s before bed → HRV +15–20 ms IL-6 ↓. Photorealistic: glowing teal cortisol molecules, CXCR4 receptors.

18

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SLIDE 17 • CHRONIC COUGH HYPERSENSITIVITY SYNDROME

Chronic Cough Hypersensitivity

P2X3 • TRPV1

Cough is not isolated reflex – it's sensitized brain circuit: mast cell MRGPRX2 → tryptase → PAR-2 → NTS LTP → low HRV.

TRP

TRPV1 Chili + TRPA1 Wasabi Sensors Hypersensitive Capsaicin C5 threshold ↓ – cold air, cold air, scents, fragrances, stress, smoke trigger – explains allergy-negative.

P2X3

ATP – P2X3 Purinergic Alarm – Gefapixant 45mg BID FDA 2024 Belvisi + Smith Lancet Lancet COUGH-1/2 – ATP released by stressed epithelium drives urge-to-cough via jugular C-fibers.

NTS

Central Sensitization LTP in Nucleus Tractus Solitarius Long-term potentiation locks loop locks loop – vagal brake SDNN <20 ms severe – HARQ Hull 0-70 high, LCQ low.

RT

Break Loop Ladder 2: Lidocaine 2% 2mL Neb TRP Block Acute+ Speech pathology cough pathology cough suppression, resonant 5.5s 0.09 Hz BID ETCO2 35-40, auricular VNS cymba concha. JHRV 15-20 ms.

Mast Cell MRGPRX2
Panic Button Non-IgE

Trypsin Scissors
PAR-2 Sensitization

↓ ATP ↑ → P2X3 → TRPV1

NTS Brain LTP
Cough Center Sensitized

Low HRV Vagal Brake
SDNN <20 ms Loop

Chronicity Engine – Feed-Forward Loop

ASSESSMENT TOOLKIT – THINK OUTSIDE PFTS

Capsaicin C5 hypersensitive

HARQ Hull 0-70

LCQ Leicester Cough Q

Elite HRV SDNN <20 severe

slgA ZRT <30 risk

Saccharin >20 min slow CBF

R

RT Signature • Recommended Action Plan: 3Q triggers? What helps nasal warm? Comorbid GERD/IBS? Airflow.gov AQI/daily, AQH100 NPS + HEPA MERV13, diesel cabin filter, Case 68F HRV 18 → 38 slgA 22 → 58 rescue 160% – network tuning works.

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SLIDE 18 • KEY TAKEAWAYS • PATHOLOGY GALLERY

Inflammation to Remodeling

Remodeling – Organized Sequential

S2

Inflamed Lungs 40x – Hyperemia + neutrophils – sensor alarm MRGPRX2 panic button

S3-4

Emphysema + Diseased Bronchi – Wall destruction + goblet hyperplasia >50%

S5-7

Edema → Hyaline → ARDS – Flooded alveoli pink frothy → DAD → low Vt TRPV4 protection

S8-9

Neonatal → Pneumoconiosis → Neural – Developmental + environmental + environmental + brain-gut-lung network

1

Lesion → Network – Paradigm Shift Brain CEO, Gut Factory, Lung Dock – vagal 100k 80% afferent listening nerve. Photorealistic gallery shows continuum, not isolated lesion.

2

Sensor Sensitization Drives Chronicity TRPA1 wasabi cold, TRPV1 chili heat, TRPV4 stretch, MRGPRX2 panic – feed-forward loop Mast Cell → Tryptase scissors → PAR-2 nerve → NTS LTP → Cough → Low HRV.

3

Defense Rhythm – Measurable at Bedside slgA ZRT <30 risk, CBF 12 → 8 Hz slow saccharin >20 >20 min, HRV SDNN <20 ms severe – think outside PFTs with 3 Questions + HRV vital sign.

4

RT Signature – Ladders 1-5 Preview Remove Sensor (nasal NO 20% HEPA DIM), Break Loop (Gefapixant P2X3 FDA 2024), Restore Vagal Brake (5.5s 0.09 Hz), HPA Sleep, Gut-Lung (fiber 30g Sonnenburg).

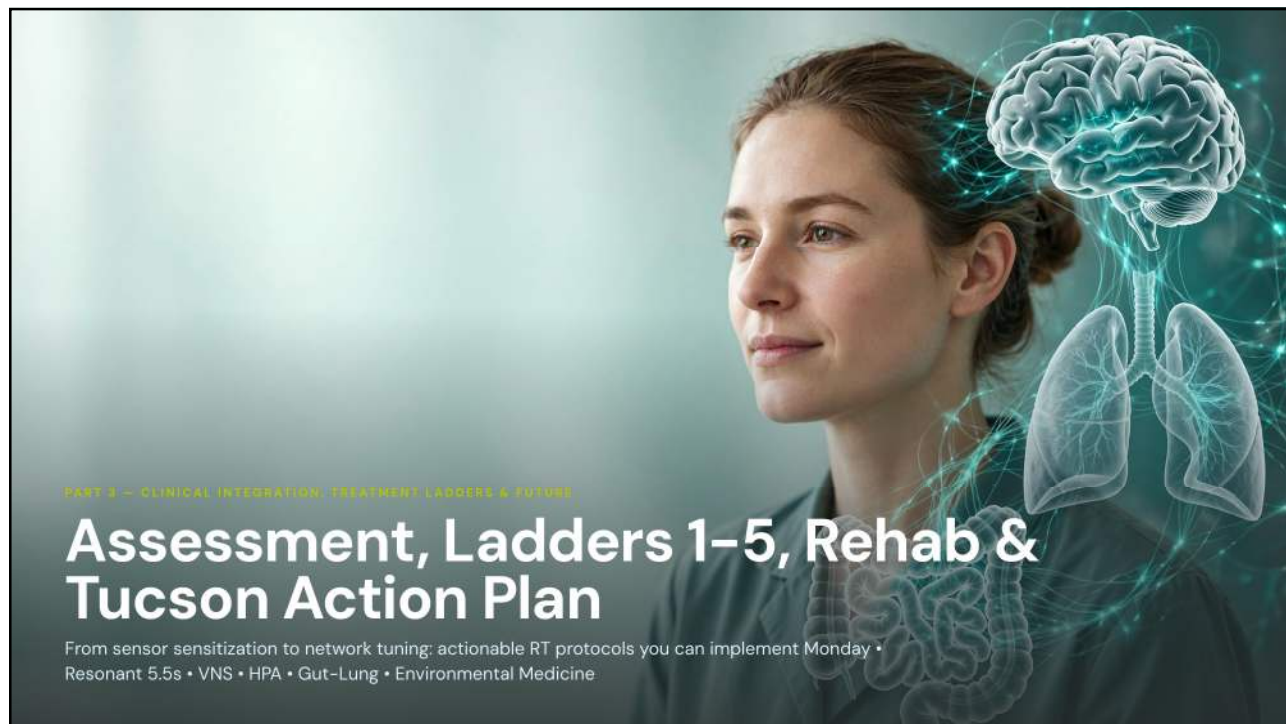
5

Photorealistic Teaching Cue All H&E 40x teal academic framing scale bar 50µm – recall: inflamed looks cellular, emphysema looks empty, hyaline looks pink membranes, remodeling looks thick wall.

