Project Tolera — A Roadmap to Patients

Antigen-specific tolerance, one patient at a time.

A citizen-scientist's roadmap for a personalized pMHC-II tolerance vaccine in eosinophilic esophagitis — from AI/ML design to first-in-patient.

Ruth-Anne Pai, PhD — PhD Scientist & Advisor | Bridging Science and Advocacy · person living with EoE
advising@ruthannepai.com · ruthannepai.com · linkedin.com/in/ruth-anne-pai *Developed during the "Built with Claude: Life Sciences Hackathon", July 2026.*

This is an independent research roadmap, not a company prospectus or an offer to invest. It maps what a credible path from AI/ML design to first-in-patient could look like, and what it would take to get there — a scoped brief for any biotech partner or funder who wants to take it forward. Preclinical-stage concept. Financial and market figures are illustrative planning assumptions, not guidance. Non-dairy epitope activity is a computational prior pending wet-lab validation. Not medical advice.

---

1. Executive Summary

Eosinophilic esophagitis (EoE) is a chronic, food-driven immune disease affecting an estimated **167,500 people in the US** and rising. It is, at its root, **antigen-specific** — a food peptide presented on an MHC-II molecule to a pathogenic T-cell clone. Yet **every approved and pipeline therapy** — dupilumab, cendakimab, tezepelumab, budesonide, PPIs — is a broad, chronically-dosed symptom suppressor. None is antigen-specific; none induces durable tolerance. Patients face a lifetime of injections, steroids, or restrictive elimination diets, punctuated by surveillance endoscopies and the ever-present fear of food impaction.

Project Tolera maps the path to a personalized pMHC-II tolerance vaccine. From a single biopsy and blood draw taken at diagnosis, the approach identifies a patient's HLA type and causal food-reactive T-cell clone and manufactures an N-of-1 vaccine that re-educates *only that clone* — Signal-1 anergy plus multivalent nanoparticle Tr1/IL-10 induction. It is the individualized-neoantigen-vaccine model of oncology, applied to food antigens: **one course, not lifelong dosing.**

The platform (**PACT™** — a shared, GPU-validated MHC-II backbone with a swappable peptide cassette) makes N-of-1 manufacturing tractable — only the peptide changes per patient — and extends beyond EoE to celiac and other food/auto-antigen disease. A **9-construct panel across dairy, wheat, and soy folds at ipTM 0.87–0.90 with 15/15 peptides in-groove**; the dairy anchor (β-casein aa59–78, HLA-DRB1*07:01) is supported by a reported tetramer-validated food epitope (a literature attribution carried from our founding brief, flagged for independent verification).

This plan folds in the findings of a patient-centered market report spanning the full antigen-specific-immunotherapy landscape — Tzield in type 1 diabetes, Nexvax2/TAK-101/KAN-101 in celiac, and the EoE biologic pipeline. Three things changed how we frame the opportunity:

1. **Our pricing is conservative, not aggressive.** The one approved analog (Tzield) prices at **$193,900 per course** — *above* what analysts expected — and still drew a **$2.9B acquisition** on a single delay-of-onset indication. Our $150k one-course price is ~23% below that precedent.
2. **The bottleneck is screening, not demand.** Tzield's uptake (~1.2% of its market in 2023) is throttled by the absence of routine screening — which is why our companion diagnostic is a day-one commercial deliverable, not an afterthought.
3. **Patient voice has arrived too late in every prior program.** No dedicated EoE patient-focused drug-development (PFDD) meeting exists, and no pMHC EoE program exists. Project Tolera charts how such

an effort could be the first in this field to put patient priorities *before* trial design — an advantage in recruitment, endpoint selection, and community trust.

What it would take. The roadmap estimates that roughly **$8M** would carry the concept from validated in-silico design through human functional validation, murine proof-of-concept, GLP toxicology, GMP/IND lots, the companion diagnostic, and regulatory filings to a **cleared IND and first-in-human dosing** — the single largest de-risking step available today. A further **~$35M** would fund through the **Phase 2 durable-remission proof-of-concept**, the point at which the science would be mature enough to justify a dedicated organization. These figures scope the work, not a raise.

---

2. The Problem — a disease managed, never cured

For many patients the path to an EoE diagnosis is long and indirect: children present with feeding difficulty or failure to thrive; adolescents and adults with dysphagia and, often, an episode of food impaction requiring emergency intervention. Because confirmation requires esophageal biopsy at endoscopy, diagnosis is frequently delayed by years and multiple sedated procedures.

Once diagnosed, patients enter a treatment landscape that is genuinely effective for many but **fundamentally incomplete**. PPIs, swallowed topical corticosteroids, elimination diets, and dupilumab each reduce eosinophilic inflammation — but none is curative, all require indefinite adherence, and inflammation typically returns when treatment stops. Elimination diets demand vigilance at every meal and serial endoscopies to test reintroduction. Left inadequately controlled, chronic inflammation can progress to **fibrostenosis** — irreversible esophageal narrowing requiring mechanical dilation.

The burden that doesn't show up in a biopsy. Patients describe chewing every bite an unusual number of times, drinking liquid with every mouthful, avoiding restaurants and travel, and a quiet, rational anxiety around choking. Meals — ordinarily a site of connection — become a site of vigilance. This is a disease that asks for constant, low-grade attention, meal after meal, for life.

