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CANCER NEUROSCIENCE

Cancer neuroscience: Mechanisms to medicine

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The nervous system is now recognized as an enabling hallmark of cancer biology. Neural inputs drive tumor growth in both central nervous system tumors and extracranial tumors through different mechanisms, including synaptic signaling, adrenergic regulation, perineural invasion, neuropeptides, immune remodeling, and bioelectric mechanisms. These insights have facilitated repurposing of neuroactive agents that are now in clinical trials as adjuncts to standard cancer therapy. The central translational challenge now is how to match the right neural circuit to the right patient and to pair appropriate neuromodulators with immunotherapy in combinations designed to restore, rather than merely supplement, antitumor immunity.

INTRODUCTION

The nervous system is now recognized as an enabling hallmark of cancer biology (*1*). In tumors of both the central and peripheral nervous systems, bidirectional cross-talk between neural circuits and malignant cells drives proliferation, invasion, immune evasion, and metastasis through diverse mechanisms including synaptic integration, neurotransmitter signaling, trophic factor gradients, and direct bioelectric coupling (*2*–*10*). These core pathophysiological mechanisms are illustrated across central nervous system (CNS) and peripheral nervous system (PNS) tumor contexts in Fig. 1. These mechanistic insights have catalyzed an equally expansive translational opportunity. Many of the agents already in clinical use for neurological and psychiatric conditions—β-blockers, antiseizure drugs, and antidepressants—are now being tested as adjuncts to standard cancer regimens, and first-in-class compounds designed specifically to interrupt neuron-tumor interfaces are entering clinical trials. Whereas prior high-quality reviews addressed specific cancer neuroscience aspects (*2*–*6*, *8*, *9*), this Review synthesizes the entire translational pipeline across both CNS and PNS tumor types, from mechanistic discoveries to clinical-stage neuromodulatory therapeutics, with emphasis on emerging opportunities for biomarker-driven patient selection and rational combination with immunotherapy.

CNS MECHANISMS

In brain tumors, malignant cells integrate physically and electrically into neural circuits through tumor microtubes (TMs) and electrochemical synapses, hijacking the same plasticity machinery that healthy neurons use to learn and adapt, including glutamate receptors, synaptic adhesion molecules, and downstream growth kinases, to sustain proliferative and invasive programs (Fig. 1A) (*11*–*16*). These interactions couple neuronal activity to tumor growth through calcium-dependent signaling and activity-driven transcriptional programs. Direct glutamatergic synaptic input from neurons drives glioma progression (*17*, *18*), in part, through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)/*N*-methyl-D-aspartate receptor (NMDAR)–mediated depolarization and downstream Ca^{2+} influx that activates calcium- and calmodulin-dependent protein kinase II and progrowth transcriptional pathways, and perisynaptic NMDAR activation promotes breast-to-brain metastasis (*19*). These interactions are bidirectional: Isocitrate dehydrogenase–wild-type glioblastoma multiforme (GBM) remodels surrounding functional circuits, degrading cognitive function and overall survival (OS) (*16*), whereas neurofibromatosis type-1 (NF1)–mutant optic pathway gliomas depend on neuronal activity for initiation and can be suppressed by sensory deprivation (*20*).

Importantly, these activity-dependent mechanisms are not restricted to adult high-grade gliomas (HGGs). Pediatric diffuse midline gliomas form γ-aminobutyric acid (GABA)–ergic neuron-to-glioma synapses that drive growth through distinct inhibitory programs (*21*), and the histologic breadth of neuron-tumor synaptic integration extends to low-grade tumors where the indolent disease course makes sustained neuromodulatory strategies particularly appealing. These findings underscore that neuron-tumor synaptic integration operates across the histologic and age spectrum of brain tumors, including low-grade and pediatric contexts. Recent work has further revealed that many primary brain tumors exhibit neural-like molecular, electrophysiological, and morphological features, with tumor cells adopting neuronal lineage programs and potentially emulating neural phenotypes to facilitate circuit integration or reflecting neurodevelopmental features such as pacemaking that govern communicating tumor cell networks in glioblastoma (*15*). These neural-like states may enhance electrical coupling, synchronization, and responsiveness to neuronal activity in tumor networks. The principle of neuron-tumor synaptic communication has now been extended beyond gliomas to brain metastases, where metastatic cells from breast cancer and melanoma can establish excitatory glutamatergic synapses with neurons during early metastatic seeding, suggesting that exploitation of neuronal signaling may represent a general adaptive strategy in the brain microenvironment (*22*–*24*).

Advances in circuit mapping and connectomics demonstrate that tumors engage distributed neuronal circuits and reshape network activity across larger anatomical scales, including interactions with neuroimmune signaling pathways (*21*, *25*). Not all neuron tumor synaptic connections are equally active, and this heterogeneity may itself be therapeutically exploitable. Many tumor-neuron synapses appear ~100-fold weaker than bona fide neuronal synapses, suggesting tonically suppressed "silent" synapses whose activation requires relief of

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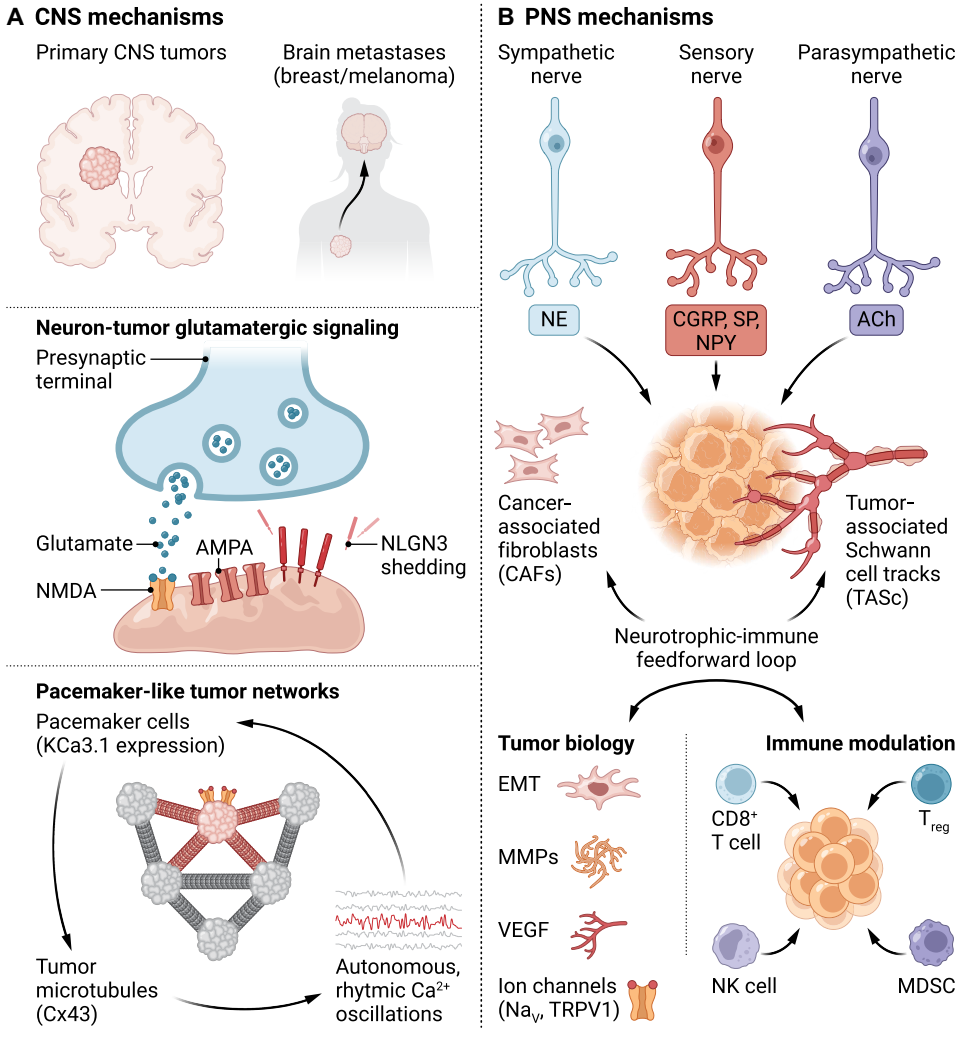

Fig. 1. Bidirectional neural-tumor cross-talk in CNS and PNS cancers. (**A**) Top and middle: In primary CNS tumors and brain metastases, particularly breast cancer and melanoma metastases, malignant cells can exploit neural-circuit activity through neuron tumor synaptic signaling. In primary brain tumors, this includes glutamatergic signaling through AMPARs and NMDARs, ADAM10-mediated NLGN3 shedding, and downstream neurotrophic/growth signaling that collectively drive activity-dependent tumor growth. Similar excitatory glutamatergic neuron-tumor interactions have also been described in brain metastases. Bottom: Tumor cells form interconnected microtube networks linked by Cx43 gap junctions, and a subset exhibit pacemaker-like behavior characterized by KCa3.1 expression and autonomous, rhythmic Ca^{2+} oscillations. (**B**) PNS mechanisms in extracranial tumors. Top: Sympathetic, sensory, and parasympathetic nerves innervate the tumor microenvironment and release distinct mediators shown in the figure: norepinephrine (NE), CGRP, SP, NPY, and ACh. Middle: These neural inputs converge on tumor cells and stromal intermediaries, including CAFs and TASc, supporting tumor growth, invasion, perineural spread, and bidirectional tumor-nerve remodeling. Bottom: Neural signaling establishes a neurotrophic-immune feedforward loop that links peripheral neural input to tumor-intrinsic programs, including EMT, MMP-mediated invasion, VEGF-driven angiogenesis, and ion-channel activity (Nav and TRPV1), as well as immune modulation involving $CD8^+$ T cells, NK cells, regulatory T cells (T_{reg} cells), and MDSCs.