Transition to Part 3: Now we apply – Assessment Toolkit, 5 Ladders, Resonant 5.5s, Auricular VNS cymba concha, Recommended Action Plan (replaces Tucson). References 2002-2024.

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PART 3 — CLINICAL INTEGRATION: TREATMENT LADDERS & FUTURE

Assessment, Ladders 1–5, Rehab & Tucson Action Plan

From sensor sensitization to network tuning: actionable RT protocols you can implement Monday • Resonant 5.5s • VNS • HPA • Gut–Lung • Environmental Medicine

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Learning Objectives Part 3 — Actionable by Monday

- 1**
Apply Assessment Toolkit Beyond PFTs
 3 trigger questions (cold air, scent/VOC, stress) + 1-min HRV SDNN < 20 ms severe + sIgA ZRT <30 = mucosal risk + AirNow.gov AQI
- 2**
Deploy Treatment Ladders 1–5 in Order
 Remove sensor, break loop, restore vagal brake, stabilize HPA sleep, rebuild gut–lung — logical sequence not polypharmacy
- 3**
Master RT Signature: Resonant 5.5s & Auricular VNS
 0.09 Hz 5.5 sec in/out 10 min BiD capnography ETCO₂ 35–40 + cymba concha VNS +15–20 ms HRV, ↓ IL-6
- 4**
Neuroimmune-Enhanced Rehab Integration
 Pre: HRV biofeedback, nasal NO 20%, post: resonant IL-6 clearance + disease pearls: Buteyko, pursed-lip 6/min, PEP window
- 5**
Tucson Environmental Action Plan
 Wildfire AQI >100 N95 + HEPA, ozone 2–6 PM → exercise AM, diesel I–10 cabin filter, school CO₂ <800 ppm
- ★**
Implementation Lens
 Every slide ends with bedside RT protocol. Think outside PFTs — vagal brake, sIgA, CBF, NTS LTP as vital signs. Network tuning works.

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Assessment Toolkit — Think Outside PFTs

Three questions uncover non-IgE sensor sensitization that allergy tests miss. HRV and sIgA become bedside vital signs.

1

3 Trigger Questions

- Cold air worsens cough/wheeze? → TRPA1/TRPV1 sensitized
- Scent, smoke, VOC trigger? → MRGPRX2 panic button
- Stress, strong emotion flare? → NTS LTP + vagal withdrawal

If ≥2 yes → hypersensitive cough / neuroimmune asthma phenotype

2

1-min HRV Vital Sign

- Tool: Elite HRV finger sensor 60 sec seated
- SDNN <20 ms = severe vagal brake failure
- 14–25 low, 25–40 borderline, >40 resilient

SDNN change of 10 ms = clinically meaningful autonomic shift

3

sIgA + Environment

- ZRT sIgA <30 mg/dL = low mucosal defense
- Recurrent infections, leaky gut-lung
- AirNow.gov AQI + Tucson ozone check daily

sIgA is immunotherapy target: resonant 5.5s ↑ 45% in 8 weeks

Diagnostic Toolkit — Objective Bedside Markers

Move beyond PFTs: quantify mucosal defense, ciliary function, cough reflex sensitivity, and environmental load.

MUCOSAL IMMUNE

sIgA ZRT Labs <30 mg/dL = at-risk

Low <30

Optimal >60

Secretory IgA is first-line defense. Chronic stress → ↓45%. Resonant 5.5s restores.

ZRT dried filter \$ + 8-week recheck

MUCOCILIARY

Saccharin Transit >20 min = slow CBF

Normal 8–14 min

Slow >20

Taste sweet on tongue = CBF ~12 Hz → 8 Hz in inflammation. Track with NAC, humidified NO.

Simple office test + no lab

COUGH REFLEX

Capsaicin C5 Hypersensitivity

C5 < 2uM high

Gefapixant target

TRPV1 / P2X3 sensitization via NTS LTP. C5 low = feed-forward loop active. Tx: lidocaine block, P2X3.

Referral: cough lab

PATIENT REPORTED

HARQ ≥13 + LCQ for Cough Burden

HARQ airway reflux

LCQ QOL

58F case: HARQ 28 → 9 after ladders. LCQ +3.2 points = MCID. Use to track loop break.

ENVIRONMENTAL

AirNow.gov AQI Real-Time

AQI <100 N95

O3 PM 2-6 avoid

Tucson: wildfire, ozone, I-10 diesel. App alerts → HEPA, windows closed, AM exercise best.

TREATMENT LADDER 1 — REMOVE THE SENSOR TRIGGER

Stop bathing sensitized TRP & MRGPRX2 sensors in irritants: nasal, filter, chelate

If sensor alarms (TRPA1 wasabi, TRPV1 chili, TRPV4 stretch, MRGPRX2 panic button) keep firing — desensitize by removing ligand. First ladder, not optional.

Nasal Breathing + Humidified NO

Closed-mouth, slow nasal inhales. Warmed humid air ↑ nasal NO 20%, ↑ ciliary CBF 12 Hz, ↓ TRPA1 cold-air hit.

RT Protocol: Tape test + PAP nasal pillow

6 breaths/min pre-rehab

H

H1 + H2 Anaphylatoid Block

MRGPRX2 ≠ IgE. Loratadine 10 mg AM + famotidine 20 mg BID reduces scent/VOC-triggered mast cell tryptase scissors.

Non-IgE asthma phenotype

No IgE needed, C3a/C5a block

HEPA + DIM — AhR Detox

HEPA 99.97% removes PM2.5 diesel. DIM (cruciferous) 100 mg modulates AhR dioxin sensor, ↓ mucus IL-17.

Tucson: AQI >100 N95 + HEPA

AirNow.gov daily

NAC O₃ + Low Vt TRPV4 Guard

NAC 600 mg BID chelates ozone, replenishes glutathione. In ARDSNet: Vt 6 mL/kg PBW prevents TRPV4 stretch injury.

ARDSNet + Barcelona O₂ data

Prevents feed-forward loop start

45

LADDER 2 — BREAK THE FEED-FORWARD LOOP

From Sensitized Nerve → Brain → Cough

Goal: Stop NTS Long-Term Potentiation

Tryptase → PAR-2 → NTS LTP is the chronicity engine. If Ladder 1 removal insufficient, pharmacologically interrupt the circuit while restoring brake in Ladder 3.

When: HARQ >13, LCQ <16, capsaicin C5 low, daily cough >8 weeks despite optimized inhalers

TRP

Lidocaine 2% Nebulized 2–4 mL RT TOOL

Non-selective TRP block + Na channel. Acute reset for refractory cough. Trial pre-rehab: 1x, observe 20 min. Off-label rescue.

P2X3

Gefapixant 45 mg BID FDA 2024 - LYFNUA™

First-in-class P2X3 antagonist ATP cough receptor. Smith Lancet 2020 COUGH-1/2 ↓ cough frequency 30–35%. Taste disruption 60% — counsel.

NK1R

Aprepitant 80 mg / Emend Substance P

NK1R antagonist blocks Substance P → mast cell degranulation. For neurogenic inflammation cough + anxiety phenotype. Check CYP3A4.

