SUNTEXT REVIEWS

SunText Review of Medical & Clinical Research
ISSN: 2766-4813

Open Access
Research Article
Volume 7:4

From Field to Microenvironment: A Mechanostromal–Immune Translational Framework for HPV-Negative Head and Neck Squamous Cell Carcinoma

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Received date: 14 April 2026; **Accepted date:** 01 May 2026; **Published date:** 12 May 2026

Citation: Mijares A, Maria SC (2026) From Field to Microenvironment: A Mechanostromal–Immune Translational Framework for HPV-Negative Head and Neck Squamous Cell Carcinoma. SunText Rev Med Clin Res 7(4): 259.

DOI: https://doi.org/10.51737/2766-4813.2026.159

Abstract

Human papillomavirus–negative head and neck squamous cell carcinoma (HPV-negative HNSCC) remains a major cause of cancer morbidity and mortality worldwide and is biologically and clinically distinct from virally driven disease [1-3]. The most reproducible "pattern" in HPV-negative HNSCC is not a single mutation but a field-to-front-to-node ecosystem trajectory: carcinogen-injured mucosa produces a molecularly altered epithelial field; dysplasia progresses to invasion; invasion triggers cancer-associated fibroblast (CAF) activation and collagen remodeling; collagen architecture and biochemical stromal programs enforce immune exclusion; and lymphatic dissemination to regional nodes and recurrence follow [1,4,5]. Immune checkpoint blockade (ICB) targeting programmed cell death protein 1 (PD-1) has improved outcomes in recurrent/metastatic (R/M) HNSCC. Pembrolizumab-based first-line regimens were established in KEYNOTE-048, and nivolumab improved overall survival in platinum-refractory disease in CheckMate-141[6,7]. Yet durable immune control remains limited in many HPV-negative tumors, consistent with a failure mode of immune activation without immune access, and access without durable function [1,8,9]. This manuscript synthesizes evidence supporting an integrated translational hypothesis: collagen architecture and rigidity at the invasive front—quantified by second harmonic generation (SHG) microscopy metrics—predict immune exclusion and checkpoint resistance; intratumoral innate priming (oncolytic virus, STING agonist, or intratumoral interleukin-12 plasmid electroporation) combined with systemic anti-PD-1 can convert immune-excluded tumors toward inflamed phenotypes; and perioperative neuro-immunoendocrine modulation (heart rate variability [HRV], cortisol, interleukin-6 [IL-6], beta-blockers, cyclooxygenase-2 [COX-2] inhibition, opioid minimization, prehabilitation) can reduce systemic suppressive pressures during a biologically sensitive window [10-15]. A key theme is clinical implementability: head and neck surgeons can access the tumor repeatedly, obtain mapped tissue from tumor center and invasive front plus adjacent mucosa ("field"), and coordinate perioperative programs. A staged translational pathway is proposed, culminating in a publishable pilot protocol with spatial/temporal sampling, mechanistic endpoints, and explicit regulatory steps (investigational new drug [IND], Institutional Biosafety Committee [IBC], Institutional Review Board [IRB], good manufacturing practice [GMP]) [16-19]. All dose ranges below are reported from clinical trial protocols, labels, or publications. Any dose/procedure not established in trials for HPV-negative HNSCC is marked experimental/unspecified and is not a treatment recommendation.

Keywords: Papillomavirus; Squamous cell; Collagen remodeling

Background and Rationale with Mechanisms

HPV-negative HNSCC often emerges from chronic mucosal injury caused by tobacco, alcohol, and related exposures, and it exhibits a strong field cancerization component. Conceptually, the tumor is not a point mass but a territory of altered tissue biology that can seed local recurrence and second primaries. The foundational "field cancerization" concept was introduced in oral squamous epithelium to explain multicentric origins and clinical recurrence patterns. [Modern disease-level syntheses reiterate field effects as a defining feature of carcinogen-associated HNSCC and emphasize that HPV-negative disease frequently carries a more suppressive microenvironmental state [1,2].

Predictable progression as a mapping problem

A clinically useful, testable progression sequence for HPV-negative HNSCC is: field → dysplasia → invasion → stromal remodeling → immune exclusion → nodal spread/recurrence.