γ-aminobutyric acid type B ($GABA_B$)–mediated presynaptic inhibition to drive proliferation, thereby enabling activity-dependent synaptic transmission that can trigger downstream proliferative signaling (*26*). Together, these insights position neuron-tumor synaptic integration as a therapeutically actionable feature of CNS malignancies (*6*, *27*), but the nervous system's influence on cancer does not stop at the blood-brain barrier. In extracranial tumors, an entirely different set of peripheral circuits shapes tumor biology through autonomic tone, neuropeptide gradients, and physical nerve invasion.

PNS MECHANISMS: CIRCUITS, SCAFFOLDS, AND METABOLIC REPROGRAMMING

Beyond the CNS, peripheral neural circuits shape tumor biology through an entirely different set of anatomical and molecular interfaces, one defined not by synapses but by autonomic tone, neuropeptide gradients, and nerve scaffold invasion (*1*, *10*). Sympathetic (adrenergic) signaling promotes progression across multiple cancers by driving β-adrenergic receptor (β-AR)–mediated vascular endothelial growth factor (VEGF) up-regulation, matrix metalloproteinase (MMP) induction, and immune suppression. Conversely, parasympathetic and cholinergic innervation plays context-dependent roles—promoting growth in gastric and colorectal cancers (CRCs) yet acting as a suppressor in pancreatic cancer (*10*, *28*–*30*). Perineural invasion (PNI) remains a major route of locoregional spread in pancreatic, prostate, and head-and-neck cancers, driven by neurotrophic gradients [nerve growth factor (NGF), glial cell line–derived neurotrophic factor, and artemin] acting on tropomyosin receptor kinase (Trk) A/rearranged during transfection (RET) receptors (*31*, *32*). This innervation is actively influenced by the cancer genome: Exosomes reprogram neurons to extend axons toward tumors (*33*), whereas p53 loss in head and neck squamous cell carcinoma (HNSCC) drives sensory-to-adrenergic transdifferentiation via microRNA remodeling in tumor-shed extracellular vesicles, significantly increasing intratumoral nerve density (*30*, *34*).

Sensory neurons have emerged as early architects of the tumor-permissive niche. Nociceptor-derived calcitonin gene–related peptide (CGRP) drives $CD8^+$ T cell exhaustion and myeloid-derived suppressor cell (MDSC) infiltration, suppresses natural killer (NK) cell function via cancer-associated fibroblasts (CAFs) in pancreatic cancer, and broadly suppresses tumor-infiltrating lymphocytes (TILs) in HNSCC (*35*–*37*). Sensory fibers further facilitate invasion via physical tracks [e.g., plexinB3 in triple-negative breast cancer (TNBC)] and form synapse-like connections that drive growth through CGRP receptor activity-modifying protein 1 (RAMP1) signaling (*38*, *39*). This axis is regulated by reciprocal feedback: B cell–derived nociceptin/orphanin FQ (NOFQ), an endogenous opioid, silences CGRP-releasing nociceptors, whereas CGRP conversely suppresses B cell NOFQ

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production, together determining the immunosuppressive tone of the tumor microenvironment (TME) (*40*). Nociceptors also link cancer pain to immune evasion; loss of transient receptor potential vanilloid 1 (TRPV1) or systemic CGRP antagonism slows tumor growth by disrupting a TRPV1–c-Jun–interleukin 6 (IL-6) axis (*41*, *42*). A critical conceptual advance is cancer-induced nerve injury (CINI): Tumor-induced myelin degradation triggers a neuronal injury program, leading to release of IL-6 and type I interferons that promote T cell exhaustion and resistance to anti–programmed cell death protein 1 (PD-1) therapy (*43*). Conversely, sympathetic signaling may be protective in colorectal cancer (CRC) and HNSCC, where it enhances $CD8^+$ T cell recruitment and cytotoxicity (*44*, *45*).

Neurons are not alone in sculpting the TME. Schwann cells, which normally ensheathe and protect peripheral axons, can be reprogrammed by tumors into dedifferentiated, invasion-promoting guides. These tumor-associated Schwann cells (TASc) form dynamic tracks that channel cancer cell migration and drive epithelial-mesenchymal transition (EMT) (*46*, *47*). This process is often metabolically driven: High-lactate environments reprogram TASc into immunosuppressive cells that impair $CD8^+$ T cell function (*48*), and TASc can drive tumor cells toward aggressive basal-like states and organize CAFs into inflammatory phenotypes via midkine and IL-1α signaling (*49*). In melanoma, tumor cells can adopt hybrid neural/Schwann cell precursor-like states that correlate with early metastasis and resistance to both mitogen-activated protein kinase inhibitors and immune checkpoint blockade, with histone deacetylase 2 (Hdac2) inhibition capable of remodeling this state and restoring immunotherapy sensitivity (*50*). CAFs further amplify sympathetic innervation through β_2-AR/NGF feedforward loops (*51*) and facilitate PNI via CXCL12-mediated chemotaxis (*52*).

Neural influence on tumor biology extends to metabolism. Cancer-associated neurons can transfer mitochondria directly to tumor cells via tunneling nanotubes, enhancing metabolic plasticity and metastatic potential (*53*). In the TME, a lactate-NOP2/Sun RNA methyltransferase family axis stabilizes proinvasive transcripts to promote PNI, whereas nonselective β-blockers reverse this by reducing lactate accumulation (*54*, *55*). The reach of these signals is systemic: Obesity-driven NGF from pancreatic adipocytes amplifies PNI (*56*), and chronic stress remodels peritumoral lymphatics to accelerate dissemination (*57*). These peripheral branches are integrated through central circuits; lung adenocarcinoma engages vagal sensory neurons (VSNs) that signal to brainstem nuclei, driving elevated sympathetic efferent activity back to the TME to suppress immunity via alveolar macrophages (*58*).

Together, these findings position peripheral neural circuits as active regulators of tumor growth, immune evasion, and metastatic dissemination, providing a mechanistic foundation for neuromodulatory therapeutic strategies. The mechanistic picture that emerges from both CNS and PNS contexts is one of remarkable therapeutic accessibility: The pathways that nerves use to talk to tumors are, for the most part, druggable, with agents already on pharmacy shelves.

CURRENT TREATMENTS TARGETING THESE VULNERABILITIES

We organize neuromodulatory strategies along two overlapping axes: the dominant neural architecture (central versus peripheral, sympathetic, parasympathetic, and sensory circuits) and therapeutic intent (disease-modifying versus symptom- and survivorship-oriented). In densely innervated tumors, pancreatic and head-and-neck cancers being the prototypes, Schwann cell–rich autonomic and sensory plexuses scaffold invasion, pain, and immune suppression. Electrically active but less invasively innervated tumors, including breast cancer and melanoma, are instead shaped by tumor-cell ion channels, neurotransmitter receptors, and tumor-derived paracrine factors (*59*, *60*). Symptom- and survivorship-oriented approaches represent an equally vital arm of cancer neuroscience, and several agents occupy a dual space, with established efficacy for cancer-associated symptoms such as seizures, pain, nausea, and depression alongside putative antitumor potential.

Building on the CNS and PNS mechanisms outlined above, we next focus on neuromodulatory strategies that directly target these circuits at the level of neurotransmitter receptors, ion channels, and neural-tumor interfaces. Establishing biomarkers for patient stratification—PNI grade, nerve density, tumor receptor expression, stress physiology, and immune composition—remains a central priority to match mechanisms to the dominant neural circuit in each tumor, as does rational combination with immune checkpoint blockade to restore $CD8^+$ T cell function and reduce MDSC infiltration. Individual treatment classes with available evidence are summarized in Table 1 and Fig. 2 and discussed in detail below.