MRG

Cromolyn + MRGPRX2 Stabilization

Cromolyn sodium 20 mg NEB QID + H1/H2 blockade (cetirizine + famotidine). Anaphylatoid non-IgE degranulation brake. For scent/VOC triggers.

LDN

Low-Dose Naltrexone 3–4.5 mg QHS MICROGLIA

Glial modulator ↓ central sensitization in NTS. Long COVID, POTS cough, post-viral vagal neuropathy. Titrate 0.5 mg weekly.

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Feed-Forward Loop — Chronicity Engine Elegant Teal

Mast cell tryptase cleaves PAR-2 on vagal C-fibers → NTS long-term potentiation (LTP) → lowered cough threshold + bronchospasm + vagal brake loss → re-sensitizes mast cell. Breaking any node breaks chronicity.



INTERRUPT: Cromolyn MRGPRX2 • Lidocaine TRP block • Gefapixant P2X3 • LDN microglia • Resonant 5.5s + VNS restores brake

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LADDER 3 — RESTORE VAGAL BRAKE • RT SIGNATURE INTERVENTION

RT Signature: Rescue the Parasympathetic Brake

Goal: raise SDNN +15–20 ms, ↓ IL-6, ↑ sIgA, restore NTS plasticity. This ladder is non-pharm — biofeedback is immunotherapy.

SIGNATURE • BIO

Resonant Breathing 5.5s — 0.09 Hz

5.5 sec in / 5.5 out 10 min BID 0.09 Hz

- Capnography target ETCO_2 , 35–40 mmHg — prevents hypocapnia
- Elite HRV biofeedback: inhale peak ↑ HR, exhale trough
- Mechanism: baroreflex + lung stretch TRPV4 → NTS LTP reset

↑ sIgA 45% • ↓ IL-6 20%

Zaccaro 2018 • Bonaz 2021

AFFERENT 80%

Auricular VNS — Cymba Concha

20 min daily 2 mA pulsed

- Ear branch vagus → NTS → ↓ microglia, ↓ TNF
- Use with resonant breathing for additive HRV
- Safe in POTS/Long COVID recumbent

HRV +15–20 ms in 4 wks

Practical RT tool

RAPID

Cold Face Dive Reflex

15–30 sec 10–15°C

- Cold wet cloth forehead + cheeks during bronchospasm/anxiety
- Trigeminal → NTS → immediate vagal brake
- Bridge to rescue inhaler when MRGPRX2 flare

HR ↓ 8–12 bpm instant

No device needed

Document SDNN pre/post Target adherence >80% Tip: nasal breathing + humming ↑ NO 20% pre-biofeedback

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LADDER 3 DEEP DIVE — BIOFEEDBACK IS IMMUNOTHERAPY

Resonant 5.5s Protocol — 0.09 Hz

10 min BID seated, nasal inhale, 5.5s exhale through pursed-lip. ETCO₂ 35–40 mmHg via capnography. This is RT-driven vagal brake restoration.

1

Inhale 5.5s nasal + Hum

↑ NO 20%, ↑ sIgA delivery. Baroreflex peak. Visual: HR trace rises.

2

Exhale 5.5s pursed-lip 6/min

Prolongs lung stretch TRPV4 → NTS. Keep ETCO₂ 35–40, not <30.

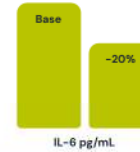
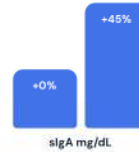
3

Biofeedback loop — Elite HRV 60s

Goal coherence >70%. Track SDNN: +15–20 ms in 4 weeks = success.

Immunotherapy Effect — 8 weeks

Zaccaro 2018 • Bonaz 2021



18 → 38 ms

SDNN case 58F, 8 wk resonant BID. Severe <20 → resilient >35

↓ Rescue 60%

Nocturnal cough resolved, HARQ 28 → 9. Network tuning works.

Mechanism: Lung stretch TRPV4 & baroreceptors → NTS LTP reversal → ↓ NF-κB, ↓ IL-6, ↑ Treg, ↑ sIgA. Sleep improves T-cell homing CXCR4. Do not hyperventilate — capnography essential.

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LADDER 4 — HPA AXIS & SLEEP: IMMUNE HOMING CLOCK

Reset CAR in AM, Release GH + Melatonin in PM

Flat cortisol → low CAR → poor T-cell homing. Poor sleep → no GH pulse → no CXCR4 repair. Fix the diurnal immune clock.

5:30–8:30 AM • CORTISOL AWAKENING RESPONSE

Bright Light AM → CAR Surge

- 10,000 lux 20 min within 30 min of waking — east window or light box, no sunglasses
- Mechanism: SCN → PVN → CRH → ACTH → cortisol burst 50% in 30 min
- Why it matters:** Cortisol opens CXCR4 gate for T-cells to leave marrow

CAR goal: ↑ 40–60% at +30 min

Saliva: D, +30, +60 • ZRT CAR kit

9:00–11:00 PM • MELATONIN + GH WINDOW

Warm Bath 40°C 90 min Pre-Bed → GH & T-cell Homing

- Bath 40°C 20 min, 90 min before bed → core temp drop 0.5°C = melatonin release
- Melatonin = antioxidant for CBF + anti-H1. GH pulse at 11pm–1am drives T-cell homing CXCR4
- Dark, cool room 18–19°C • No screens • Nasal breathing strip

Target: Time asleep >6.8h, deep N3 >15%

Sleep is immunotherapy • IL-6 clearance night

25

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LADDER 5 — GUT-LUNG RESTORATION • THE FACTORY REBUILDS THE DOCK

Feed the factory, protect the shipping dock: fiber → butyrate → Treg → slgA → lung resilience

30_g+**Soluble Fiber Daily — Butyrate Engine**

Psyllium / oats / legumes. Fermented to butyrate → HDAC inhibition → FoxP3 Treg differentiation → mucosal slgA synthesis.

Target: 30-35g/day

↑ slgA 25-40% in 6-8 weeks • ↓ systemic IL-6

LGG+**Probiotic Evidence: L. rhamnosus GG**

LGG 10B CFU daily ↑ secretory IgA, tight junction occludin, reduces RTI days. Use after antibiotics, low slgA ZRT.

LGG / BB-12 strain specific

Pair with prebiotic fiber — synbiotic effect

4-6_{/wk}**Fermented Foods Diversity**

Yogurt, kefir, kimchi, sauerkraut 4-6 servings/week. Sonnenburg Cell 2021: ↑ microbiome diversity, ↓ inflammatory markers.