Each step offers measurable biomarkers and spatial targets:

- Field: adjacent mucosa can harbor premalignant or clonally related alterations; sampling enables study of "territorial risk" beyond the gross tumor margin [1,4,5].
- Invasion: breach of basement membrane initiates wound-healing–like stromal programs and recruitment of fibroblasts and myeloid cells [1,10].
- Stromal remodeling: collagen deposition, alignment, and crosslinking increase stiffness and alter migration topology. Lysyl hydroxylase 2 (PLOD2)–driven collagen crosslink switching has been mechanistically linked to metastasis in HNSCC models, supporting collagen remodeling as a causal node [20].
- Immune exclusion: T cells may localize to stroma but fail to penetrate tumor nests, producing "excluded" phenotypes with poor response to PD-1 axis monotherapy [8,21].
- Nodal spread lymphatic dissemination occurs along known anatomic routes and is promoted by invasion programs and immune escape [1].

Collagen and mechanobiology as immune gatekeepers

The extracellular matrix (ECM) is a physical and signaling substrate that can restrict immune trafficking and alter immune phenotype. Collagen can drive immune dysfunction directly and indirectly. A mechanistic study demonstrated collagen promotes anti-PD-1/PD-L1 resistance via leukocyte-associated immunoglobulin-like receptor 1 (LAIR-1)–dependent CD8+ T-cell exhaustion . Another mechanistic study demonstrated tumor discoidin domain receptor 1 (DDR1) promotes collagen fiber alignment that instigates immune exclusion—an archetype of geometry-mediated immune blockade [23]. These causal demonstrations support a translational strategy: quantify collagen architecture at the invasive front (alignment, density, anisotropy, and related metrics) and test whether barrier phenotypes predict immune exclusion and therapeutic response, including response to tumor-inflaming intratumoral interventions.

Fibroblast–TGF-β–ECM programs and checkpoint resistance

Cancer-associated fibroblasts and TGF-β signaling frequently couple to ECM gene programs. A widely cited analysis identified a TGF-β–associated extracellular matrix signature linked to CAF activation, immunosuppression, and failure of PD-1 blockade [10]. This provides a mechanistic rationale for combining immune priming with barrier-lowering strategies (TGF-β axis, LOX/LOXL2, antifibrotics) and for measuring CAF/ECM programs in clinical tissue.

Immune suppression modules in HPV-negative HNSCC

HPV-negative HNSCC tumors often contain suppressive immune compartments and dysfunctional myeloid programs. Regulatory T cells (Tregs), typically identified by forkhead box P3 (FoxP3), can correlate with outcomes and represent a measurable suppressive axis [24]. Myeloid-derived suppressor cells (MDSCs) and suppressive macrophage programs are central to immune failure in HNSCC and thus should be measured and targeted in integrated models [25].

Perioperative neuro-immunoendocrine modulation

Surgery is a predictable physiologic perturbation that affects autonomic tone, inflammatory cytokines (including IL-6), cortisol, pain, sleep, and opioid exposure. Heart rate variability (HRV) is a standardized signal of autonomic regulation, with well-defined measurement standards [26]. Observational and interventional oncology literature supports that perioperative beta-adrenergic and COX inhibition can modulate biomarkers relevant to metastatic biology and immunity, though cancer-specific outcome benefits remain unproven in most settings [27,28]. In head and neck surgery, enhanced recovery after surgery (ERAS) programs can reduce opioid use and maintain analgesia, supporting feasibility of opioid-sparing perioperative designs [29].

Therapeutic and measurement landscape

- Measuring collagen architecture and immune exclusion in HPV-negative HNSCC

Second harmonic generation (SHG) microscopy is a label-free method to visualize fibrillar collagen and quantify structure. A human HPV-negative HNSCC cohort study used SHG to quantify collagen density and fiber alignment, demonstrating feasibility of mechanobiology quantification in HPV-negative HNSCC and supporting integration with immune infiltration modeling [11]. Beyond HNSCC, validated SHG features include collagen orientation coherence, density proxies, and forward/backward SHG scattering ratios as fibril packing indicators [30]. Minimum SHG features for a translational HNSCC program (measurement-only; not prescribing clinical use): invasive-front collagen alignment/coherence, collagen density, and front-to-center gradients.

  - Therapeutic classes to "convert" immune-excluded tumors

The translational logic for HPV-negative HNSCC conversion is: induce local inflammation and antigen presentation, then prevent adaptive immune shutdown.