Neurotransmitter signaling pathways

β-adrenergic signaling

Supported by meta-analytic data from observational cohorts and more than 20 active prospective clinical trials, β-adrenergic signaling is one of the most translationally advanced neuromodulatory targets in cancer neuroscience for the PNS. In high-PNI and stress-responsive tumors, norepinephrine/β-adrenergic (NE/β-AR) signaling is a prototypical tumor-promoting sympathetic circuit: Chronic β-adrenergic tone drives angiogenesis, epithelial-mesenchymal transition (EMT), metastasis, and immunosuppression, whereas β-blockers reverse these programs and may synergize with chemotherapy and immunotherapy (*61*). A small, signal-generating propranolol-pembrolizumab trial in metastatic melanoma reported a striking objective response rate, although the uncontrolled single-arm design limited conclusions (*62*). Larger observational studies suggest a modest survival benefit with β-blocker use during immune checkpoint inhibitor (ICI) therapy, with nonselective agents appearing more immunologically active than β_1–selective agents (*63*); quantitative details are provided in Table 1. However, detrimental associations have also been noted in pancreatic and head-and-neck cancers, where β-blockade may exert countervailing influences on tumor growth and antitumor immunity (*63*, *64*).

These findings highlight the need for biomarker-stratified trials that account for tumor genotype (e.g., tumor protein p53 status), β-AR subtype expression (*65*), and tumor immunogenicity when evaluating β-blocker interventions. Patient selection will likely hinge on AR subtype: β_2-AR dominates in TNBC and melanoma, whereas β_1-AR appears more relevant in oral SCC (*65*). Complementary functional readouts, tumor β_2-AR expression by immunohistochemistry (IHC) and heart-rate variability as a vagal tone index, may further sharpen stratification (*66*, *67*). Structural barriers also matter, given that systemically administered β-blockers often fail to reach therapeutic concentrations within solid tumors (*2*). More than 20 active clinical trials are prospectively investigating β-blockade as an oncologic neuromodulatory strategy, spanning neoadjuvant breast cancer, metastatic melanoma, gastrointestinal (GI) cancers, non–small cell lung cancer (NSCLC), bladder cancer, angiosarcoma, and TNBC; selected trials are summarized in Table 1.

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Table 1. Neuromodulatory agents and emerging targets in cancer neuroscience. Organized by mechanistic class, this integrated table spans the translational spectrum from FDA-approved agents under oncologic repurposing to first-in-class compounds and preclinical targets. Evidence levels reflect the highest-quality data available; biomarkers listed are candidate stratification tools and have not been prospectively validated. Dash entries indicate not applicable. 4-AP, 4-aminopyridine; CA, cancer; CHRM3, cholinergic receptor muscarinic 3; CI, confidence interval; CIPN, chemotherapy-induced peripheral neuropathy; DMG, diffuse midline glioma; EA, electroacupuncture; FLNA/FLNC, filamin A/filamin C; GOJ, gastroesophageal junction; GsMTx4, *Grammostola spatulata* mechanotoxin 4; HA-WBRT, hippocampal-avoidance whole-brain radiotherapy; HRV, heart rate variability; M2, M2-polarized tumor-associated macrophage; mAbs, monoclonal antibodies; mo, month; mOS, median overall survival; ORR, objective response rate; PIEZO1, Piezo-type mechanosensitive ion channel component 1; PR, partial response; RCT, randomized controlled trial; RFS, recurrence-free survival; R/M, recurrent/metastatic; RR, relative risk; RT, radiotherapy; SD, stable disease; SLC7A11, solute carrier family 7 member 11 (xCT gene); ST-36, stomach meridian acupoint 36; TMZ, temozolomide; UNC5B, unc-5 netrin receptor B; vs., versus; 5-HT, serotonin [5 hydroxytryptamine (5-HT)]; α2δ-1, voltage-gated calcium channel α2δ-1 subunit.

Treatment class	Exemplar agents	Tumor types	Evidence level	Key clinical evidence	Notable biomarkers
β-Adrenergic blockers	Propranolol, carvedilol, atenolol	Breast, melanoma, ovarian, prostate, GI, angiosarcoma, TNBC	Phase 2 + extensive observational; >20 active trials	Propranolol + pembrolizumab ($n = 9$ melanoma): ORR 78% (*62*). BB + ICI meta-analysis (12 studies): HR 0.91 (0.85–0.98) OS (*63*). Nonselective BB > β1-selective for immune modulation (*63*). >12 phase 1/2 trials across breast, GI, lung, bladder, sarcoma, TNBC recruiting	β_2-AR IHC H-score: High β_2-AR → improved RFS/OS in esophageal/GOJ (HR 0.48–0.57) (*67*). HRV as vagal-tone index (survival HR 0.59, $n = 2539$) (*66*)
CGRP pathway	Rimegepant, erenumab, fremanezumab, eptinezumab, olcegepant	Gastric, HNSCC, thyroid, melanoma, CRC, solid tumors	Phase 2 registered; strong preclinical	First antitumor CGRP trial: Rimegepant + anti–PD-1 in liver-met CRC (NCT06999252), not yet recruiting. RAMP1 blockade nearly triples survival in melanoma models (*35*). Rimegepant reduces gastric tumor volume in vivo (*39*). FDA-approved anti-CGRP mAbs provide immediate repurposing pathway	RAMP1 expression (IHC/RNA): Pan-cancer poor prognosis (*141*). CGRP gene signature: Suppressed antitumor immunity across solid tumors (*37*)
Dopamine receptors (DRD2/ClpP)	ONC201 (dordaviprone), ONC206, chlorpromazine	H3K27M DMG, GBM, AML, NETs, breast	FDA accelerated approval (DMG); phase 3 ongoing	ONC201 accelerated FDA approval for H3K27M DMG: mOS ≈ 21–22 mo vs. historical 11–15 mo. ACTION phase 3 in newly diagnosed H3K27M DMG (NCT05580562) ongoing (*74*). Outside DMG: Mostly stable disease, few PR; several trials completed (*75*)	DRD2 protein/mRNA: 4–17-fold overexpression in GBM vs. normal brain (*77*). ClpP expression as an ONC201/imipridone sensitivity marker (*78*)
Glutamate pathway (AMPA, NMDA, xCT)	Perampanel, memantine, sulfasalazine	GBM, glioma, brain metastases, melanoma	Phase 1/2 (glioma); symptom-based phase 3	Talampanel/perampanel + chemoRT in glioma: Acceptable safety, modest signals supporting larger studies (*81–84*). Memantine standard-of-care neuroprotectant with HA-WBRT (*86*). Multiple sulfasalazine phase 1/2 trials; one terminated early. GLUGLIO trial: Gabapentin + sulfasalazine + memantine + chemoRT vs. chemoRT in GBM (*142*)	xCT (SLC7A11) expression: Glutamate export dependence (*87*). MEG gamma power/functional connectivity as nonmolecular marker (*16*)

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Treatment class	Exemplar agents	Tumor types	Evidence level	Key clinical evidence	Notable biomarkers
Axon guidance: netrin-1/SEMA4D	NP137 (anti–netrin-1), pepinemab (anti-SEMA4D)	Endometrial, cervical, HNSCC, melanoma, osteosarcoma	Phase 1/2 with clinical signals	NP137: 8/14 SD, 1 PR (>50% reduction) in endometrial CA (NCT02977195) (*103*). KEYNOTE-B84: Pepinemab + pembrolizumab in R/M HNSCC doubled ORR vs. historical (NCT04815720) (*104*). Combination trials with ICI ongoing (GYNET; NCT04652076)	Netrin-1 overexpression correlates with EMT scores and worse prognosis in endometrial cancer (*103*). UNC5B may serve as a companion biomarker for netrin-1 dependence for NP137 (*143*)
NLGN3/ADAM10 synapse pathway	INCB7839 (ADAM10 inhibitor)	Pediatric HGG, GBM, medulloblastoma	Phase 2 ongoing (pediatric HGG)	NLGN3 validated as master regulator of activity-dependent glioma growth. ADAM10 inhibition blocks neuron-glioma synapse formation; suppresses HGG xenografts. INCB7839 phase 2 in pediatric HGG (NCT04295759); repurposed from Alzheimer's (*12–14*)	NLGN3 cleavage/ectodomain shedding activity
Gap junction blockers (connexins)	Meclofenamate, tonabersat, carbenoxolone	GBM, brain metastases	Preclinical + early clinical (meclofenamate)	Cx43 mediates tumor microtube networks → nutrient sharing, chemoresistance meclofenamate (FDA-approved NSAID) blocks Cx43; reduces GBM invasion, enhances TMZ (*105*). Phase 1/2 ongoing in GBM (EudraCT 2021-000708-39). Trial for brain metastases registered (not yet recruiting) (NCT02429570)	–
GABA pathway ($GABA_{A/B}$)	Valproic acid, baclofen, benzodiazepines	GBM, AML, prostate, lung, medulloblastoma	Phase 1/2; extensive but inconclusive	Systematic review of VPA as glioma radiosensitizer: HR 0.80 (retrospective-driven) (*90*). VPA + RT/TMZ in GBM (NCT00302159): mOS ~ 29.6 mo (single-arm) (*89*). Benzodiazepine use associated with increased cancer risk (RR 1.19, $n = 44$ studies) (*91*)	HDAC activity/histone acetylation as VPA pharmacodynamic marker. $GABA_{A\text{-}R}$ subunit expression (context-dependent)
Acetylcholine pathway (M3, nAChR)	Botulinum toxin, bethanechol, darifenacin, donepezil	Gastric, PDAC, prostate, CRC, HNSCC	Phase 2 (BTX gastric; bethanechol PDAC)	Bethanechol ± gemcitabine/nab-paclitaxel in PDAC (NCT03572283, NCT05241249). BTX phase 2 in inoperable gastric adenoCA (NCT01822210): Completed, no results posted. Donepezil: No convincing benefit for cancer-related cognitive impairment (5 RCTs) (*95*)	M3R (CHRM3): Overexpressed in gastric/CRC; correlates with EGFR transactivation (*93*). ChAT expression as autocrine ACh marker (*94*)