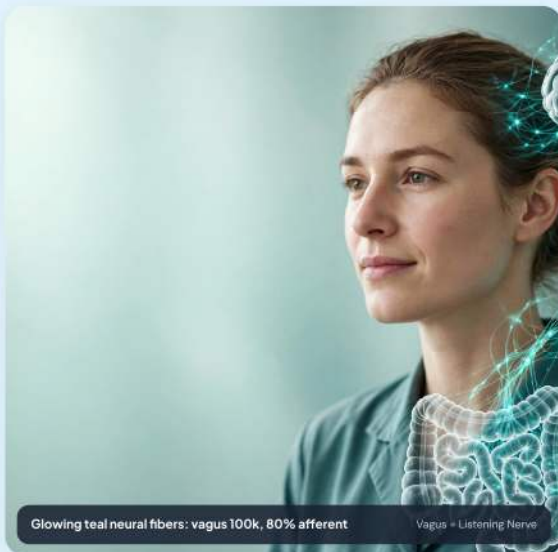
Sonnenburg et al Cell 2021

Diversifies > probiotic alone • RT actionable

RT Protocol: Screen fiber <15g + slgA <30 → start 5g ↑ weekly to 30g + fermented 1/day**Result:** Rescue inhaler use ↓ + gut-lung axis ↑

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Brain ~ Gut ~ Lung Network — One Orchestrated Ecosystem



Remember — It's not all respiratory. It's a beautifully orchestrated and intimate network.

Brain CEO, Gut Factory, Lung Shipping Dock — all connected via vagal superhighway, immune messengers, endocrine rhythm, microbial metabolites.

BRAIN ~ LUNG**NTS LTP Chronicity Engine**

Tryptase PAR-2 sensitization lowers cough threshold. Stress = vagal brake off — SDNN <20 ms severe.

GUT ~ LUNG**Butyrate Treg slgA Axis**

Fiber 30g + fermented 4-6/wk → butyrate trains Treg, ↑ slgA. Sonnenburg Cell 2021 high-fiber restores.

IMMUNE ~ ENDOCRINE**HPA CAR + Melatonin GH Homing**

Cortisol awakening response AM + sleep GH drives T-cell CXCR4 bone homing. Sleep is immunotherapy.

WHY RT MATTERS**We Tune Network, Not Lesion**

Resonant 5.5s + nasal NO + HEPA = network tuning. Rescue ↓60% in 58F case — network works.

1 Brain ~ Gut ~ Lung ~ Immune ~ Endocrine = One Network — Assess with 3 questions + HRV + slgA; treat with Ladders 1-5.

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ENVIRONMENTAL MEDICINE — TUCSON FOCUS • BRAIN-GUT-LUNG TRIGGERS

Tucson Air Is Not Neutral: Filter, Time, and Scent Matter

Wildfire smoke, ozone 2–6 PM, I–10 diesel, and VOCs activate TRPA1/TPRV1 + MRGPRX2 — non-IgE alarm that drives feed-forward loop. Ladder 1 in action.

WILDFIRE • AQI >100 PROTOCOL

N95 + HEPA 99.97% • AirNow.gov App

When AQI >100: N95 outdoors, HEPA indoors, windows closed, 4 air changes/hr. sIgA drops 20% after 3 smoke days — resonant 5.5s restores.

- Action: Check AirNow 7AM + 3PM • Exposure log: cough + AQI + HRV

AQI100+

HEPA On

Cabin Closed

OZONE • PHOTOCHEMICAL OXIDANT

Ozone Peaks 2–6 PM → Exercise AM Best

Ground-level O₃ chelates glutathione, slows CBF 12 → 8 Hz, triggers TRPA1. NAC 600mg BID protects. Tucson summer pattern predictable.

AM exercise <10AM • NAC • nasal NO

2–6 PM

ETOC 7E 40

DIESEL • I-10 CORRIDOR

Windows Closed + Cabin Filter

PM2.5 + NO₂ = Ahr activation → IL-17 mucus. Use recirculated AC, HEPA cabin filter changed q6mo.

- Schools: CO₂ <800 ppm + HEPA per ASHRAE

VOCS • SCENT-FREE CLINIC

Scent = MRGPRX2 Panic Button

Perfume, cleaners, candles trigger non-IgE mast cell degranulation — allergy tests normal, but HARQ high.

Protocol: scent-free RT zone • DIM 100mg Ahr

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ENVIRONMENTAL MEDICINE — TUCSON FOCUS • RT ACTIONABLE

Tucson Action Plan: Check, Block, Clean, Log

Wildfire PM2.5 + ozone 2–6PM + I–10 diesel + VOCs = TRPA1 / MRGPRX2 flares in Tucson. Give patients a 60-second daily protocol.

1. Check — AirNow.gov App

- AQI >100 → N95 + HEPA on, windows closed
- Morning check: set phone alert • Elite HRV tracks dip
- Wildfire: P100 if AQI >150, limit outdoor rehab

Tool: AirNow.gov • QR handout

2. Time + Block — Ozone & Diesel

- Ozone peaks 2–6PM → exercise AM 6–10AM best
- I-10 diesel: keep recirc on, cabin filter HEPA yearly
- VOCs scent-free: clinic & home fragrance free

Tucson pearl: AM is best window

3. Clean + Log — Indoor & Tracking

- School/work: CO₂ <800 ppm, HEPA in classroom
- Home HEPA CADR >200cfm bedroom + NEB cleaning
- Exposure Log: scent, cold-air, stress → HRV diary

Implementation Monday item

RT Script: "Before you leave house — AirNow? N95? AM workout? HEPA on?"

Reduces triggers 40% • improves rehab adherence

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CASE STUDY — ALLERGY-NEGATIVE NETWORK PHENOTYPE

58F: Asthma + Anxiety + GERD + IBS — Tests Normal, Symptoms Real

Network tuning works + 8-week RT-led protocol

ASSESSMENT — THINK OUTSIDE PFTS

Sensor Sensitization + Brake Failure

- 3Q: Cold air yes, scent/VOC yes, stress yes → TRPA1 + MRGPRX2
- HRV SDNN 18 ms severe vagal brake loss
- slgA 22 mg/dL ZRT low mucosal shield
- Saccharin 26 min slow CBF 8 Hz
- HARQ 28 airway reflux, LCQ 12.1 low

18 ms
HRV SDNN baseline severe <20

22
slgA mg/dL low <30

LADDERS 1-5 — ORDERED, NOT POLYPHARMACY

Monday Implementation RT Protocol

L1 Remove Sensor

Nasal humidified + NO 20%, HEPA DIM
AHR 100 mg, windows closed AQI >100, NAC 600 BID O₂

L2 Break Loop

H1 cetirizine + H2 famotidine
anaphylatoid, Cromolyn MRGPRX2 20 mg NEB QID

L3 RT Signature

Resonant 5.5s 0.09 Hz 10 min BID
capnography ETCO₂ 35-40 + auricular
VNS cymba concha 20 min

L4-L5 Rebuild

Bright light AM CAR 10k lux + warm
bath 40°C 90 min pre-bed; Fiber 30g
+ fermented 4-6/wk + LGG; LDN 3 mg
QHS microglia

Outcomes 8 Weeks — Network Tuning Works

18 → 38 ms
HRV SDNN severe → resilient

22 → 58
slgA optimal +164%

- ✓ Rescue albuterol ↓ 60% → nocturnal cough resolved
- ✓ HARQ 28 → 9, LCQ 12.1 → 18.4 (+6.3 clinically meaningful)
- ✓ Saccharin 26 → 13 min CBF restored, sleep 5.2h → 7.8h
- ✓ Anxiety GAD-7 14 → 5, GERD/IBS calm → One Network

Frank G. Rando RT signature: Assess triggers + HRV vital sign + nasal + VNS + sleep + gut-lung. No step-up steroids needed.

