Discovery Report

Breaking the Competitive Landscape in Anti-Tumor Immunity:
A Three-Target Degrader Platform Spanning Myeloid Immunosuppression

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Targets: ACOD1/IRG1 (PROTAC) | TREX1 (PROTAC) | SLAMF8 (LYTAC)

Modalities: Targeted Protein Degraders | Lysosome-Targeting Chimeras | Small Molecules

Abstract

Immune checkpoint inhibitors have transformed oncology, yet most solid tumors remain resistant — particularly "cold" tumors where the myeloid compartment actively suppresses anti-tumor immunity. We propose a three-target degrader platform addressing the complete immune evasion axis: (1) **ACOD1/IRG1**, the enzyme producing immunosuppressive itaconate in tumor-associated macrophages, targeted by a CRBN-based PROTAC; (2) **TREX1**, the cytosolic DNA exonuclease preventing cGAS-STING activation in tumor cells, targeted by an allosteric-site PROTAC; and (3) **SLAMF8**, a macrophage surface receptor driving M2 polarization, targeted by a LYTAC. Through systematic competitive landscape analysis, structural feasibility assessment, and cross-target pathway mapping, we identify a novel ACOD1-STING-TREX1 feedback loop wherein TREX1 eliminates the trigger for innate immune activation while ACOD1-derived itaconate suppresses the STING response — representing parallel, non-redundant immune evasion mechanisms. Simultaneous degradation of both proteins is predicted to synergistically amplify cGAS-STING-IFN-I output beyond what either target alone can achieve. We demonstrate that the IP landscape for ACOD1 degraders is open (key patent ceased), ACOD1 is accessible to the ubiquitin-proteasome system (lacks mitochondrial targeting sequence, cytosolic accumulation under inflammatory conditions), and TREX1 possesses non-enzymatic functions (cGAS-DNA phase separation interference, OST complex regulation) that only degradation — not inhibition — can eliminate. This report provides complete assay cascades for all three targets, comprising 37 laboratory assays across six tiers, and proposes a 12-month development timeline with defined decision gates.

1. Introduction

1.1 The Problem: Cold Tumors and Myeloid Immunosuppression

Despite the success of anti-PD-1/PD-L1 checkpoint inhibitors, objective response rates remain below 30% across most solid tumor types. The primary failure mode is the immunosuppressive tumor microenvironment (TME), where tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and tumor-intrinsic immune evasion mechanisms prevent effective anti-tumor immunity. These "cold" tumors lack T cell infiltration, have suppressed innate immune signaling, and are refractory to current immunotherapies.

The competitive landscape in immuno-oncology is dominated by three approaches: next-generation checkpoint antibodies (TIGIT, LAG-3, TIM-3), STING agonists, and ENPP1 inhibitors. All face significant competition with 5-20+ programs each. Breaking into this landscape requires targeting unexploited nodes in immune evasion with differentiated modalities.

1.2 The Opportunity: Targeted Protein Degradation

Targeted protein degradation (TPD) offers fundamental advantages over inhibition for immune targets: elimination of both catalytic and scaffolding functions, catalytic mechanism enabling sub-stoichiometric dosing, and sustained effect requiring protein resynthesis. Despite this, no degrader targeting the innate immune checkpoint space has entered clinical development. The intersection of novel myeloid targets and degrader modalities represents a white space in immuno-oncology drug discovery.

1.3 Three Targets, One Immune Evasion Axis

We identified three targets that collectively cover the complete immune evasion axis in the tumor microenvironment:

- **TREX1** — Tumor-intrinsic: degrades cytosolic DNA to prevent cGAS-STING detection (removes the immune trigger)
- **ACOD1/IRG1** — Myeloid metabolic: produces itaconate to suppress STING signaling and CD8+ T cell function (removes the immune response)
- **SLAMF8** — Myeloid surface: drives M2 macrophage polarization via PI3K/AKT and JAK/STAT3 (maintains immunosuppressive phenotype)

2. ACOD1/IRG1 — Primary Target

2.1 Target Biology

ACOD1 (cis-aconitate decarboxylase, EC 4.1.1.6) catalyzes the decarboxylation of cis-aconitate to itaconate in the mitochondrial compartment. In tumor-associated macrophages, ACOD1 is upregulated via NF-κB signaling, producing excess itaconate that: (1) inhibits TET DNA dioxygenases to dampen inflammatory gene expression; (2) suppresses CD8+ T cell infiltration and cytotoxicity; (3) is taken up by cancer cells via SLC13A3 to promote checkpoint inhibitor resistance; (4) activates the KEAP1-NRF2 antioxidant pathway; and (5) directly alkylates STING cysteine residues (Cys65, 71, 88, 147) to inhibit signalosome assembly.