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Treatment class	Exemplar agents	Tumor types	Evidence level	Key clinical evidence	Notable biomarkers
Serotonin pathway (SERT, 5-HT)	Fluoxetine, sertraline, imipramine, telotristat ethyl	Glioma, CRC, AML, SCLC, breast, NETs	Phase 1 (oncology);	FLIRT trial: Fluoxetine + TMZ in glioma (NCT05634707). Fluoxetine immune modulation window study in CRC (NCT06225011). Sertraline + cytarabine in AML (NCT02891278). No tumor-control or survival outcomes available yet	SERT (SLC6A4) on $CD8^+$ T cells: High intratumoral SERT → poorer survival; predicts SSRI immune potentiation (*80*). TPH1 in TILs as autocrine serotonin circuit marker (*80*)
NK1R antagonists (neurokinin/substance P)	Aprepitant, fosaprepitant	Breast, NSCLC, CRC, PDAC, HNSCC, GBM	Observational only; FDA-approved antiemetic	Aprepitant associated with improved breast cancer survival vs. other antiemetics (HR 0.83) (*124*). No prospective antitumor trial conducted. Strong preclinical: SP/NK1R inhibition reduces growth/metastasis (*123*)	TACR1 (NK1R): Overexpression as pan-cancer prognostic marker (*123*). Sex-specific expression in PDAC (higher in female) (*125*, *126*). Plasma substance P
TRPV1 pathway	Capsaicin, capsazepine, RTX, nanoparticle formulations	HCC, ovarian, CRC, HNSCC, breast, oral SCC	Phase 1 (RTX for pain only); preclinical for oncology	RTX phase 1 (NCT00804154): 38% pain reduction, 57% opioid reduction (*119*). TRPV1 inhibition sensitizes to PD-1 blockade (*115*). RTX denervation: 5-fold increase $CD8^+$ TILs in oral SCC (*118*). No dedicated antitumor capsaicin/capsazepine trials	TRPV1-high tumors and sensory nerves; pan-cancer TRPV1 expression signature linked to TMB/MSI; EGFR activation and plasma EGF for immunotherapy combinations (*115*)
Voltage-gated Na^+ channels (Nav1.5/1.7)	Lidocaine, ranolazine, phenytoin	Breast, melanoma, prostate, colon, TNBC, HNSCC	Phase 1/2; observational signals	Ranolazine: ~60% lower cancer-specific mortality (retrospective) (*107*). Peritumoral lidocaine improves OS in early breast CA; many trials underway (*108*). Preclinical: 50–60% metastasis reduction with Nav blockade (*106*)	Nav1.5 protein (IHC): Correlates with metastasis in breast CA TMA. Nav1.7 (SCN9A) expression correlates with tumor size, lymph node metastasis, and 5-/10-year survival in endometrial cancer; neonatal splice variant nNav1.5 distinguishes metastatic from nonmetastatic breast cancer cells (*106*)
Potassium channels (Kv1.3, KCa3.1)	Senicapoc, amiodarone, clofazimine, 4-AP	TNBC, melanoma, glioma, pancreatic	Phase 1 (SENIPERA trial in GBM)	SENIPERA: Senicapoc ± perampanel in newly diagnosed GBM (NCT07284069)—first trial cotargeting ion channel + glutamatergic signaling. Preclinical only for amiodarone, clofazimine, TRAM-34 (*109, 110*)	Kv1.3/KCa3.1 expression on tumor cells. Bioelectric membrane potential as functional readout (*109*, *110*).

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Treatment class	Exemplar agents	Tumor types	Evidence level	Key clinical evidence	Notable biomarkers
Calcium channels (α2δ, Cav3.2, L-type)	Gabapentin, pregabalin, mibefradil	GBM, melanoma, breast, pancreatic	Phase 1 mibefradil (NCT02202993) Retrospective signal (gabapentinoids)	Extensive preclinical evidence for gabapentin; use at GBM diagnosis: 4–6 mo OS benefit (HR ~ 0.65; discovery $n = 693$, validation $n = 379$) (*112*). Gabapentin phase 3 mainly for mucositis/symptom end points. Ketorolac + pregabalin in early ER+ breast CA (NCT06150898) recruiting	Serum TSP-1: Lower in patients with gabapentin-treated GBM (*112*). α2δ-1 subunit expression as target engagement marker
Surgical/chemical denervation	Vagotomy, BTX injection, celiac plexus neurolysis	Gastric, PDAC, prostate	Phase 2 + established palliative procedures	Vagotomy reduces recurrence with gastrectomy. Celiac plexus neurolysis: Standard-of-care for pancreatic cancer pain. Radical denervation in preclinical models: 87.5% complete regression (*144*, *145*). BTX phase 2 in gastric adenoCA completed; no efficacy results posted	PNI grade: Independent predictor of biochemical recurrence in prostate CA (meta-analysis) (*132*). 3D PNI morphometry emerging (*131*)
Tumor-treating fields	Optune (200–300 kHz)	GBM	FDA approved (GBM standard of care)	FDA approved for newly diagnosed GBM: 5-Month OS extension with TMZ; pivotal phase 3 efficacy in PDAC (*133*). Mechanism: Disrupts microtubule dynamics and mitosis	Not specifically biomarker-stratified
NPY/Y1R antagonism	BMS-193885, BIBO3304	PDAC, gastric, breast, CRC	Preclinical (2025 discovery)	NPY identified as key metastasis driver in PDAC; sensory neuron NPY release → liver metastasis. Y1R antagonism blocked metastasis in preclinical models (*70*). No clinical trials registered	–
PIEZO1 mechanosensitive channels	Yoda1 (agonist), GsMTx4 (antagonist)	Breast, ovarian, gastric	Preclinical	Piezo1 overexpression enhances migration and peritoneal metastasis, whereas genetic or pharmacologic Piezo1 inhibition (including with GsMTx4) reduces invasive behavior. Context dependent (*121*, *122*). No clinical trials	–
Neuromodulation: VNS	Transcutaneous auricular VNS, implanted VNS	Breast, lung, melanoma, various solid tumors	Preclinical (antitumor); FDA-approved (cluster headache, depression)	VNS enhances $CD8^+$ TIL function in lung cancer models (*135*). taVNS reduces insomnia/fatigue/depression in breast CA (NCT06006299) (*136*). No prospective antitumor outcome data yet	–

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Treatment class	Exemplar agents	Tumor types	Evidence level	Key clinical evidence	Notable biomarkers
Neuromodulation: TMS	Repetitive TMS (low-frequency rTMS)	GBM, NSCLC, CIPN	Preclinical (antitumor); FDA-approved (depression)	Low-freq rTMS suppresses GBM growth via FLNA/FLNC down-regulation (*137*, *138*). Clinical trials limited to pain control and chemo-brain cognition. No human antitumor outcome data	–
Neuromodulation: Electroacupuncture	ST-36 bilateral EA	TNBC, CRC, HCC, osteosarcoma	Preclinical FDA-cleared	Enhanced anti–PD-1 efficacy in CRC (*139*). No human antitumor trials	–

CGRP pathway

If adrenergic signaling represents the sympathetic arm of tumor innervation, then sensory neuropeptides, particularly CGRP, are its nociceptive counterpart, with equally direct consequences for immune surveillance (*37*). The discovery that pain-signaling neurons actively suppress tumor immunity reframed CGRP, a peptide best known for causing migraines, as one of the most compelling targets in cancer neuroscience. Nociceptor-derived CGRP drives $CD8^+$ T cell exhaustion and MDSC infiltration in melanoma via the CGRP-RAMP1 axis, where RAMP1 blockade nearly triples survival in preclinical models (*35*). CGRP-RAMP1 signaling on CAFs suppresses IL-15 and NK cell function in pancreatic cancer, and CGRP upregulation is associated with poor outcomes and immunotherapy resistance across a broad range of advanced solid tumors (*37*).