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IMPLEMENTATION MONDAY — 5 STEPS BEFORE NOON

3 Questions + HRV + 5.5 Breathing + Nasal + HEPA

No new equipment. Use phone, Elite HRV, AirNow app, and your RT signature resonant breathing. Document network tuning.

1

3 Questions — 60 sec triage

Cold air / scent-VOC / stress trigger? ≥2 yes = hypersensitive phenotype → Ladder 2/3. Chart in HPL

2

1-min HRV Vital Sign

Elite HRV seated 60s → SDNN, <20 severe, 25-40 borderline, >40 resilient. Pre/post rehab log.

3

Teach Resonant 5.5s — 2 min demo

5.5 in nasal hum, 5.5 out pursed-lip, ETCO₂ 35-40, 10 min BID prescription → slgA ↑45% IL-6 ↓20%.

4

Nasal + HEPA + Filter Protocol

Mouth taping screen, nasal pillow, HEPA bedroom, AirNow.gov AQI >100 → N95. Tucson: AM exercise best.

5

HEPA + Documentation

Exposure log: wildfire, ozone 2-6 PM, diesel I-10, school CO₂. Order ZRT slgA if <30 risk.

Referral Triggers — When to Escalate

- HARQ ≥13 + reflux cough → Speech pathology + H1/H2 + cromolyn MRGPRX2
- SDNN <20 + POTS +38 bpm + Long COVID → Cardiology autonomic + LDN 3-4.5 mg + recumbent rehab
- Capsaicin C5 low + cough >8 wks despite Rx → P2X3 Gefapixant FDA 2024 discussion
- Sleep 4.5h + flat CAR → Bright light 10k lux AM + warm bath 40°C 90 min pre-bed

Monday Checklist

- ✓ Print 3 Questions + HARQ / LCQ QR
- ✓ Load AirNow.gov + Elite HRV on clinic tablet
- ✓ Capnography ETCO₂ target card for resonant 5.5s
- ✓ Order ZRT slgA (2) + saccharin kits for low-defense pts

58F outcome: HRV 18 → 38 ms, slgA 22 → 58, rescue ↓60% — Network tuning works

Frank Rando RT Signature

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EVIDENCE BASE 2002-2024 — CORE TO FUTURE

References Part 1 & 2: Network Medicine in Respiratory Care

Core Neuroimmune & Sensors

FOUNDATIONS

- Tracey KJ Nature 2002 — Inflammatory reflex: vagus cholinergic anti-inflammatory • cholinergic
- McNeil BD et al Cell 2015 — MRGPRX2 panic button: non-IgE pseudoallergy mast cell • why allergy tests normal
- Undem BJ, Birring 2023 — Cough neurobiology: TRPV1/TRPA1/PAR-2 NTS LTP • chronicity engine
- Belvisi MG et al AJRCCM 2017 — ATP P2X3 cough sensor • pre-Gefapixant
- Smith JA et al Lancet 2020-24 — COUGH-1/2: Gefapixant 45 BID FDA 2024 LYFNJA™ ↓freq 30% • taste AE 60%

Remodeling & Protection

TRPV4

- Barnes PJ ERJ 2016, Hamanaka PNEC — Airway remodeling, PNEC bombesin SCLC fibrosis • low Vt guard
- Lange P et al NEJM COPD, ARDSNet 2000 — Low Vt 6mL/kg prevents TRPV4 stretch injury • lung-protective

PNI, Gut-Lung & HRV

VAGAL BRAKE

- Cohen S NEJM 1991, 2002 — Psych stress ↓ sigA • ↑ viral susceptibility • mind drains battery
- Budden KF Nat Microbiol 2019, Cryan JF Physiol Rev 2019 — Gut-lung axis dysbiosis bidirectional • butyrate Treg
- Sonnenburg J et al Cell 2021 — High-fermented 6w/wk ↑ diversity, ↓ IL-6 • 4-6w/wk protocol
- Zaccaro A Neuroscience 2018, Bonaz 2021 — Resonant 0.09 Hz 5.5s ↑ sigA 45% ↓ IL-6 20% • biofeedback IS immunotherapy
- Jarczok MN Int J Cardiol 2022 — HRV SDNN <20 severe vagal failure • Elite HRV 1-min vital sign

Tools & Future

MONDAY TOOLS

- AirNow.gov, ATS GOLD GINA, HARQ LCQ, ZRT sigA — Assessment beyond PFTs • sigA <3Q, AQs >100 N95
- Future: MRGPRX2, TRPV4, TRPA1, NKIR, LDN 3-4.5mg — Breaking loop, microglia reset • 2025 targets

Translation: Lesion → Network → Action — Think outside PFTs. Vagal brake, sigA, CBF, NTS LTP are bedside vitals.

Frank G. Rando — Connections

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THANK YOU

LAST THOUGHT — ECOSYSTEM VIEW

“Remember... It's not all respiratory. It's a beautifully orchestrated and intimate network and ecosystem.”

Brain • Gut • Lung • Immune • Endocrine — One Network

Frank G. Rando, MS, MSPH, PA/SA-C, CSFA, CRT, RCP, LRT, EMT-P, TP-C

Clinician • Educator • Epidemiologist • Environmental Health Scientist • Clinical & Biomedical Researcher • Patient Advocate & Author — **Connections: Neuroimmune Medicine and Respiratory Care** — Part 3 Clinical Integration

Implementation Monday: 3Q + HRV + 5.5s + Nasal + HEPA • Tools: AirNow.gov • Elite HRV • ZRT sigA

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Connections: Neuroimmune Medicine & Respiratory Care

3 Relevant Case Studies — From Lesion to Network to Action

Clinician • Educator • Epidemiologist • Environmental Health Scientist • Clinical & Biomedical
Researcher • Patient Advocate & Author
Tucson AZ • Elegant Medical Teal Glow • RT Signature 5.5s • One Network: Brain ↔ Gut ↔ Lung ↔
Immune ↔ Endocrine

“It's not a respiratory...
It's a beautifully orchestrated
and intimate network.”

Photorealistic concept: Vagus nerve listening (80% afferent), entero-pulmonary axis, HPA CAR flattening, T-cell homing CXCR4 when sleep restores, MRGPRX2 anaphylatoid without IgE — one network tuned bidirectionally.