2.2 Genetic Validation

ACOD1 is supported by convergent genetic evidence from multiple independent groups:

- Pooled CRISPR screen of metabolic genes identified ACOD1 as a top regulator of macrophage inflammatory state
- ACOD1-knockout CAR-macrophages showed enhanced tumor repression and improved survival in ovarian and pancreatic cancer models, with synergy with anti-PD-1
- Irg1 conditional knockout in myeloid cells suppressed MC38 tumor growth and enhanced anti-PD-L1 efficacy
- ACOD1 inhibitors (ERG344/ERG350) produced complete or partial tumor regression in syngeneic models

2.3 PROTAC Feasibility — Critical Finding

The primary concern for ACOD1 PROTAC development was mitochondrial matrix localization, which would render the protein inaccessible to the ubiquitin-proteasome system. Our Edison Platform analysis resolved this:

- **No mitochondrial targeting sequence:** ACOD1 lacks a classical N-terminal MTS
- **Outer membrane association:** The ACOD1-Rab32-LRRK2 complex localizes to the outer mitochondrial membrane, not the matrix
- **Cytosolic accumulation:** Under inflammatory conditions (the disease-relevant context), substantial ACOD1 accumulates in the cytosol and engages HSP70 for proteasomal degradation
- **UPS accessibility confirmed:** β-Arrestin 2 promotes ACOD1 ubiquitination and proteasomal degradation, directly demonstrating that the protein is a UPS substrate

These findings establish that a conventional CRBN-based PROTAC approach is feasible for ACOD1.

2.4 Non-Catalytic Functions (Degrader Superiority)

Edison identified three protein-protein interaction complexes demonstrating non-catalytic ACOD1 functions:

Complex	Partners	Function	Degrader Advantage
Mitochondrial trafficking	OLFML3-IRG1-AIFM1	Promotes IRG1 mitochondrial localization	Eliminates mitochondrial recruitment
Pathogen defense scaffold	RAB32-IRG1-LRRK2	Delivers itaconate to bacterial vacuoles	Eliminates scaffolding function
Stability regulation	β-Arrestin 2-IRG1	Promotes IRG1 ubiquitination/degradation	Confirms UPS accessibility for PROTAC

2.5 Warhead and PROTAC Design

The best available warhead is (Z)-2-ethylbut-2-enedioic acid (ethylcitraconate), with Ki = 235 ± 21 nM against human ACOD1, representing a 160-fold improvement over first-generation citraconate (Ki = 38 μM). SAR analysis indicates the octyl ester position tolerates modifications, providing a linker attachment vector. CRBN is the recommended E3 ligase recruiter to maintain drug-like molecular weight given the small, polar warhead.

2.6 IP Landscape

The broadest patent covering ACOD1 degraders for oncology (WO2024103313A1, Fudan University) has legal status: **Ceased**. Remaining patents cover citraconate derivatives for inflammation (not oncology) or IRG1 blockade for CAR-T armoring (different modality). No PROTAC-specific IP exists for ACOD1. This represents a first-mover opportunity for composition-of-matter claims.

2.7 Secondary Indications

- Other cold solid tumors: pancreatic, ovarian, glioblastoma, MSS-CRC
- Sepsis immunoparalysis (IRG1 elevated, itaconate drives immunosuppression)
- Chronic infections: TB, chronic hepatitis
- Vaccine adjuvant (transient ACOD1 blockade to boost responses)

3. TREX1 — Secondary Target

3.1 Target Biology

TREX1 (three prime repair exonuclease 1) is the most abundant 3'-5' DNA exonuclease in mammalian cells. Cancer cells upregulate TREX1 to degrade immunostimulatory cytosolic DNA before cGAS can detect it, preventing activation of the STING-IFN-I pathway that would recruit T cells. TREX1 is particularly relevant in the context of radiation therapy: doses above 12-18 Gy induce massive TREX1 upregulation, which explains why high-dose radiation fails to synergize with checkpoint inhibitors.

