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Mini Review

Pharmacologic Modulation of cGAS for Infection and Cancer: Toward IFN-Ready, Inflammation-Sparing Therapy

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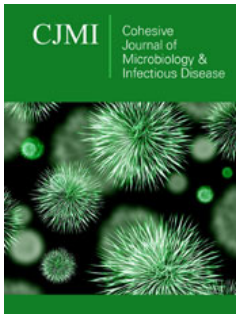

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Abstract

The Cyclic GMP-AMP Synthase (cGAS) pathway is a central DNA-sensing axis that instructs type I interferon (IFN) programs and bridges innate and adaptive immunity. While direct STING agonists have dominated clinical translation, small-molecule cGAS modulators, both inhibitors and activators, are rapidly maturing. Inhibitors such as RU.521 and next-generation human-specific scaffolds provide tools for restraining auto-inflammation, whereas pharmacologic sensitization of cGAS can potentiate tumor-intrinsic IFN and improve responses to chemotherapy or immunotherapy. Here we synthesize recent advances in medicinal chemistry and disease biology, highlight species selectivity and dosing-window pitfalls and propose practical biomarker sets to guide development. We outline indications where cGAS activation may be advantageous (host-directed antivirals, immunogenic tumors) versus contraindicated (IFN-driven autoimmunity) and we sketch a near-term research agenda to de-risk translation.

Keywords: cGAS; STING; Small-molecule; Host-directed antivirals; Cancer immunotherapy; Interferon; Innate immunity

Introduction

Cytosolic DNA engages cGAS, generating 2,3-cGAMP that binds and activates STING to drive TBK1-IRF3 signaling and type I IFN responses [1]. Pharmacologic control of this axis is attractive in infection, cancer and auto-inflammation. Most clinical efforts target STING, such as cyclic dinucleotides and non-CDN agonists [2]. But a complementary strategy is to modulate cGAS itself, either to dampen pathological IFN in sterile inflammation or to sensitize IFN for antimicrobial and anti-tumor benefit [3]. Recent reviews catalog both sides of this pipeline and underscore translational nuances such as species differences, context-dependent IFN biology and delivery challenges.

What counts as "pharmacologic cGAS modulation"?

The tool compound RU.521 emerged as a selective inhibitor of murine cGAS and reduced constitutive IFN in Aicardi-Goutières syndrome macrophages, establishing proof-of-concept for small-molecule cGAS blockade [4]. However, potency and selectivity can diverge between mouse and human enzymes and RU.521's activity against recombinant human cGAS is weaker, an early warning about species selectivity and the need for human-specific scaffolds [5,6]. Medicinal chemistry campaigns subsequently disclosed inhibitors with improved human activity and clarified binding modes, keeping cGAS inhibition on the table for interferonopathies and neuroinflammation. Beyond autoimmunity, RU.521 has shown benefit in preclinical neuroinflammation models, such as subarachnoid hemorrhage, where cGAS/STING-driven microglial activation fuels injury, again suggesting disease windows where cGAS brake therapy could be valuable [7].

Activation/sensitization to enhance anti-infective and anti-tumor immunity

Direct cGAS activators are rarer than STING agonists, but the emerging concept of pharmacologic sensitization, lowering the DNA threshold required for cGAS activation, has support [8]. Notably, brivanib was reported to bind cGAS, enhance DNA binding and amplify tumor-intrinsic type I IFN, thereby synergizing with platinum chemotherapy and boosting $CD8^+$ T-cell responses in a cGAS-dependent fashion. Such sensitizers may help transform "IFN-cold" tumors into "IFN-ready" states without high-dose inflammatory surges [9]. Alongside small molecules, cGAS-agonistic oligonucleotides represent a parallel modality with potential advantages over STING agonists, such as intracellular generation of cGAMP, different PK/PD levers [10,11]. These molecules mimic the structure of the endogenous second messenger cGAMP. The representative drug ADU-S100, modified with a phosphothioester bond, significantly enhances resistance to the hydrolase ENPP1 and improves stability. However, the inherent strong hydrophilicity and negative charge of CDN molecules result in poor cell membrane permeability. Systemic administration readily induces systemic inflammatory responses, limiting most current clinical trials to intratumoral injection and severely restricting their application scope [12]. These nucleic acid-based agonists reinforce the feasibility of directly tuning cGAS rather than relying solely on downstream STING.