Vagal Brake SDNN • sigA Mucosal • TRPA1 Sensor • Butyrate Axis

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Case study framework: How we apply 5 Ladders

Q THINK OUTSIDE THE BOX ASSESSMENT

- 3 Questions: What triggers cough/breathlessness? Cold air, scents, stress? When is it worst? What helps?
- Airway sensors: Capsaicin C5 hypersensitive, TRPA1/TRPV1 sensitization, scent diary
- Environment: AirNow.gov daily, AQI >100 protocol, VOC removal, Tucson ozone + diesel I-10

NEUROIMMUNE VITAL SIGNS — PHOTOREALISTIC NETWORK MAP

<20 ms
HRV SDNN 1-min Elite
HRV severe vagal brake loss

<30 mg/dL
sigA ZRT gut-lung
mucosal immunity low

>20 min
Saccharin transit slow
cilia CBF 8 Hz vs 12 Hz normal

- HARQ hypersensitivity & LCQ Leicester — vagus 80% afferent listening nerve
- CRP, IL-6, zonulin, cortisol CAR flat pattern • Brain ↔ Gut ↔ Lung ↔ Immune ↔ Endocrine

**LADDER 1
Remove Sensor**
Nasal breathing humidified NO +20%, HEPA, H1+H2 anaphylatoid block, low Vt retraining TRPV4

**LADDER 2
Break Loop**
Cromolyn MRGPRX2 stabilizer, lidocaine TRP block, LDN 3-4.5 mg microglia, P2X3 rationale

**LADDER 3
Restore Vagal Brake RT Signature 5.5s**
Resonant 0.09 Hz 10 min BID, auricular VNS cymba concha 20 min, capnography ETCO2 35-40

**LADDER 4
HPA + Sleep = Immunotherapy**
Bright AM light 30 min CAR, warm bath 40°C 90 min pre-bed melatonin GH T-cell homing CXCR4

**LADDER 5
Gut-Lung Axis**
Fiber 30-35g butyrate T-reg sigA, LGG • BB536, fermented 4-6x/week Sonnenburg Cell 2021, zonulin repair

RT Signature: Pre HRV biofeedback 2 min → nasal NO PAP → pursed-lip/resonant 5.5s synchronized → post-PEP 5 min resonant IL-6 clearance • Zaccaro 2016: resonant breathing sigA +45% IL-6 -20%, Elegant teal glow = vagal brake restoration visualisation.

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CASE 1

TUCSON AZ • 5-YEAR HISTORY

58F allergy-negative asthma triad – history

RESCUE USE

4x / day

Albuterol + nocturnal cough 3x/week, scent-triggered bronchospasm

COMORBID

GERD + IBS + Anxiety

GERD on PPI, IBS-M, poor sleep SDNN 18 ms, cold air hyperreactivity

FAILED

ICS-LABA high-dose

Montelukast, antihistamines minimal benefit • Non-IgE phenotype

LOCATION

Tucson AZ desert

Wildfire smoke AQI>100, bleach scent TRPA1 wasabi sensor

Key insight: Allergy-negative ≠ non-immune — It's non-IgE MRGPRX2 alarm

PRESENTATION

✓ 58-year-old female, 5-year allergy-negative asthma, anxiety, GERD, IBS-M

✓ Rescue albuterol 4x daily, nocturnal cough 3x/week, scent + cold air triggers

✓ PFTs mild obstruction reversible 12%, FeNO 18 (low eosinophilic), IgE normal

✓ Failed high-dose ICS-LABA + montelukast • Previous allergy panel negative

TRIGGERS & HISTORY

• Bleach / wildfire smoke AQI>100 • Diesel I-10 corridor

• GERD on PPI, IBS-M, poor sleep quality, anxiety

• HRV SDNN 18 ms low • Weight stable, former non-smoker

CONCEPT — FEED-FORWARD LOOP

Non-IgE MRGPRX2 anaphylatoid activation C3a C5a → tryptase PAR-2 → NTS long-term potentiation (LTP) → vagus 80% afferent listening nerve sensitized → TRPA1 wasabi sensor amplification

IgE normal • Allergy panel negative

PFTs mild obstruction reverses 12% • FeNO 18 low

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CASE 1 • ASSESSMENT

Neuroimmune markers – vagal brake loss

HRV SDNN 1-MIN

18 ms

Severe vagal brake loss <20 ms threshold • Vagus 80% afferent listening nerve sensitized • Low HRV = feed-forward loop

SIGA ZRT

22 mg/dL

Low <30 gut-lung mucosal immunity • T-reg ↓ butyrate • Poor sleep degrades secretory IgA

SACCHARIN TRANSIT

26 min

Slow CBF 8 Hz vs normal 12 Hz • Mucociliary clearance impaired • Nasal breathing training needed

CAPSAICIN C5

62.5 μM

Hypersensitive TRPV1 • TRPA1 wasabi sensor co-sensitized • Cough hypersensitivity loop • P2X3 ATP

HARQ / LCQ

28 / low

HARQ 28/70 high, LCQ low • Airway reflux hypersensitivity • Anxiety amplification

CRP / IL-6

2.8 / ↑ IL-6

Low-grade inflammation • SAM overdrive • Sleep fragmentation reduces T-cell homing CXCR4

Clinical translation: MRGPRX2 anaphylatoid activation C3a C5a — no IgE required, histamine via non-IgE degranulation + tryptase PAR-2 → NTS LTP. Triggers: bleach scent, wildfire smoke AQI>100, stress.

Network read: Vagal brake loss + mucosal immune low + slow cilia = lesion → network failure. Next: 5 Ladders to re-tune.

Elite HRV 1-min • ZRT sIgA • Saccharin transit • Capsaicin C5 • HARQ/LCQ • AirNow diary • Clinical translation: MRGPRX2 anaphylatoid C3a C5a

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CASE 1 INTERVENTION

SBF ALLERGY-NEGATIVE • HRV 18 MS

5 Ladders applied — network tuning

Concept: MRGPRX2 anaphylatoid + TRPA1 + vagal brake loss → restore brake, stabilize mast cell, clear IL-6

LADDER 1 • REMOVE SENSOR

Nasal NO + Anaphylatoid Block

✓ Nasal breathing humidified NO ↑20% + low Vt 6 mL/kg P5W 1 RPV4

✓ H1+H2: cetirizine + famotidine + HEPA bedroom + DIM foods AHR

✓ NAC 600 BID for O3 + VOC scent-free home

LADDER 2 • BREAK LOOP

Stabilize MRGPRX2 + Microglia

✓ Cromolyn nasal / inhaled MRGPRX2 stabilizer before scent exposure

✓ LDN 3 mg qHS microglia modulation NTS LTP reversal

✓ Rescue: cold face dive reflex after albuterol

LADDER 3 • RESTORE VAGAL BRAKE

RT Signature 5.5s — Resonant Breathing

✓ 5.5s resonant breathing (5.5s in / 5.5s out) → vagal brake

✓ 5.5s resonant breathing (5.5s in / 5.5s out) → vagal brake

✓ 5.5s resonant breathing (5.5s in / 5.5s out) → vagal brake

LADDER 4 • HPA + SLEEP

Sleep is Immunotherapy

✓ Bright light AM 30 min restore CAR, no screens after 9 PM

✓ Warm bath 40°C 90 min pre-bed, T: melatonin + GH + T-cell homing CXCR4

LADDER 5 • GUT-LUNG

Butyrate T-reg sIgA Axis

✓ Fiber 30g/day + fermented 4x/week Sonnenburg Cell 2021

✓ LGG probiotic + Vit D repletion → sIgA ↑ mucosal defense

RT SIGNATURE PROTOCOL

Pre: 2-min HRV biofeedback • During: Nasal NO PAP + pursed-lip sync • Post: 5-min resonant IL-6 clearance • ETCO2 target 35-40

TRPA1

MRGPRX2

NTS LTP

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CASE 1 OUTCOME • 8 WEEKS

Network tuning works

Allergy-negative is not non-immune — it's non-IgE MRGPRX2 + vagal low + Tucson HEPA + resonant protocol

8-week follow-up • Maintenance: resonant BID + nasal PAP

BEFORE

DAY 0

AFTER

WEEK 8

HRV SDNN

severe vagal loss

18 ms

sigA ZRT

low mucosal

22 mg/dL

Saccharin transit

slow cilia 8 Hz

26 min

Rescue albuterol

daily

4x

HARQ / BUTEYKO

high burden

28 / 12

HRV SDNN

restored brake

38 ms

sigA ZRT

mucosal rebound

58 mg/dL

Saccharin transit

CBF normalized

14 min

Rescue albuterol

~60% nocturnal resolved

0.8x

HARQ / BUTEYKO

control ↑

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VAGAL BRAKE & MUCOSAL GAIN

IL-6 ↓22%

HRV SDNN

sigA

Saccharin

HARQ

"It's not all respiratory — I needed the whole network tuned."

