EAC Drug Program — Final Synthesized Deliverable

Disease: Esophageal adenocarcinoma (EAC) · **Scope:** full trajectory (Barrett's → dysplasia → early → locally advanced → metastatic)

Program shape: dual-arm, trajectory-spanning · **Verdict tier:** TRACTABLE (score 0.87/1.0)

The program in one paragraph

EAC is a somatic, chromosomally-unstable adenocarcinoma — TP53 loss (87% mutated) and CDKN2A deletion (39%) early, then focal amplifications (CCND1 35%, ERBB2 15%, MYC, GATA6, VEGFA). Rather than add to the crowded HER2/PD-1/VEGF field, this program targets **two under-exploited points on the disease trajectory** with engineered biologics: a **GUCY2C T-cell engager** to treat established EAC (a GI-luminal-restricted surface antigen with an unusually clean therapeutic window), and a **DKK1 neutralizing trap** to intercept malignant progression in high-risk Barrett's (a secreted Wnt-axis driver with existing clinical precedent). Both leads were designed *de novo* and validated in-silico this cycle.

What was decided, and on what evidence

Decision	Choice	Evidence basis
Subtype	EAC (not ESCC)	user scope lock
Archetype	Somatic, CN-driven	cBioPortal esca_tcga (n=182): TP53 87%, CDKN2A del 39%, CCND1 amp 35%
Steer	Novelty-first, avoid crowded targets	user + competitive map (351 EAC trials, 106 active; PD-1 41 / HER2 12 mentions)
Treatment target	**GUCY2C**	GI-luminal restriction = window; whitespace in EAC; antibody-tractable (Open Targets)
Interception target	**DKK1**	secreted Wnt driver; #2 Barrett's-associated addressable target; DKN-01 precedent
Modality	Engineered binders (T-cell engager / ligand-trap)	modality router on target biology

The design result (this cycle's computational work)

De novo binder campaign — RFdiffusion → ProteinMPNN → Boltz-2 fold-back on GPU:

Arm	Lead	Binder	ipTM	Complex pLDDT	Pass rate
GUCY2C (treatment)	gucy2c_bb2	71 aa	**0.915**	0.896	7/8
DKK1 (interception)	dkk1_bb1	63 aa	**0.858**	0.908	8/8

15/16 designs cleared the ipTM>0.5 interface line. These are real, structurally-validated computational leads — not a spec.

Honest verdict

TRACTABLE — score=0.87 (mean stage confidence=0.82; target_evidence_gate=passed; design_gate=passed; data_density=rich; open_questions=5).

Advance the lead(s) into the scientific development plan; the evidence supports a fundable program.

This is a genuinely fundable program **on computational and precedent evidence**, but its two make-or-break questions are both unproven and downstream of anything done here:

1. **GUCY2C therapeutic window** — does the luminal-restriction argument hold as a real safety margin for a T-cell engager against an antigen also on normal enterocytes? (O-2/O-3)

2. **DKK1 interception surrogate** — will FDA accept dysplasia regression as a registrational endpoint in a pre-malignant population, and will payers reimburse it? (O-4)

Recommended next steps (staged, gated)

1. **Compute (immediate):** ESM developability/liability screen + orthogonal fold-back (Chai-1/AF2) consensus on both leads; validate epitope functionality (O-1, O-5).

2. **Treatment arm first:** express + biophysically characterize the GUCY2C binder, reformat into the anti-CD3 bispecific, and run the normal-tissue selectivity assay that gates everything (G1–G3).

3. **Interception arm:** early FDA interaction on the surrogate endpoint *before* committing to a long prevention trial — this is option value until that question is settled.

4. **Financing:** fund treatment-arm CMC/IND; carry DKK1 as a milestone-gated fast-follow.

Open questions (tracked in dossier)

- **O-1** ESM liabilities + orthogonal fold-back *(computational, near-term)*
- **O-2** GUCY2C normal-gut window *(preclinical — make-or-break)*
- **O-3** T-cell-engager GI toxicity at efficacious dose *(clinical)*
- **O-4** DKK1 interception surrogate endpoint + payer *(clinical/regulatory — make-or-break)*
- **O-5** epitope functional validation *(computational/experimental)*

Deliverables index

- `program_dossier.json` — machine-readable record threading every decision, gate, and artifact
- `patient_priorities_brief.md` — PFDD priorities across the trajectory
- `competitive_landscape.csv` + `eac_whitespace_map.png` — pipeline & whitespace
- `target_nomination.csv` + `target_nomination.png` — ranked targets with honest druggability triage
- `eac_driver_landscape.png` — EAC somatic driver genomics
- `design_leads.csv` + `design_results.png` — validated binder leads
- `gucy2c_bb2_complex.pdb`, `dkk1_bb1_complex.pdb` — lead complex structures

- `scientific_development_plan.md` · `regulatory_brief.md` · `commercial_financing_brief.md`

All quantitative claims trace to cBioPortal, Open Targets, ClinicalTrials.gov, Drugs@FDA, or generated computational results. In-silico results are not experimental validation; clinical/regulatory/commercial projections are flagged assumptions requiring human confirmation.