Where might cGAS drugs fit? indication-oriented view

First, viral infection, Host-Directed Antivirals (HDA). HDA strategies that prime IFN readiness can provide broad-spectrum activity and higher barriers to resistance [13,14]. cGAS sensitizers could, in principle, raise basal antiviral tone in permissive tissues, but careful dosing is essential to avoid IL-6/TNF-biased inflammation or precipitating interferonopathies [15]. Preclinical literature and up-to-date overviews support the plausibility of cGAS/STING-axis boosting for antiviral defense, though most clinical data so far center on STING agonists rather than cGAS drugs. Second, oncology, synergy with DNA damage and checkpoint blockade. Tumors experiencing chemotherapy-or radiotherapy-induced DNA damage generate cytosolic DNA, enabling cGAS-STING-driven immunogenicity [16]. Sensitizing cGAS could enhance this effect, support dendritic cross-priming via cGAMP transfer and cooperate with PD-1/PD-L1 inhibitors [17]. Meanwhile, the STING field is addressing delivery and tolerability via non-CDN agonists and nanomedicine-lessons that cGAS-targeted agents can borrow (formulation, tissue targeting) [18]. For example, manganese-based nanomaterials not only serve as carriers, but the Mn^{2+} ions they release can directly bind to cGAS, enhancing its DNA sensitivity by several orders of magnitude to achieve "metal ion-immunity" synergistic therapy. Arsenic-, zinc- and copper-based materials, on the other hand, induce cGAS-STING pathway activation indirectly yet potently by causing cytoplasmic DNA accumulation through mechanisms such as DNA damage, mitochondrial dysfunction or copper-induced cell death [19,20]. Third, auto-inflammation and neuroinflammation, turning the dial down. In interferonopathy-like settings, such as AGS models, brain injury, cGAS inhibitors may reduce maladaptive IFN and microglial activation [21]. Species-aware medicinal chemistry and brain-penetrant PK will be decisive for translation.

Practical development pitfalls and how to avoid them

First, species selectivity and structural pharmacology. Several inhibitors display divergent potencies for mouse vs human cGAS; structural differences at the active site can flip SAR trends. Early human enzyme profiling and co-crystal structures are non-negotiable [22]. Second, context-specific cytokine balance. "More IFN" is not always better; Chronic or atypical cGAS-STING activation, particularly in highly chromosomally unstable cancer cells, may preferentially induce the production of pro-survival factors such as IL-6 via the NF-κB pathway, thereby promoting tumor progression, treatment resistance and metastasis [23]. track ISG panels (e.g., ISG15, IFITs), cGAMP levels and p-TBK1/p-IRF3 together with IL-6/TNF to avoid drift into hyper-inflammation. Third, on-target and pathway-adjacent effects. Some "activators" may indirectly increase cytosolic DNA, such as mitochondrial stress, rather than directly bind cGAS [24]; orthogonal assays (SPR/ITC + DNA-free basal activity and competition vs dsDNA) are needed to claim direct cGAS pharmacology. Forth, tumor-intrinsic and stromal immunity. Distinguish tumor-cell cGAS effects from myeloid/DC STING responses; pair tumor-intrinsic IFN readouts with $CD8^+$ TIL function and cross-primingmetrics in-vivo [25,26]. Fifth, Formulation and delivery. Lessons from STING agonists (rapid degradation, multi-dose needs, tolerability) argue for depot/targeted delivery or nano-platforms when aiming at intratumoral or mucosal compartments-likely relevant for cGAS agonists too [27].

Future Directions

A. Define dosing windows for sensitizers that lift IFN readiness without NF-κB-dominant surges; include adaptive designs with ISG-gated dose escalation.

B. Combination logic: Pair cGAS sensitizers with DNA-damaging chemo or hypofractionated RT; in infection models, test post-exposure prophylaxis paradigms against RNA/DNA viruses with host-benefit but low cytokine spillover.

C. Human-first chemistry: Prioritize human cGAS in screening cascades to avoid RU.521-like species gaps; seek brain-penetrant inhibitors for neuroinflammation.

D. Delivery innovation: Adapt nano-formulations and depot systems proven in STING to cGAS agonists; explore intratumoral or mucosal administration to localize effects.

E. Modalities beyond small molecules: Advance cGAS-agonistic oligonucleotides (alone or with immune-editing regimens) and benchmark against non-CDN STING agonists.

Conclusion

The cGAS node is druggable on both sides of the switch. Inhibitors hold promise for IFN-mediated inflammatory diseases,

while sensitizers/activators could render tissues and tumors IFN-ready without excessive cytokine noise, if dosing and delivery are well-controlled. Converging chemical biology, human-specific screening and biomarker-guided trials should unlock stratified indications in infection and oncology, positioning cGAS modulators as a precise complement to the better-explored STING agonist class.

Conflict of Interest

The authors do not have anything to declare.

Author Contribution

Conceptualization and supervision: Y. Z.; Formal analysis: X. C.; Original draft preparation: Y. Z.; Writing-review and editing: X. C. and F. Y.; Project administration: Y. Z.

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