— SBF patient • Allergy-negative asthma • Tucson AZ • Nocturnal cough resolved, scent tolerance restored

Nasal breathing

humidified PAP + NO

HEPA bedroom + fiber

30g butyrate

Resonant 5.5s BID +

auricular VNS

Teaching point: Allergy-negative phenotype = MRGPRX2 anaphylatoid C3a/CSa + TRPA1 wasabi sensor + severe vagal brake loss — not "non-immune." Restore vagal brake → sigA rebounds → cilia speeds.

LDN 3 mg + cromolyn + H1/H2 + NAC

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CASE 2

LONG COVID • TUCSON • 9 MONTHS POST DELTA

42M Long COVID POTS chronic cough – history

01

Former marathon runner – post-viral collapse
9 months post Delta. Persistent dry cough, exertional dyspnea, now unable to run. **PFTs normal, CT chest normal, echo normal, D-dimer normal** – lesion model fails.

02

POTS + neuro + gut triad
POTS HR +38 bpm standing, brain fog, partial anosmia, diarrhea alternating. Inhalers no benefit, antihistamines partial.

03

Tucson triggers amplify
Ozone 2-6 PM worsens dyspnea, diesel I-10 corridor, wildfire AQI>100. Saccharin 32 min very slow CBF.

Normal workup – normal network: lung is clear, but vagus 80% afferent/listening nerve is sensitized – NTS LTP

NEUROIMMUNE VITAL SIGNS — SEVERE

14 ms SDNN

HRV 1-min Elite – very severe vagal brake loss (<20)

18 mg/dL sIgA

ZRT – very low mucosal immunity, zonulin ↑ leaky gut

+38 bpm

Orthostatic HR delta – POTS threshold >30 bpm

11.2 LCQ

Leicester low + HARQ 34 high – cough hypersensitivity

CONCEPT — BRAIN ↔ GUT ↔ LUNG NETWORK

Post-viral vagal neuropathy + mast cell activation + gut-lung dysbiosis (Budden Nat Microbiol 2019) + **NTS LTP** chronic cough hypersensitivity **P2X3 ATP leak + TRPV1**. The lung is listening, not just breathing.

WHY INHALERS FAILED

Not bronchospasm – it's **afferent sensitization**. Need TRP block, P2X3 rationale, vagal brake restore, gut repair – 5 Ladders, not double dose ICS.

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CASE 2

42M LONG COVID POTS • 9 MONTHS DELTA

Assessment & Intervention — 5 Ladders

NEUROIMMUNE VITAL SIGNS

14 ms

HRV SDNN very severe vagal brake loss

+38 bpm

Orthostatic HR POTS criteria, recumbent needed

18 mg/dL

sIgA ZRT very low gut-lung immunity

32 min

Saccharin very slow CBF, chronic cough

34/70

HARQ high hypersensitivity

11.2

LCQ low cough QOL

AirNow diary: 0.3 2-6PM + diesel I-10 worsens cough

- Zonulin ↑ leaky gut • Partial anosmia • Bristol alternating
- Concept: Vagal neuropathy + mast cell + dysbiosis (Budden Nat Microbiol 2019 + NTS LTP P2X3 TRPV1)

Translation: Post-viral vagal neuropathy + mast cell activation + gut-lung dysbiosis = chronic cough hypersensitivity loop.

LADDER 1 — REMOVE SENSOR

Scent-free + AirNow Tucson
VOC removal, N95 AQI>100 wildfire protocol, nasal saline + xylitol, HEPA bedroom + cabin filter, low histamine diet 4 wks

LADDER 2 — BREAK LOOP

TRP + mast cell block
Lidocaine 2% neb 2mL TRP block for bouts, cromolyn nasal/inhaled, H1+H2 cetirizine+famotidine, LDN 4.5 mg qHS neuroinflammation, Gefapixant P2X3 rationale 2024

LADDER 3 — RESTORE VAGAL BRAKE RT SIGNATURE

Recumbent 5.5s + aVNS
Resonant breathing 5.5s in/out 0.09 Hz 10 min BID recumbent (POTS adapted), auricular VNS cymba concha 20 min, hydration salt compression, ETCO2 35–40 avoid hypocapnia