- Systemic PD-1 blockade: pembrolizumab and nivolumab are validated in HNSCC [6,7].
- Intratumoral immune priming:
- Oncolytic viruses (talimogene laherparepvec/T-VEC; adenovirus ONYX-015; pelareorep/reovirus; Coxsackievirus A21/V937)
- STING agonists (MIW815/ADU-S100; ulevostinag/MK-1454)
- Intratumoral IL-12 plasmid electroporation (tavokinogene telseplasmid; "tavo")
- Barrier-lowering:
- LOX/LOXL2 inhibition (crosslinking modulation)
- Anti-TGF-β axis agents
- Antifibrotics (as investigational adjuncts)
- Perioperative systems modulation:
- Beta-blockers (propranolol; atenolol)
- COX-2 inhibitors/NSAIDs (celecoxib; indomethacin)
- Opioid minimization + prehabilitation + HRV monitoring/biofeedback
- Table of key agents/devices: mechanism, status, trials, dosing ranges, safety (table1).

Table of stromal and perioperative modulators (Table 2)

Perioperative interventions with practical parameters

This section provides practical parameters suitable for protocolization in a translational program. These are not clinical prescriptions and must be tailored to local standards.

Prehabilitation template for HPV-negative HNSCC surgery pathways

Prehabilitation is commonly defined as structured rehabilitation before treatment to improve functional reserve. A head and neck cancer systematic review/meta-analysis supports improvements in quality of life and perioperative outcomes, though heterogeneity remains [52]. A feasibility study provides a realistic multimodal template including exercise, protein-enriched diet, cessation counseling, mental support, and speech/swallow support [53].

A protocolizable prehabilitation template:

- Timing: ideally 2–6 weeks preoperatively (adjust based on oncologic urgency).
- Exercise: moderate aerobic activity plus resistance training with progressive targets; include inspiratory muscle training when appropriate.
- Nutrition: dietitian-led assessment; protein enrichment and sarcopenia mitigation; address dysphagia and consider enteral support when required.
- Psychological support: structured stress management and sleep hygiene, and smoking/alcohol cessation support.

Heart rate variability monitoring and biofeedback

Heart rate variability (HRV) is a noninvasive measure of autonomic regulation; measurement standards are codified by international task forces [26]. HRV biofeedback is described as a nonpharmacologic perioperative adjunct, but oncologic endpoint evidence is not established: thus, it belongs as a measured host-state intervention rather than a cancer therapy claim [47].

Practical parameters

Acquisition: 5-minute resting recordings (fixed time/day; seated or supine), with artifact correction rules. - Metrics: RMSSD (root mean square of successive differences) and SDNN (standard deviation of Normal-to-Normal intervals) as core measures.

Biofeedback: daily 10–20 minutes of paced breathing with adherence logging; assess feasibility and acceptability as endpoints.

Multimodal analgesia and opioid-sparing strategies

Enhanced Recovery After Surgery (ERAS programs) in head and neck surgery have reduced opioid use and improved postoperative analgesia outcomes in implementation studies [29]. Opioid-sparing multimodal analgesia in free-flap reconstruction cohorts has been associated with reduced morphine equivalents while maintaining pain control [51].

Protocolizable components: - Standardized pain scoring schedule and inpatient/outpatient morphine milligram equivalents tracking. - Where safe, scheduled nonopioid analgesics; regional/local anesthesia strategies when feasible; rescue opioid criteria.

Perioperative beta-blockade and Cyclooxygenase-2 inhibition as investigational modules

A randomized trial in breast cancer tested perioperative beta-blockade plus COX-2 inhibition for biomarker modulation, supporting the investigational concept of a perioperative "stress–inflammation clamp." [27] The ProCel protocol provides a contemporary trial template using propranolol plus celecoxib around surgery with intratumoral immune endpoints [50]. Application to HPV-negative HNSCC is experimental/unspecified pending dedicated trials and must incorporate strict contraindication screening and anesthesia co-management.

Integrated translational pilot protocol for HPV-negative HNSCC

This pilot protocol is designed to generate publishable mechanistic results and set the stage for larger pragmatic trials.

Core hypothesis

Collagen architecture and rigidity at the invasive front predict immune exclusion and reduced responsiveness to checkpoint-based strategies; intratumoral innate priming combined with systemic anti-PD-1 increases intratumoral CD8+ T-cell infiltration and type I interferon programs; perioperative systems modulation reduces inflammatory and neuroendocrine signals that may oppose immune conversion.

Trial overview

Design: window-of-opportunity translational protocol with mapped sampling. Staged approach:

- Stage A (atlas): observational mapping of collagen-immune phenotypes.
- Stage B (interventional): intratumoral priming + systemic anti-PD-1 and/or perioperative propranolol + celecoxib versus control.