CGRP blockade with rimegepant reduces gastric tumor volume and prolongs survival in vivo (*39*), and CGRP knockout increases $CD8^+$/NK TIL infiltration in oral SCC (*68*, *69*)—together positioning sensory neuropeptides as direct modulators of antitumor immunity and linking nociceptor activity to immunotherapy resistance and cancer pain across multiple tumor types. Translationally, the first phase 2 trial specifically targeting CGRP in oncology, combining rimegepant plus anti–PD-1 in liver-metastatic CRC (NCT06999252), has been registered. RAMP1 expression by IHC or RNA, together with a CGRP pathway gene-expression signature associated with suppressed antitumor immunity, may serve as candidate stratification biomarkers for future CGRP-directed neuromodulatory strategies (*37*).

Neuropeptide Y pathway

The preclinical case for neuropeptide Y (NPY) as an oncologic target rests on the same principle as CGRP: A peptide classically associated with appetite and energy homeostasis turns out to have potent immunosuppressive and prometastatic effects in the TME (*58*, *70*). In this context, NPY has recently been identified as a driver of pancreatic cancer metastasis (*70*). Sensory neurons within the tumor microenvironment release NPY, which acts through its Y1 receptor (NPY1R) on tumor cells to promote migration and liver colonization (*70*). In an autochthonous KPR172HC pancreatic ductal adenocarcinoma (PDAC) mouse model, both genetic knockout of Npy1r and pharmacologic inhibition with the Y1R antagonist BIBO3304 significantly reduced liver metastasis (*70*). Npy1r blockade also attenuated cancer-associated cachexia in these models, suggesting a potential link between NPY signaling and cachexia beyond direct tumor burden reduction (*71*).

NPY2R and purinergic receptor P2Y1 neurons account for most lung-innervating vagal sensory neuron (VSN) fibers, and ablation of Npy2r VSNs, but not P2ry1 VSNs, significantly reduces lung tumor burden in preclinical models (*58*). Adrb2 genetic deletion abolishes the tumor-promoting effects of vagal NPY2R VSNs in lung adenocarcinoma, enhancing antitumor T cell immunity via reprogramming of immunosuppressive alveolar macrophages, suggesting potential added therapeutic benefit with β-blockade (*58*). NPY has also been implicated in breast and prostate cancer, where it has been shown to link to psychological depression, adrenergic signaling, and tumor progression (*72*).

Despite strong preclinical rationale linking neural, metabolic, and immune signaling, no clinical trials targeting the NPY/Y1R axis in cancer have yet been initiated. NPY in the plasma has been found to have additive value combined with prostate-specific antigen for prostate cancer screening, suggesting a potential priority biomarker for investigation in other tumors (*73*).

Dopamine pathway

Translating the neural-tumor concepts into the clinic, ONC201 (dordaviprone) has already changed practice: As the first neurotransmitter-pathway drug to receive US Food and Drug Administration (FDA) approval for a primary brain tumor, it established proof of concept that targeting dopamine receptor signaling can improve survival in molecularly defined gliomas (*74*).

Outside this molecular niche, ONC201 monotherapy in GBM, neuroendocrine tumors (NETs), and breast or endometrial cancer has generally yielded stable disease with occasional partial responses, and repurposed dopamine-pathway agents (antipsychotics) have shown biological but not practice-changing activity (*75*, *76*). These data suggest that dopamine-directed strategies may require stringent molecular selection and rational combinations rather than broad application across tumor types.

Dopamine receptor D2 (DRD2) is overexpressed in GBM as compared with adjacent normal brain (*77*), and caseinolytic protease P (ClpP) expression is a potential marker for ONC201 sensitivity (*78*). Together, these findings position DRD2 and ClpP as candidate biomarkers for patient stratification and support ongoing efforts to refine the therapeutic window for dopamine-pathway targeting in CNS and selected extracranial malignancies.

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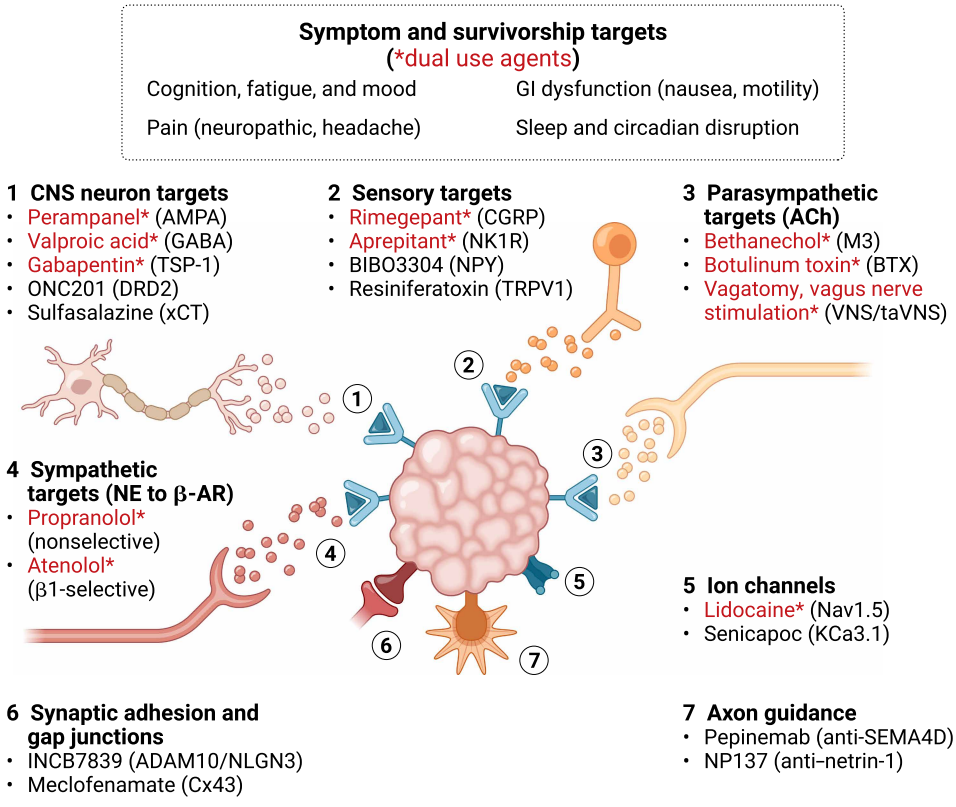

Fig. 2. Therapeutic landscape of neuromodulatory strategies targeting neural-tumor interactions. Representative neuromodulatory agents are organized by neural input and molecular target class. CNS neuron targets include glutamate receptors (AMPA, NMDA, and metabotropic glutamate receptor) and DRD2, addressed by perampanel, valproic acid, gabapentin, ONC201, and sulfasalazine. Sensory targets [RAMP1, neuropeptide Y receptor (NPY-R), and NK1R] are addressed by rimegepant, BIBO3304, aprepitant, and resiniferatoxin. Sympathetic targets (β_1-AR and β_2-AR) are addressed by propranolol and atenolol. Parasympathetic targets (M2/M3 muscarinic acetylcholine receptor) are addressed by bethanechol, botulinum toxin (BTX), vagotomy, and VNS. Additional target classes include ion channels (senicapoc targeting KCa3.1; lidocaine targeting Nav1.5), axon guidance molecules (pepinemab targeting SEMA4D; NP137 targeting netrin-1), and synaptic adhesion and gap junction proteins (INCB7839 targeting ADAM10/NLGN3; meclofenamate targeting Cx43). Many of these agents (marked with an asterisk *) hold dual-use potential as symptom and survivorship therapies, addressing cognition, fatigue, mood, pain, GI dysfunction, and sleep disruption. Individual agents, tumor types, evidence levels, and candidate biomarkers are detailed in Table 1.

Serotonin pathway

Evidence for the serotonin pathway in oncology remains predominantly preclinical, with early-phase clinical trials initiated but no tumor-control or survival outcomes reported to date. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and tricyclic antidepressants such as imipramine induce apoptosis and potentiate chemosensitivity in glioma, small cell lung cancer (SCLC), and other preclinical systems (*79*). Serotonin reuptake (SERT) blockade on $CD8^+$ T cells suppresses melanoma, colon, bladder, breast, and neuroendocrine prostate tumors and enhances anti–PD-1 activity, positioning SSRIs as potential immune-checkpoint–like modulators of the intratumoral serotonin axis (*80*).