3.2 Competitive Landscape

TREX1 has more competition than ACOD1, with 5+ inhibitor programs:

Company	Compound	IC50 (human)	Site	Stage
Tempest Therapeutics	Compound 4A	0.97 nM	Active site	Lead optimization
Gilead/Sprint Bioscience	Undisclosed	Undisclosed	Active site	Preclinical (acquired $14M+$386M)
Constellation/MorphoSys	CPI-38	Undisclosed	Active site	Early preclinical
Insilico Medicine	Undisclosed	0-100 nM	Undisclosed	Preclinical
Fox Chase (academic)	Compound #296	1.81 μM	DNase activity	Discovery

No clinical trials have been registered for any TREX1 inhibitor. Critically, **no PROTAC or targeted protein degrader exists for TREX1**.

3.3 Non-Enzymatic Functions — The Case for Degradation

Edison analysis revealed multiple non-catalytic TREX1 functions that persist under enzyme inhibition but would be eliminated by degradation:

- **cGAS-DNA phase separation interference:** TREX1 forms a physical shell around cGAS-DNA liquid-liquid phase-separated condensates. Even catalytically inactive TREX1 would sterically impede DNA access to cGAS. Only degradation removes this barrier.
- **OST complex regulation:** The TREX1 C-terminus regulates oligosaccharyltransferase independent of DNase activity. TREX1 knockout increases free glycans — a distinct immune-modulatory output. Inhibitors have no effect on this function.
- **SET complex scaffolding:** C-terminal domain mediates ER interactions independent of catalysis. C-terminal frameshift mutations cause retinal vasculopathy with cerebral leukoencephalopathy (RVCL) despite preserved catalytic activity.
- **PPII helix signaling:** Polyproline II helix is a canonical docking motif for SH3/WW/EVH1 domain proteins — a signaling scaffold.

3.4 Allosteric Binding Site for PROTAC Warhead

A novel druggable allosteric site was confirmed at the α7-α8 loop (PDB: 9KJG-9KJS). Compounds NSC37203, NSC37204, and NSC37215 induce a disordered-to-ordered transition via "multivertex

clamping," engaging Trp188, Lys175, and Arg174. The 4-hydroxynaphthalene-2-sulfonic acid core scaffold provides a starting point for PROTAC warhead design with selectivity advantages over the DEDDh active site.

3.5 Radiation Combination Thesis

TREX1 is induced by radiation above 12-18 Gy, peaking at 24-48 hours post-irradiation. The dosing strategy: administer TREX1 degrader before or concurrent with hypofractionated radiation, then follow with anti-PD-1. This triple combination (TREX1 degrader + RT + anti-PD-1) addresses a defined clinical need — locally advanced solid tumors receiving radiation that fail to respond to checkpoint inhibitors.

3.6 Secondary Indications

- MSI-H/dMMR tumors: upregulate TREX1 despite high mutational burden (explains ICI non-response in 20-40% of MSI-H patients)
- Drug-resistant SCLC: TREX1 upregulated in treatment-resistant disease
- Chronic viral infections (HBV, HPV): enhanced innate immune detection of viral DNA

Note: TREX1 loss-of-function causes autoimmune disease (AGS, lupus, RVCL). Therapeutic window requires intermittent dosing or tumor-selective delivery.

4. SLAMF8 — Tertiary Target

4.1 Target Biology

SLAMF8 (CD353/BLAME) is a type I transmembrane glycoprotein on macrophages that drives M2 polarization via PI3K/AKT and JAK/STAT3 signaling. It is a homophilic receptor (SLAMF8 binds SLAMF8 on adjacent cells) and a negative regulator of NADPH oxidase (Nox2)-dependent ROS production. SLAMF8 is atypical within the SLAM family: it lacks ITSM motifs, does not bind SAP or EAT-2, and has only a short cytoplasmic tail (~30 amino acids).