Eligibility

Inclusion: a- Adults with r esectable HPV-negative head and neck squamous cell carcinoma (HNSCC), confirmed by standard HPV testing protocols. b- Planned definitive surgery with curative intent. c- Lesion accessibility for baseline biopsy; for intratumoral arms, at least one safely injectable lesion.
Exclusion: a- Active autoimmune disease requiring systemic immunosuppression (for immunotherapy arms). b- Contraindications to beta-blockers or NSAIDs/COX-2 inhibitors for perioperative module. c- Immunocompromised status for oncolytic virus platforms per label constraints (e.g., talimogene laherparepvec).

Spatial sampling schema

Spatial sampling is the defining strength of surgeon-led head and neck translational work.
Minimum regions:

- Tumor center
- Invasive front (highest priority region for collagen–immune coupling)
- Peritumoral stroma
- Adjacent mucosa/field (standardized distance; ideally two distances when feasible)
- Regional nodes (mapped by neck level)

Rationale: field cancerization and front-dominant stromal remodeling make non-mapped tumor-only sampling insufficient for ecosystem inference [1,4,5].

Temporal sampling schema

- T0 (baseline): biopsy + blood (IL-6, optional IFN-β, cortisol) + HRV.
- T1 (optional pre-op): re-biopsy after intratumoral priming (safety permitting).
- T2 (surgery): mapped resection specimen + nodes; intraoperative blood.
- T3 (post-op): POD1, POD3, POD7 blood + HRV; opioid/MME capture.

Assays

Mechanobiology - Second harmonic generation (SHG) microscopy collagen metrics: density, alignment/orientation coherence, anisotropy, front-to-center gradients [11,30]. Immunology - Immunohistochemistry (IHC): CD8, PD-L1 (combined positive score), FoxP3. - Multiplex immunofluorescence: spatial immune neighborhoods and tumor-stroma ratios. Innate activation - RNA interferon signature; cGAS/STING (cyclic GMP-AMP synthase / stimulator of interferon genes) activation proxies (transcriptional, and protein markers where feasible). Systemic - IL-6 (primary), optional IFN-β and cortisol.

Endpoints

Primary mechanistic endpoint: - Change in intratumoral CD8 density and distribution (center and invasive front) between baseline and post-window/surgery.
Key secondary endpoints: - Change in interferon signatures and STING activation proxies (for STING/OV arms). - PD-L1 dynamics (adaptive resistance marker). - Safety and feasibility metrics: sampling completeness, injection feasibility, perioperative complications.
Exploratory endpoints: - Pathologic response where applicable, progression-free survival (PFS), and model-based prediction performance.

Sample size rationale and statistical plan

This is powered for biomarker change, not survival.

- Stage A (atlas): ~40–60 patients to estimate variance and build stable multivariable models linking collagen metrics to immune exclusion.
- Stage B (interventional): ~15–20 per arm for paired biomarker changes (CD8 and IFN signatures), with stopping rules for safety and feasibility (biomarker-powered precedent exists in perioperative modulation trials) [27,50].

Statistical framework: - Mixed effects models with patient-level random intercepts; fixed effects for time, region, arm, and collagen metrics. - Interaction term (arm × collagen barrier score) to test whether mechanobiology modifies immune conversion. - False discovery rate correction for multiplex and transcriptomic panels.

Translational correlative analyses and data analysis plan

Collagen pattern prediction and ecosystem phenotyping

Primary deliverable: a collagen barrier score derived from SHG metrics (alignment + density + gradient features) that predicts immune exclusion and modifies intervention response.

Modeling: - Logistic or ordinal models to classify immune phenotype (inflamed vs excluded vs desert) using consensus definitions [54]. - Regression models to predict CD8 penetration and changes after intervention. - Include covariates: site, stage, smoking/alcohol exposure proxies, PD-L1 CPS, baseline CD8.