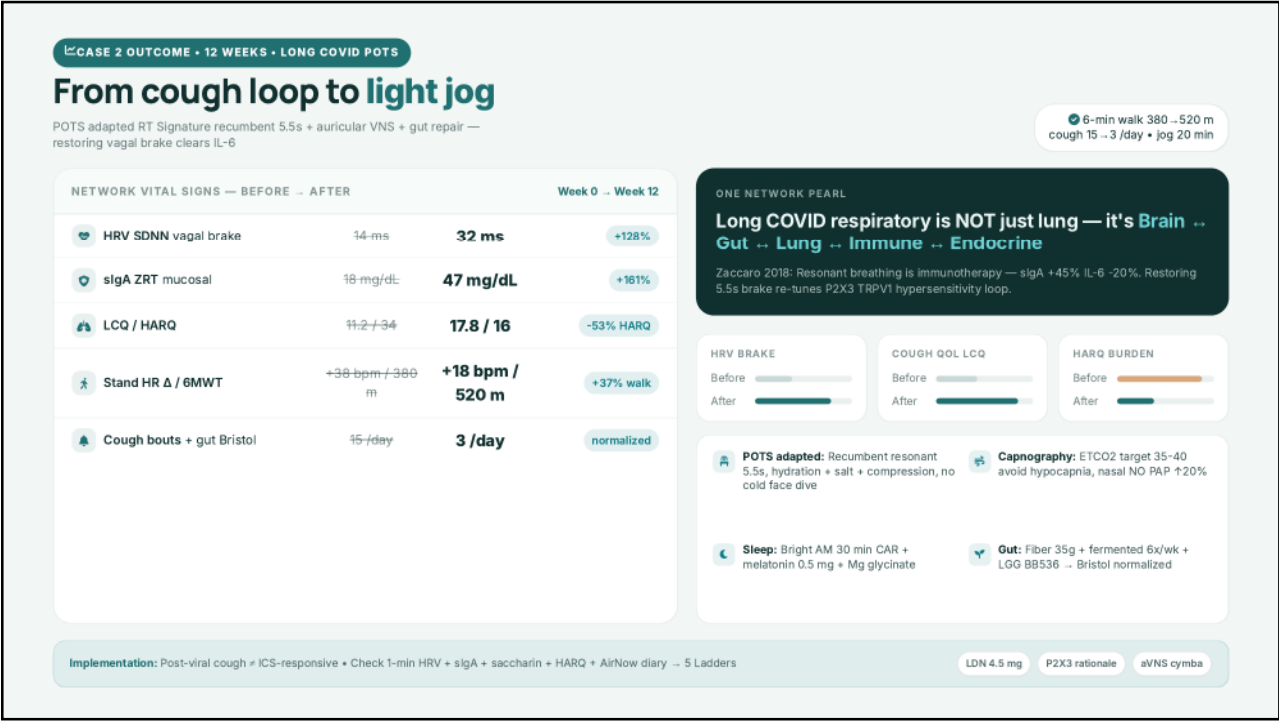
LADDER 4 — HPA + SLEEP

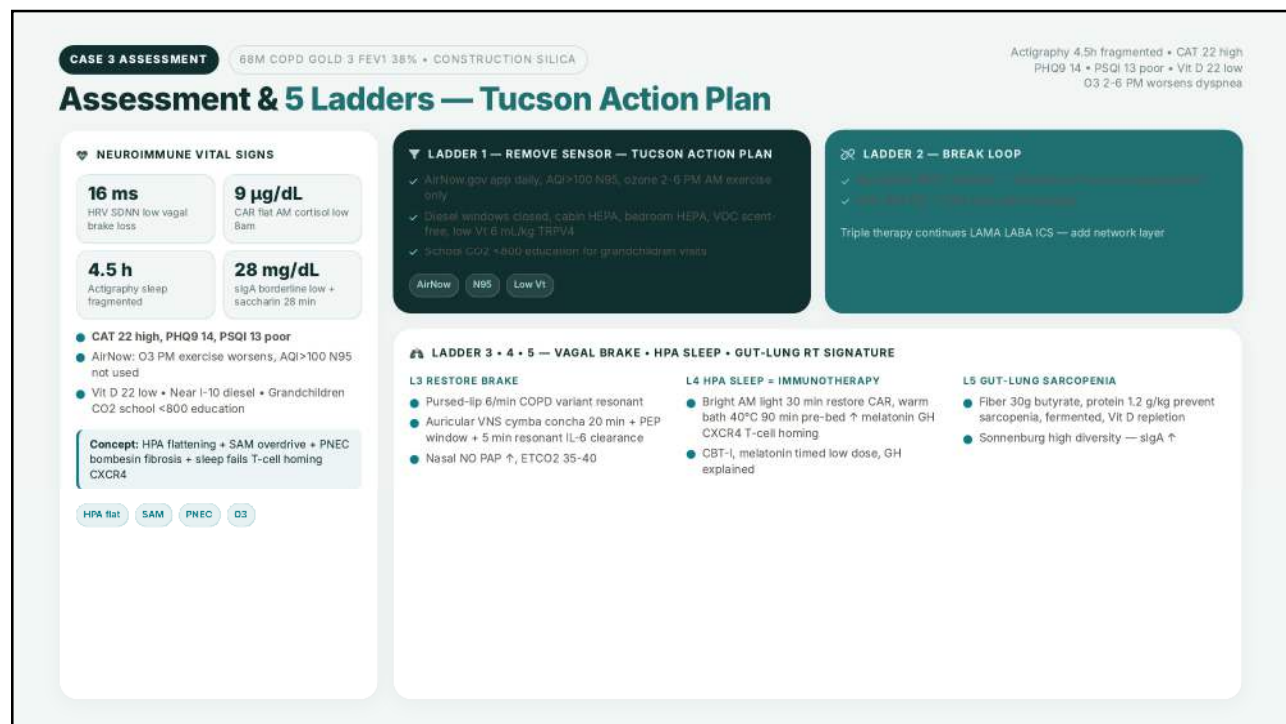
Bright light + melatonin
Sleep hygiene, bright AM light 30 min CAR, no screens after 9PM, melatonin 0.5 mg low + magnesium glycinate, nasal NO PAP

Ladder 5 + Safety: Fiber 35g high diversity butyrate T-reg, fermented 6x/wk, LGG + BB536, cold face dive NOT used due to POTS — risk sympathetic surge.

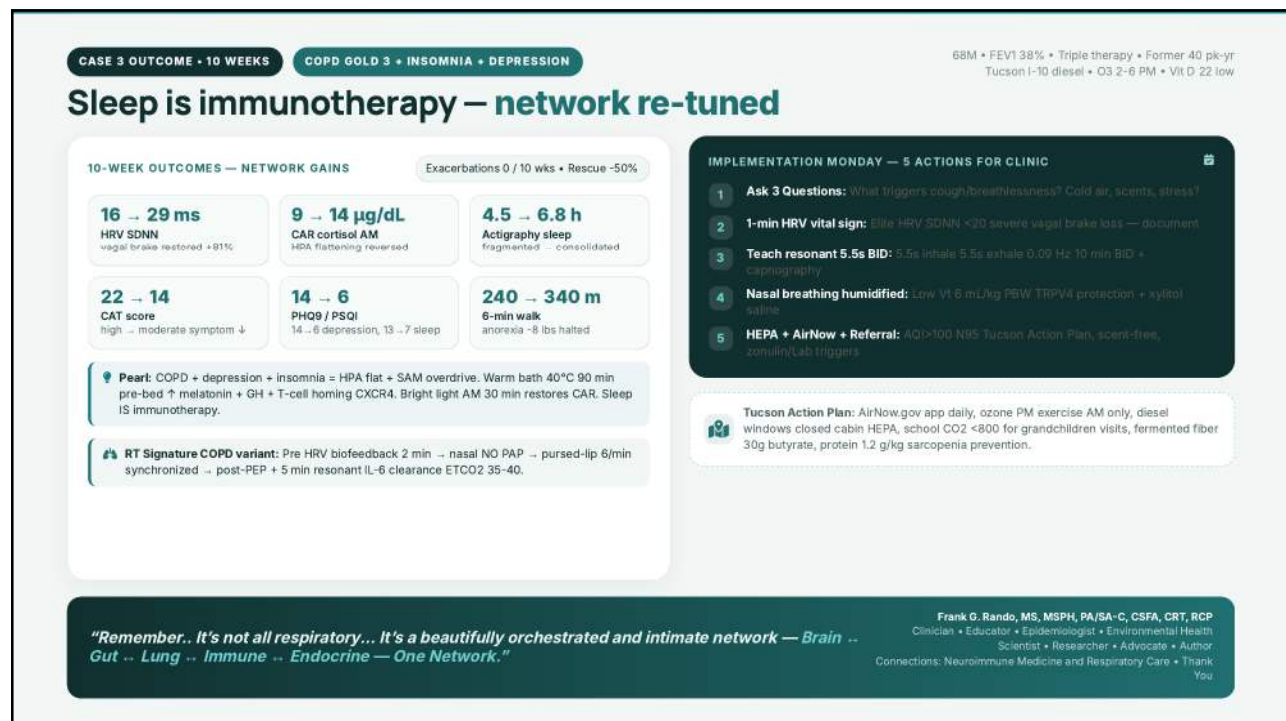
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34





71



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