4.2 Disease Validation (Expanded)

Edison analysis expanded SLAMF8 validation well beyond the original CRC data:

Disease	Finding	Pathway
Colorectal cancer	High SLAMF8 on TAMs → poor DFS/OS; KD restores CD8+ T cells	PI3K/AKT, JAK/STAT3
Prostate cancer	Overexpressed; drives metastasis via TLR4-NF-κB; correlates with poor survival	TLR4/NF-κB, MMP9
ALCL (lymphoma)	Interacts with ALK and SHP-2; KD reduces growth, increases apoptosis	SHP-2/ALK
Clear cell RCC	High expression = negative prognostic factor	Unknown
Glioma	High expression = negative prognostic factor	Unknown
Rheumatoid arthritis	KO attenuates CIA via inhibiting TLR4/NF-κB	TLR4/NF-κB

Zero drug programs exist targeting SLAMF8.

4.3 Modality: LYTAC, Not PROTAC

As a cell-surface transmembrane receptor with minimal intracellular domain, SLAMF8 faces the same topology challenge as PD-L1 for conventional PROTACs. The recommended modality is a Lysosome-Targeting Chimera (LYTAC), which has been validated for PD-L1 degradation at >70-80% efficiency. The development path requires generating an anti-SLAMF8 monoclonal antibody first, then conjugating it to M6P glycopeptide for lysosomal targeting.

4.4 Secondary Indications

SLAMF8 is unique among the three targets in having a cross-indication profile spanning both oncology and autoimmune disease with the same modality (blocking/degrading): rheumatoid arthritis, IBD, secondary progressive MS, and post-transplant immune complications.

5. Novel Cross-Target Discovery: The ACOD1-STING-TREX1 Feedback Loop

The most significant discovery from our cross-target analysis is a previously unrecognized feedback loop connecting ACOD1 and TREX1 through the STING pathway:

- **TREX1** degrades cytosolic DNA → removes the trigger for cGAS-STING activation
- **cGAS-STING activation** (when it occurs) drives ACOD1 expression via a STING1-MYD88-dependent mechanism
- **ACOD1-derived itaconate** directly alkylates STING cysteine residues (Cys65, 71, 88, 147), suppressing signalosome assembly
- Additionally, itaconate activates KEAP1-NRF2, which further downregulates STING expression

This creates a self-reinforcing immunosuppressive circuit: even if TREX1 is inhibited alone (allowing cytosolic DNA to accumulate and activate cGAS-STING), the resulting STING activation drives more ACOD1/itaconate production, which in turn suppresses STING — partially defeating the purpose of TREX1 inhibition.

The dual-targeting prediction: Simultaneous degradation of both TREX1 and ACOD1 would: (1) increase the cGAS-STING trigger by preserving cytosolic DNA (TREX1 removal), and (2) prevent the feedback brake by eliminating itaconate-mediated STING suppression (ACOD1 removal). This is predicted to produce synergistic amplification of IFN-I output beyond what either target alone can achieve.

No published study has proposed this dual-target strategy.

6. Complete Assay Cascade

We designed a six-tier assay cascade comprising 37 laboratory assays across all three targets:

Tier	Assay Type	ACOD1 Assays	TREX1 Assays	SLAMF8 Assays
1	Biochemical	Enzymatic (LC-MS), DSF, SPR	DNase (FP/SYBR/probe), Allosteric SPR, DSF	ECD binding (SPR/BLI), Fragment screen, FP
2	Target Engagement	CETSA, NanoBRET, Ternary complex	CETSA, HiBiT-TREX1	Surface expression (flow)
3	Degradation	HiBiT, Western, Proteomics, Ub assay	HiBiT, Cytosolic DNA accumulation (IF)	LYTAC surface depletion (flow)
4	Functional	Itaconate LC-MS, M1/M2 polarization, Phagocytosis, NF-κB/STING reporter	cGAS-STING response, IFN/cytokine panel, T cell recruitment	M1/M2 polarization, PI3K/STAT3, FcR phagocytosis
5	Co-culture	Macrophage-tumor, 3-cell + CD8, Spheroid/organoid	Tumor cell killing, Radiation synergy matrix	T cell co-culture
6	In vivo	MC38, CT26 syngeneic ± anti-PD-1	MC38 ± RT ± anti-PD-1; MSI-H subline	4T1 syngeneic ± anti-PD-1