Table 1: *Intratumoral priming and checkpoint backbone (trial/label dosing ranges; non-directive).*

Table A: *Intratumoral priming + checkpoint backbone (compact).*

Class	**Agent**	**Key trial/anchor**	**Trial/label dosing anchor (non-directive)**	**Safety signal highlights**
Anti-PD-1	Pembrolizumab	KEYNOTE-048; KEYNOTE-689; FDA approval	Label dosing options; periop schedule per FDA approval summary	irAEs (multiple organs), infusion reactions
Anti-PD-1	Nivolumab	CheckMate-141	Trial dose 3 mg/kg q2w; label flat dosing options	IAEs
Oncolytic virus	T-VEC	MASTERKEY-232; EMA/FDA label	10^6 PFU/mL then 10^8 PFU/mL; visit volume caps (label)	Viral shedding, herpetic infection risk, fever
Oncolytic adenovirus	ONYX-015	Phase II SCCHN	Intratumoral dosing and schedules per trial	Biosafety, neutralizing antibodies
Oncolytic reovirus	Pelareorep	Phase I IV reovirus	Dose escalation up to 3×10^10 TCID50 IV d1–5 q28d	Flu-like symptoms, antivector immunity
Oncolytic virus	V937 (CVA21)	CAPRA (NCT02565992)	IT days 1/3/5/8 then q3w; pembrolizumab day 8	Injection feasibility, fever
STING agonist	MIW815	Phase I; phase Ib combo	IT 50–3,200 µg weekly 3-on/1-off or q4w; PD-1 inhibitor fixed dose	Pyrexia, injection-site pain
STING agonist	Ulevostinag	Phase I/II; NCT04220866	RP2D 540 µg IT; combo with pembrolizumab in trials	Pyrexia, cytokine-like toxicity
IL-12 EP	tavo-EP	NCT01502293; phase II	IL-12 plasmid 0.5 mg/mL; days 1/5/8	Pain, tissue injury/necrosis risk

Table B. *Perioperative and stromal modulators (compact).*

Axis	**Agent/class**	**Evidence anchor**	**Status for HPV-negative HNSCC**
Periop sympathetic	Propranolol	Biomarker RCT framework in cancer surgery; ProCel protocol	**Experimental/unspecified** (HNSCC)
Periop inflammation	Celecoxib	ProCel protocol; label warnings	**Experimental/unspecified** (HNSCC)
Periop physiology	HRV monitoring	HRV Task Force standards	Implementable measurement module
Periop cytokines	IL-6	Prognostic association in HNSCC/OSCC	Mechanistic biomarker module
Stroma/ECM	Galunisertib	TGF-β inhibitor development	**Experimental/unspecified**
Stroma/ECM	Bintrafusp alfa	Phase I SCCHN cohort	**Experimental/unspecified**
Crosslinking	PXS-5505	Human dose precedent in myelofibrosis	**Experimental/unspecified**

Axis	Agent/class	Evidence anchor	Status for HPV-negative HNSCC
Antifibrotics	Pirfenidone/nintedanib	Preclinical tumor-stroma evidence	**Experimental/unspecified**

Table 2: *Barrier-lowering and perioperative system modulators (trial/label anchors; non-directive).*

Agent/class	Mechanism (brief)	Clinical status	Dosing ranges available?	Notes and safety signals
Galunisertib (TGF-β receptor I inhibitor)	Inhibits TGF-β signaling (SMAD pathway)	Investigational	Trials often used 150 mg orally twice daily, 14-days-on/14-days-off (example schedule)	Requires cardiovascular and safety monitoring; efficacy in HNSCC not established
Fresolimumab (anti-TGF-β antibody)	Neutralizes TGF-β ligands	Investigational	Phase I dose escalation 0.1–15 mg/kg IV (schedule per trial)	On-target effects possible; cancer-specific efficacy uncertain
Bintrafusp alfa (PD-L1/TGF-β trap)	Dual PD-L1 blockade + TGF-β sequestration	Investigational	Dosing varied in early trials; experimental/unspecified if not protocol-specific	Cutaneous lesions and irAE-like effects reported; selection critical
Simtuzumab (anti-LOXL2)	LOXL2 blockade to reduce collagen crosslinking	Failed efficacy in IPF; not an oncology standard	Protocol-specific; do not extrapolate	Key cautionary clinical translation example
PXS-5505 (pan-LOX inhibitor)	LOX family inhibition (crosslinking reduction)	Early clinical in myelofibrosis	Dose escalation reached 200 mg twice daily; 200 mg BID selected in trial	Oncology use experimental/unspecified
Pirfenidone (antifibrotic)	Anti-fibrotic ECM modulation	Approved for IPF	Oncology use experimental/unspecified	Preclinical ECM normalization evidence; not established in HNSCC
Nintedanib (antifibrotic/anti-CAF)	Multi-kinase inhibition with antifibrotic activity	Approved for IPF; oncology approvals in lung contexts	HPV-negative HNSCC use experimental/unspecified	Potential synergy with checkpoint in models; bleeding/GI risks
Propranolol (beta-blocker)	Nonselective β-adrenergic blockade	Approved cardiovascular drug	Perioperative oncology schedules are trial-specific (e.g., ProCel protocol)	Bradycardia/hypotension/bronchospasm risk; requires periop governance
Atenolol (beta-blocker)	β1-selective blockade	Approved cardiovascular drug	Label dosing by indication; periop oncology use experimental/unspecified	Dose adjustment in renal impairment; bradycardia risk
Celecoxib (COX-2 inhibitor)	Reduces prostaglandin signaling	Approved NSAID	Label dosing by indication; periop oncology schedules trial-specific	CV/GI boxed warnings; renal risk
Indomethacin (NSAID)	COX inhibition	Approved NSAID	Label dosing by indication; periop oncology use experimental/unspecified	CV/GI boxed warnings; renal risk; bleeding concerns