Early trials are testing SSRIs in combination with chemotherapy and immunotherapy across glioma, CRC, and acute myeloid leukemia (AML), but no efficacy outcomes are yet available. Specific agents and trial designs are summarized in Table 1. Given their established clinical use for depression and anxiety, SSRIs are attractive dual-purpose candidates, with emerging tumor-directed potential in SERT-high contexts. Intratumoral SERT [solute carrier family 6 member 4 (serotonin transporter gene; SLC6A4)] expression on $CD8^+$ T cells, together with tryptophan hydroxylase 1 (TPH1) in TILs, serve as candidate biomarkers of the autocrine serotonin circuit and may guide patient selection for serotonin-directed neuromodulatory strategies (*80*).

Glutamate pathway

Moving from monoamine to amino acid neurotransmitters, glutamatergic signaling represents the most directly synaptic of the pathways discussed here and the one with the most direct mechanistic link to the tumor microtubes and electrochemical synapses described in the "CNS mechanisms" section. Glutamatergic signaling is among the most advanced neurotransmitter-targeting classes in the CNS, supported by a prior phase 2 survival signal and multiple ongoing early-phase trials. Preclinical work has established glutamatergic synapses and glutamate release as critical drivers of progression, invasion, and treatment resistance in brain tumors (*11*, *13*–*19*). Pharmacologic AMPAR blockade with perampanel, a European Medicines Agency/FDA–approved add-on antiseizure drug, reduces glioma proliferation, invasion, and tumor microtube formation in patient-derived xenograft models (*17*, *18*, *21*). A short-acting analog, talampanel, produced an apparent survival benefit when added to chemoradiotherapy in a phase 2 GBM trial (*81*).

Building on these data, phase 2a "window-of-opportunity" and early-phase combination trials of perampanel in newly diagnosed and recurrent glioblastoma are underway (*81*–*84*). Memantine (an NMDAR antagonist) enhances antitumor immunity preclinically (*85*) and is the clinical standard of care for neuroprotection during whole-brain radiation (*86*), supporting its dual-use potential. Combinatorial approaches are emerging, exemplified by GLUGLIO, a phase 1b/2 trial adding gabapentin, sulfasalazine, and memantine to chemoradiotherapy in patients with newly diagnosed GBM (summarized in Table 1). For patient stratification, two complementary approaches are emerging: molecular (AMPAR subunit expression on tumor cells as a receptor engagement marker) and functional [magnetoencephalography (MEG) gamma power and calcium imaging as readouts of glutamatergic network activity (*16*)]. Separately, xCT (SLC7A11) overexpression in glioma, breast, and lung cancer predicts glutamate export dependence and sulfasalazine sensitivity, making it a biomarker candidate for the glutamate-export arm of this class (*87*). The convergence of strong mechanistic data, prior survival signals, and ongoing combinatorial trials positions glutamatergic signaling as a leading therapeutic target in CNS cancer neuroscience.

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GABA pathway

Unlike the other neurotransmitters discussed above, GABA has a more context-dependent role in oncology, with tumor-suppressive effects in some settings and growth-permissive effects in others. Clinically, most available data come from valproic acid (VPA), which increases brain GABA levels indirectly through GABA transaminase inhibition but also has anticancer effects through histone deacetylase (HDAC) inhibition (*88*). As a radiosensitizer in glioma, VPA has been associated with an improved overall survival, largely by retrospective data, and single-arm studies adding VPA to chemoradiotherapy in patients with newly diagnosed glioblastoma have reported prolonged median survival (*89*, *90*); regimens are summarized in Table 1. $GABA_A$ receptor signaling itself appears context dependent, with tumor-suppressive roles in several brain tumor models but epidemiologic and preclinical data suggesting that pharmacologic GABA potentiation via benzodiazepines may increase cancer risk or promote growth in some settings (*21*, *91*, *92*). Together, these findings highlight the context-dependent and clinically uncertain role of GABA signaling in cancer, underscoring the need for careful mechanistic and biomarker-driven approaches.

Cholinergic signaling

Cholinergic pathway modulation has reached early-phase 1/2 clinical testing and appears most relevant in high-PNI, cholinergically innervated tumors such as gastric, pancreatic, and prostate cancers. In these settings, muscarinic receptor 3 (M3R)– and nicotinic acetylcholine receptor (nAChR)–mediated signaling drives tumor proliferation, immune evasion, and programmed cell death ligand 1 (PD-L1) up-regulation, whereas interventions such as botulinum toxin, muscarinic antagonists, and nAChR inhibitors suppress growth and reduce PD-L1 expression preclinically (*29*, *93*). Conversely, cholinergic activation with bethanechol extends survival in PDAC models (*94*), reflecting the context-dependent role of cholinergic tone across tumor types. Clinically, early-phase trials are evaluating bethanechol combination with chemotherapy in pancreatic cancer and intratumoral botulinum toxin in gastric cancer; details are summarized in Table 1.

Regarding dual-use potential, donepezil is FDA approved for Alzheimer's disease and prevents brain metastasis in preclinical models but has not shown consistent benefit for cancer-related cognitive impairment in randomized trials (*95*, *96*). Cholinergic signaling remains context dependent, with tumor-promoting or suppressive effects depending on tumor type and autonomic context (*10*). Patient selection will be essential here. M3R overexpression is a logical stratification marker in gastric and colorectal cancers, whereas choline acetyltransferase (ChAT) expression marks autocrine acetylcholine-producing tumors; heart-rate variability may offer a functional index of parasympathetic tone in future trials, although none of these biomarkers has been clinically validated prospectively (*66*, *93*, *94*).

An emerging frontier linked to cholinergic modulation is the gut-brain-microbiome axis, particularly in GI cancers. The enteric nervous system provides the neural substrate through which cholinergic and vagus-nerve–targeted interventions can influence tumors locally and at distant sites. The potential to convert immune-resistant "cold" tumors into immune-responsive "hot" ones may hold promise for immune checkpoint inhibitors (*97*). Although proof-of-concept targeting of this axis has been demonstrated with fecal microbiota–based interventions, substantial uncertainty still exists in modulating the interactions among the microbiome, immune, and nervous systems (*98*). In the near term, more controlled neuromodulatory strategies such as vagus nerve stimulation (VNS) may offer a tractable path to clinical translation.

Defining when cholinergic tone is tumor promoting versus tumor restrictive will likely be critical for successful clinical translation of vagal and enteric neuromodulatory strategies. Whereas neurotransmitters mediate fast, receptor-level signaling between nerves and tumors, neurotrophins and axon-guidance cues operate on a slower timescale, governing whether nerves grow toward tumors, invade along them, and sustain them over time (*1*).

Neurotrophin signaling, synaptic adhesion, and axon guidance

No other pathway in cancer neuroscience illustrates the full arc from bench to bedside quite as clearly as neurotrophin signaling, from the discovery that tumors secrete NGF to recruit axons to FDA approvals of TrkA/B/C inhibitors now in routine oncologic use. Neurotrophins and axon-guidance cues define how nerves enter, pattern, and sustain the TME, PNI, and pain in multiple cancers. NGF/TrkA and neurotrophic receptor tyrosine kinase (NTRK) fusions demonstrate that neurotrophin receptors are highly druggable, with larotrectinib and entrectinib achieving high response rates with durable benefit across NTRK fusion-positive tumors (*99*). Although these agents primarily target tumor-cell fusion kinases, they validate TrkA/B/C as actionable axes and provide a conceptual bridge to brain-derived neurotrophic factor (BDNF)/TrkB signaling. In pancreatic and colorectal cancer models, Trk inhibition with agents such as larotrectinib and the highly selective TrkA/B/C inhibitor selitrectinib reduces tumor innervation and slows growth by interrupting β_2-adrenergic–neurotrophin signaling, linking activity-dependent neuroplasticity, adrenergic tone, and tumor progression (*51*, *100*, *101*). Trk inhibitors, however, frequently cause adverse effects, including weight gain, ataxia, paresthesia, and withdrawal pain, with treatment discontinuation in roughly one-third of patients, highlighting the need for more targeted peritumoral delivery; early work with extracellular vesicle–based approaches is promising (*102*).

In the CNS, the synaptic adhesion molecule neuroligin-3 (NLGN3) has been extensively validated as a master regulator of activity-dependent glioma growth, with a disintegrin and metalloprotease 10 (ADAM10)–mediated cleavage of neuronal NLGN3 driving paracrine growth and ADAM10 inhibition robustly suppressing neuron-glioma synapse formation in high-grade glioma (HGG) (*12*–*14*). INCB7839, an ADAM10 inhibitor originally developed for Alzheimer's disease and shown safe in prior phase 1 studies, is now being evaluated in a phase 2 trial in pediatric high-grade glioma, representing direct clinical translation (detailed in Table 1).