7. Competitive Position Summary

Dimension	ACOD1 PROTAC	TREX1 PROTAC	SLAMF8 LYTAC
Competitor degrader programs	NONE	NONE	NONE
Competitor inhibitor programs	2-3 (all preclinical, academic)	5+ (Gilead, Tempest, Constellation, Insilico, academic)	NONE
Clinical trials (any modality)	None	None	None
IP freedom	HIGH (key patent ceased)	MEDIUM (active site inhibitor IP; allosteric site open)	HIGH (no IP)
Structural data	PDB 6R6U (1.7Å apo)	12+ PDB entries (active + allosteric)	AlphaFold only
Best warhead Ki	235 nM	0.97 nM (active); μM (allosteric)	N/A (antibody-based)
KO validation	Strong (5+ studies)	Strong (3+ studies)	Moderate (2-3 studies)
Degrader advantage over inhibitor	STRONG (3 PPIs, scaffolding)	STRONG (phase separation, OST, PPI)	N/A (LYTAC is only option)
Estimated time to first hit	6-9 months	9-12 months	12-18 months

8. Proposed Development Timeline

Phase	Months	ACOD1	TREX1	SLAMF8	Decision Gate
1	1-3	Biochemical assays; PROTAC synthesis (3-5 molecules)	Obtain allosteric binders; SPR [illegible]	Immunization; Begin PROTAC design [illegible]	[illegible] for blocking mAbs
2	3-6	Cellular degradation; Itaconate measurements; M1/M2 [illegible]	PROTAC synthesis; cGAS-STING reporter; [illegible]	[illegible] characterization; LYTAC; [illegible]	ACOD1 [illegible] recapitulate KO?
3	6-9	Co-culture models; Combination with anti-PD-1	Co-culture; Triple combo [illegible]	PROTAC/LYTAC assays; Phagocytosis; [illegible]	TREX1: [illegible] disrupted?
4	9-12	In vivo MC38/CT26; PK/PD	In vivo MC38 with radiation; Dual combo with TREX1 [illegible]	[illegible] 4T1; Autoimmune models (RA)	Cross-target synergy confirmed?

9. KEGG Pathway Context

KEGG ID	Pathway	Target(s)	Relevance
hsa00020	TCA Cycle	ACOD1	ACOD1 diverts cis-aconitate → itaconate; metabolic rewiring in TAMs
hsa04623	Cytosolic DNA-sensing	TREX1, ACOD1	TREX1 is negative regulator; itaconate suppresses STING downstream
hsa04151	PI3K-Akt signaling	SLAMF8	SLAMF8 activates PI3K/AKT for M2 polarization
hsa04630	JAK-STAT signaling	SLAMF8	SLAMF8 signals through JAK/STAT3
hsa05235	PD-L1/PD-1 checkpoint	All three	All targets synergize with checkpoint inhibitors
hsa04066	HIF-1 signaling	ACOD1	Itaconate → SDH inhibition → HIF-1α stabilization
hsa04064	NF-κB signaling	TREX1, SLAMF8	STING→NF-κB (TREX1); TLR4→NF-κB (SLAMF8)
hsa04622	RIG-I-like receptor	TREX1	Cross-talk with cytosolic nucleic acid sensing

10. Conclusions

This discovery report presents a three-target degrader platform for anti-tumor immunity that addresses fundamental limitations of current immunotherapy approaches:

- ACOD1 PROTAC: First-in-class degrader for myeloid metabolic immunosuppression. Open IP landscape, feasible UPS access, strong genetic validation, clear warhead (Ki = 235 nM).
- TREX1 PROTAC: Differentiated from 5+ inhibitor programs by degrader modality and radiation combination thesis. Non-enzymatic functions (phase separation, OST, scaffolding) provide mechanistic superiority over inhibition.
- SLAMF8 LYTAC: Zero-competition target with expanding multi-disease validation. LYTAC modality appropriate for surface receptor topology.
- ACOD1-TREX1 dual targeting: Novel combination strategy exploiting a previously unrecognized feedback loop. Predicted synergistic amplification of cGAS-STING-IFN-I output.

The 37-assay cascade and 12-month timeline provide a complete experimental roadmap from biochemical validation through in vivo proof-of-concept, with defined decision gates at months 6 and 9.

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Analysis powered by Edison Platform (Kosmos LITERATURE_HIGH). Full trajectory data available in Edison Project: anti-tumor-immunity-competitive-landscape.