Machine learning module (exploratory)

- Use nested cross-validation and hold-out test sets.
- Prefer interpretable methods (regularized regression; gradient boosting with SHAP).
- Explicitly pre-register features and evaluate calibration.

Regulatory and implementation roadmap

Stepwise path to first-in-human / first-in-institution programs

- Step 1: observational collagen–immune atlas (low regulatory burden; high publishability).
- Step 2: perioperative propranolol + celecoxib module (IRB; anesthesia and internal medicine co-management).
- Step 3: intratumoral priming + systemic anti-PD-1 (IND likely required; IBC oversight for gene/viral platforms; GMP partner) [55,56].

Regulatory/ethical requirements

- IND: required for investigational intratumoral biologics and gene-adjacent platforms.
- IBC: oversight for recombinant/synthetic nucleic acid research and certain viral vector programs (NIH guidelines) [55].

- IRB: consent, risk disclosure, data governance.
- GMP: manufacturing quality systems and chain of custody for investigational products.

Multidisciplinary program roles

- Surgeon: sampling fidelity and safety, injection feasibility, perioperative integration.
- Medical oncologist: systemic therapy oversight and irAE management.
- Pathologist: spatial annotation (front vs center vs field).
- Immunologist: assay and immune phenotype architecture.
- Bioengineer: SHG pipelines and reproducibility.
- Statistician/data scientist: modeling plan, power, ML governance.
- IRB/IBC/pharmacy/GMP partner: compliance and logistics.

Latin American context integration

Latin American cohorts demonstrate differences in stage at diagnosis and system-level constraints that are relevant for implementation feasibility and trial logistics. The South American InterCHANGE study identified predictors of survival and highlighted late stage as a major determinant. A Latin American consensus guideline provides region-appropriate management considerations. A Mexican hospital experience study provides real-world treatment timeliness patterns in stage III–IV disease.

Limitations, risks, and avoiding pseudoscience while acknowledging beliefs

Scientific limitations

- Collagen alignment may be a marker or mediator; causality in HPV-negative HNSCC requires interventional testing rather than correlation alone.
- Biomarker heterogeneity across subsites and exposures (oral cavity vs larynx vs hypopharynx) requires stratification.

Clinical risks

- Intratumoral injection in head and neck sites may carry airway, bleeding, and tissue injury risks.
- Perioperative beta-blockade/NSAID modules require strict contraindication screening and stopping rules.

Pseudoscience guardrails (patient belief acknowledgement)

Common claims include: "432 Hz has healing properties," "heart torus/heart field coherence cures disease," "Fibonacci/golden ratio governs biology and can be used therapeutically," and "Tesla's frequency quotes prove an anti-cancer law."

Evidence-aligned framing:

- A randomized dental trial found music (including 432 Hz) can reduce anxiety and salivary cortisol during tooth extraction; this supports stress modulation, not cancer cure.
- HRV is a measurable physiologic variable with standardized measurement; HRV biofeedback may improve stress coping but claims of biofield-mediated tumor control are not supported by oncology evidence.
- Evidence-based critiques caution against over-extending "golden ratio" claims into biology and clinical decision making; such pattern narratives should not guide cancer therapy.
- Tesla quote attribution and relevance do not constitute biomedical evidence; the appropriate translation is to testable physiology (HRV, cortisol, cytokines) and testable tumor biology (collagen metrics, immune signatures).

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