More broadly, the INCB7839 trial highlights a substantial gap in the field: targeting pediatric and low-grade brain tumors, such as NF1-associated optic pathway gliomas (*20*) and diffuse midline gliomas (*21*). Nearly all neuromodulatory clinical trials to date have been designed for adult high-grade populations. Given that many repurposed neuroactive agents, such as perampanel, gabapentinoids, and senicapoc, carry favorable toxicity profiles relative to conventional cytotoxic therapy, pediatric and low-grade tumors represent a particularly compelling context for clinical investigation, where the chronic, indolent disease course aligns well with sustained neuromodulatory strategies.

Axon-guidance molecules operate at the nerve-tumor-immune interface, especially in high-PNI settings. The anti–netrin-1 antibody NP137 restores apoptosis by blocking dependence-receptor

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survival signals, with early-phase trials showing predominantly stable disease; combination studies with checkpoint inhibitors are ongoing (*103*). The anti–semaphorin 4D (SEMA4D) antibody pepinemab has demonstrated manageable safety and encouraging disease control in early-phase trials combined with pembrolizumab (*104*) (details are summarized in Table 1). Netrin-1 expression and SEMA4D on tumor and immune cells represent candidate stratification biomarkers for these agents.

Last, glioblastoma cells form extensive TM networks connected by connexin-43 (Cx43) gap junctions, enabling calcium-wave propagation, nutrient sharing, and chemoresistance across the tumor syncytium. Meclofenamate, an FDA-approved nonsteroidal anti-inflammatory drug (NSAID), disrupts Cx43-mediated TM connectivity, reduces GBM invasion, and sensitizes tumor cells to temozolomide in preclinical models (*105*). A phase 1/2 trial is evaluating meclofenamate plus temozolomide in progressive MGMT-methylated glioblastoma, and a separate feasibility trial in brain metastases is registered (specific dosing and design details are summarized in Table 1).

Together, these pathways position neurotrophin signaling, synaptic adhesion, and axon-guidance cues as integrated regulators of tumor-nerve interactions, with emerging opportunities for targeted and biomarker-driven therapeutic intervention. Neurotrophins and guidance cues explain how nerves are recruited to tumors, and ion channels explain how tumors exploit the electrical properties of that innervation for their own proliferative and invasive programs.

Ion channel modulation in lower-PNI but electrically active tumors

Voltage-gated sodium channels

Evidence for voltage-gated sodium channel targeting is primarily preclinical and observational at this stage. Voltage-gated sodium channel 1.5 (Nav1.5) and Nav1.7 act as metastatic "switches" in breast, melanoma, prostate, and other lower-PNI but electrically active tumors. Preclinically, ranolazine and classical Nav blockers suppress invasion substantially while sparing primary tumor growth, consistent with Nav1.5 as a metastasis-enabling switch rather than a growth driver (*106*). Retrospective data on chronic ranolazine use suggest a meaningful reduction in cancer-specific mortality, although confounding limits interpretation (*107*) (data are in Table 1). Perioperative or peritumoral lidocaine injection has improved overall survival (OS) in early breast cancer, with multiple trials underway across solid tumor types (*108*).

Nav1.5 protein expression by IHC correlates with metastasis and shortened cancer-specific survival in breast cancer tissue microarrays, and the neonatal splice variant nNav1.5 distinguishes metastatic from nonmetastatic cells (*106*) positioning channel expression at the invasive front as a logical biomarker to optimize future trials. Collectively, these studies support voltage-gated sodium channels primarily as regulators of metastatic competence and invasion in electrically active tumors rather than simple drivers of tumor growth.

Potassium channels

Potassium channels are emerging targets in glioblastoma and other solid tumors, with early-phase clinical testing underway and strong mechanistic support from preclinical work. Voltage-gated potassium channel 1.3 (Kv1.3) and calcium-activated potassium channel 3.1 (KCa3.1) modulate membrane potential and inflammatory signaling in TNBC, melanoma, pancreatic cancer, glioma, and other cell types (*109*, *110*). Recently, KCa3.1 was identified as an integral ion channel for tumor pacemaker cells in glioma. Although these pacemaker cells are a numerically small subpopulation, they appear to coordinate network-wide electrical oscillations that drive invasion (*15*). Glioblastoma dependence on these intrinsically rhythmic cells was shown to be effectively targeted by two KCa3.1 inhibitors, senicapoc and TRAM-34 {1-[(2-chlorophenyl)diphenylmethyl]-1H-pyrazole}, which disrupted network synchrony and reduced glioma migration (*15*). Similar effects have been shown with TRAM-34 in melanoma metastasis, lung adenocarcinoma, TNBC, hepatocellular carcinoma (HCC), and PDAC (*109*, *110*).

Clinically, senicapoc is highly brain penetrant and has shown an acceptable safety profile in phase 2/3 sickle-cell disease trials, supporting its repurposing potential (*111*). The SENIPERA phase 1 trial of senicapoc with or without the AMPAR antagonist perampanel in patients with newly diagnosed glioblastoma exemplifies a combinatorial strategy that cotargets ion-channel–driven excitability and glutamatergic signaling (regimens and end points are summarized in Table 1). Kv1.3 overexpression has been detected in many cancers and, together with bioelectric membrane potential, represents emerging functional readouts for future patient stratification (*109*, *110*). These data support potassium-channel inhibition as a promising combinatorial strategy to disrupt glioma network synchrony, invasion, and electrically coordinated tumor behavior.

Calcium channels

With multisite observational data and multiple completed phase 1 trials targeting calcium channels, calcium channel modulation represents a promising connection between neuroelectric activity and radiosensitivity/chemosensitivity. Gabapentin, which is a calcium channel blocker that also inhibits the matricellular protein thrombospondin-1 (TSP-1), reduces glioma growth and enhances radiotherapy/temozolomide responses in preclinical models (*16*). In addition, a large, multisite retrospective GBM cohort found that gabapentinoid use at diagnosis was associated with a 4- to 6-month OS benefit [hazard ratio (HR) $\sim$ 0.65], identifying this pathway as a strong candidate for prospective evaluation (*112*). Beyond their direct antitumor effects, gabapentinoids are prototypical dual-intent agents: potential tumor-directed radiosensitizers in α2δ/Cav3.2-expressing tumors and established survivorship drugs for neuropathic pain. Phase 3 and early-phase trials are evaluating gabapentin for opioid sparing in mucositis during head and neck chemoradiotherapy and pregabalin in the perioperative setting to probe how pain control and inflammation influence metastatic spread in early estrogen receptor–positive breast cancer; specific designs are summarized in Table 1. Together with ongoing potassium channel studies, ion channel modulation represents one of the most promising dual-use targets in cancer neuroscience. Lower serum TSP-1 in patients with gabapentin-treated glioblastoma serves as a pharmacodynamic marker, and α2δ-1 subunit and CACNA1D (Cav1.3) expression are candidate stratification biomarkers (*112*, *113*).

TRPV1 pathway

TRPV1 sits at the intersection of nociception and tumor bioelectric signaling, a mechanistically compelling target whose antitumor evidence, although still preclinical, spans multiple cancer types and therapeutic modalities. Capsaicin has been shown to induce TRPV1-mediated Ca^{2+} overload, mitochondrial disruption, and apoptosis in hepatocellular carcinoma (HCC), breast cancer, CRC, tongue SCC, and ovarian cancer models and augments cisplatin via calpain and autophagy pathways (*114*). TRPV1 inhibition also sensitizes tumors to PD-1 blockade by reversing resistance to cytotoxic T lymphocyte–mediated killing via epidermal growth factor/epidermal growth factor

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receptor (EGF/EGFR) signaling (*115*), and improved delivery has been shown with TRPV1-targeted nanoparticles to amplify thermo-immunotherapy and anti–PD-L1 efficacy (*116*). Resiniferatoxin (RTX), an ultrapotent capsaicin analog derived from a cactus-like plant, selectively ablates TRPV1-expressing nociceptive neurons at doses orders of magnitude below those needed for capsaicin, a property that makes it uniquely suited for therapeutic denervation (*117*). RTX denervation of $TRPV1^+$ neurons increases $CD8^+$ TILs fivefold and reduces oral SCC tumor growth in mice (*118*). TRPV1 thus exemplifies a dual-purpose target: exploitable for lethal calcium flux in tumor-directed strategies and for nociceptive circuit modulation in survivorship. Clinically, RTX has demonstrated meaningful pain and opioid reduction in an early-phase trial for intractable cancer pain (trial details are summarized in Table 1) (*119*). For stratification, pan-cancer analysis shows that differential TRPV1 expression carries prognostic importance across multiple tumor types, and plasma EGF levels, elevated via TRPV1-driven autophagy-dependent secretion, may serve as a response-tracking biomarker (*115*, *120*). The convergence of nociceptive signaling, immune modulation, and calcium-dependent tumor vulnerability may make TRPV1 particularly attractive for integrated tumor-control and symptom-directed strategies.

Mechanosensitive ion channels (Piezo-type mechanosensitive ion channel component 1)

Extending beyond voltage- and ligand-gated mechanisms, mechanosensitive ion channels—particularly Piezo-type mechanosensitive ion channel component 1 (Piezo1)—transduce physical cues from the tumor microenvironment into intracellular signaling. In preclinical models, inflammation-induced extracellular matrix (ECM) stiffening boosts hyperinnervation of the pancreatic precursor lesions, which is mediated via neurotrophic factor (BDNF/NGF) signaling from ECM tension (*121*). Mechanistically, Piezo1 transduces mechanical stimuli (matrix stiffness and fluid shear stress) into intracellular calcium influx, inducing features of EMT, proliferation, neuronal invasion, and immune evasion (*122*). Pharmacologic tools exist to modulate this pathway in both directions [agonist (Yoda1) and inhibitor (GsMTx4)] but remain preclinical, and no oncology trials have been initiated. These findings position Piezo1 as a context-dependent mechanotransducer linking tumor biomechanics to neural remodeling and metastatic behavior, highlighting its potential as a future biomarker-driven and neuromodulatory therapeutic target.

Neurokinin-1 receptor antagonists and symptom-tumor overlap

Similar to TRPV1, evidence for substance P (SP)–neurokinin-1 receptor (NK1R) is limited to preclinical and observational data but has high translational potential with FDA-approved agents targeting this mechanism. SP is a tachykinin neuropeptide released from sensory and autonomic nerves that mediates pain transmission, neurogenic inflammation, and stress responses via its high-affinity receptor NK1R [encoded by TACR1 (tachykinin receptor 1)]. NK1R is frequently overexpressed in cancers, where SP/NK1R signaling promotes proliferation, migration, angiogenesis, and resistance to apoptosis (*123*).

Preclinically, substance P/NK1R inhibition reduces tumor growth and metastasis in breast cancer, NSCLC, CRC, and other models, and an epidemiological study found that aprepitant use was associated with improved breast cancer survival compared with other antiemetics (*124*). Aprepitant, an FDA-approved NK1R antagonist used as an antiemetic and under evaluation for immune checkpoint inhibitor (ICI)–induced pruritus, thus holds potential for multiple dual-use roles; however, no prospective dedicated antitumor trial has been registered (trial details are summarized in Table 1).

TACR1 (NK1R) overexpression serves as a pan-cancer prognostic marker (cervical cancer, HNSCC, and GBM) with notable sex-specific expression patterns in PDAC (*125*, *126*), suggesting potential for patient stratification should dedicated trials be initiated. Despite strong biologic rationale and the availability of FDA-approved NK1R antagonists with established safety profiles, dedicated prospective oncology trials targeting the SP-NK1R axis remain limited (*123*). Nonetheless, the pathway remains an attractive therapeutic target in cancer neuroscience.

Local denervation and interventional neuromodulation

Several of the ion channel and neurotransmitter targets discussed above serve double duty: They drive tumor biology and simultaneously generate the pain, seizures, and cognitive dysfunction that define the lived experience of cancer. This overlap is not coincidental; it reflects the fact that the same neural circuits that tumors co-opt are those that normally process sensation, mood, and cognition (*2*, *4*).

Denervation strategies have early-phase trials ongoing, supported by a strong preclinical signal, and routine clinical use for pain. In high-PNI cancers, these strategies directly target the nerve scaffold, which may confer distinct advantages in avoiding systemic and off-target toxicities with localized delivery, although chemical denervation may require repeated procedures. Vagotomy in gastric cancer has been associated with reduced recurrence and improved chemotherapy efficacy in some clinical series and preclinical models (*127*, *128*). Celiac plexus neurolysis remains the standard of care for patients with pancreatic cancer pain (*129*) and may indirectly reshape tumor-nerve signaling. Radical denervation in preclinical models has induced complete tumor regression in most treated animals, including abscopal-like effects on remote tumors, providing a strong rationale for clinical translation (*130*). An early-phase trial of intratumoral botulinum toxin A in inoperable gastric adenocarcinoma has completed without posted results; trial details are summarized in Table 1. PNI grade serves as a ready-made stratification biomarker, functioning as an independent predictor of biochemical recurrence in multiple cancers, and emerging three-dimensional (3D) PNI morphometric features may improve prognostication further (*131*, *132*).

Neuromodulatory treatments likewise offer distinct advantages owing to their favorable toxicity profiles and can disrupt cancer cell division and microtubule dynamics. Tumor-treating fields (Optune, TTFields) are FDA approved for adjunctive use in newly diagnosed GBM and recently demonstrated pivotal phase 3 efficacy in combination with gemcitabine/nab-paclitaxel in patients with unresectable locally advanced pancreatic adenocarcinoma, positioning it as a strong platform for combination strategies with repurposed neuromodulatory agents (*133*).

Building on the impact of TTFields in glioblastoma and pancreatic cancer, several additional neuromodulatory approaches merit attention. VNS, available as an implanted or noninvasive transcutaneous auricular device (taVNS) and FDA approved for drug-resistant epilepsy, depression, and cluster headaches, activates the nucleus tractus solitarius (NTS) to modulate inflammation, pain, and immune signaling (*134*). The NTS forms an integral part of the vagal-brainstem circuit described previously, driving immunosuppressive sympathetic output via NPY and TRPV1 signaling in lung adenocarcinoma models (*58*). By engaging this circuit, VNS has been shown to enhance $CD8^+$ T cell effector function in NSCLC models (*135*), suggesting a

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promising translational strategy to therapeutically modulate this pathway. Clinically, taVNS has reduced insomnia, fatigue, and depression in patients with breast cancer, reinforcing its dual-use potential (*136*). Trial details are summarized in Table 1.

Low-frequency repetitive transcranial magnetic stimulation (rTMS), FDA approved for refractory depression, suppresses glioblastoma growth in vitro and in vivo by down-regulating cytoskeletal proteins and inhibiting EGFR/phosphatidylinositol 3-kinase/mechanistic target of rapamycin (EGFR/PI3K/mTOR) signaling, and small completed studies suggest dual-use potential for cancer-related neuropathic pain and cognitive impairment (details in Table 1) (*137*, *138*). Electroacupuncture enhances anti–PD-1 efficacy in CRC models (*139*). These neuromodulatory modalities are FDA approved and very well tolerated, positioning them well as survivorship (pain and depression) and immune-priming tools, but additional corroboration is needed before prospective human studies.

Their favorable toxicity profiles, compatibility with existing systemic therapies, and potential immune-modulatory effects make local denervation and neuromodulatory approaches promising candidates for future combination strategies. As patient stratification improves, these interventions may offer a more practical and well-tolerated way to disrupt tumor nerve signaling while also helping address symptoms such as pain, fatigue, and depression.

CONCLUSION

As outlined here, the field now stands at a transition point. Mechanistic understanding has outpaced clinical translation, and the path forward runs through three converging priorities: biomarker-driven patient selection to match neural circuits to tumor contexts, rational combination with immune checkpoint blockade as the shared downstream logic, and formal recognition that the "dual-intent" profile of many agents, antitumor and symptom directed, is a feature, not a footnote. Embedding survivorship end points alongside efficacy measures in trial design will be essential to capture the full benefit of repurposed neuromodulatory agents. One underappreciated implication of the CINI paradigm is that treating (or preventing) nerve injury may itself be an antitumor strategy (*43*, *140*). No neuroprotective agent has reached FDA approval for cancer-related neurotoxicity, but the emerging link between peritumoral nerve damage, immunosuppressive cytokines, and checkpoint resistance suggests that survivorship-directed interventions and disease-modifying interventions may ultimately be the same intervention. For CNS tumors, the same glutamatergic and neurotrophic mechanisms that promote invasiveness also underpin fundamental, healthy neuronal behavior (*11*–*16*), presenting substantial challenges to translating these discoveries without compromising neurocognitive function. The convergence of these circuits, adrenergic, sensory, and synaptic, into overlapping downstream immune consequences suggests that rational combinations, rather than single-pathway inhibition, will be the productive clinical strategy. GLUGLIO and SENIPERA exemplify this logic in the CNS; analogous combination designs in PNS-dominant tumors are the natural next step. Similar strategies may also be beneficial in the PNS, for example, combining β-blockers with CGRP, TRPV1, or NPY antagonists, given the proper stratification. This strategy is especially pertinent for pediatric and low-grade tumors, where prolonged survival necessitates treatments with minimal long-term neurocognitive or systemic impact, which is a profile that many repurposed neuromodulatory agents may be well suited to provide. Even with biomarker enrichment, however, successful end points are not likely to be realized simply by inhibiting isolated neurotransmitter pathways. Similarly, the dramatic responses seen in some patients with immunotherapies are unlikely to be realized with repurposed neuroactive agents. Rather, cancer neuroscience may find success in sustainably reprogramming the dominant neural circuits to induce a shift in metabolism, vasculature, and immune function toward a state more responsive to mainstay treatments.

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