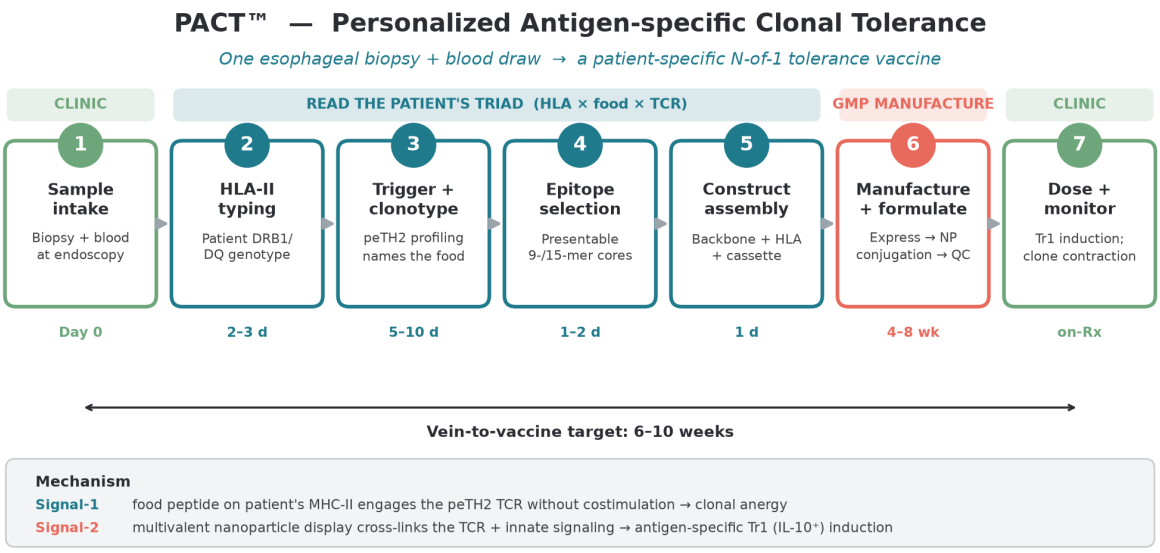
That lived reality is not incidental to this project; it is its origin. the project's originator is an immunologist who lives with EoE, which makes patient experience a design input rather than a marketing note.

---

3. The Solution — retire the clone, don't suppress the system

Current therapies work downstream, blocking a cytokine or cell in the inflammatory cascade. An antigen-specific tolerance vaccine takes a different aim: **retraining the immune system's response to the specific food antigens driving disease**, so the pathogenic clone is anergized or converted to a regulatory (Tr1) phenotype — leaving the rest of the immune system intact.

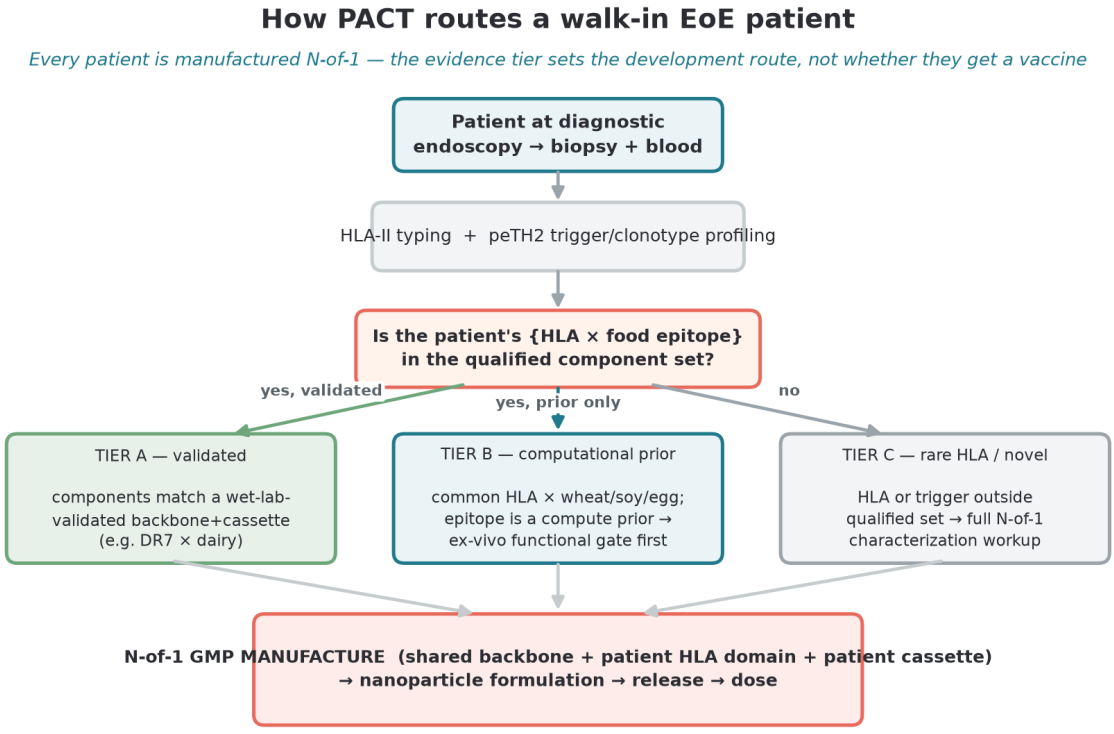
Mechanistically, TOL-EoE delivers the patient's dominant allergen epitope **already loaded on their own MHC-II molecule** (the truest "pMHC vaccine"), in a tolerogenic multivalent context that induces Signal-1 anergy and IL-10-biased Tr1 cells rather than effector Th2 activation. If successful, this offers what patients consistently say they want most: **not just fewer symptoms, but less vigilance** — fewer doses, addressing a cause rather than a consequence.



4. Platform — PACT™ and the N-of-1 manufacturing thesis

Personalized therapy is only investable if manufacturing is tractable. **PACT™ solves this with a shared, GPU-validated MHC-II backbone and a swappable peptide cassette: only the peptide changes per patient**, so the expensive, regulated components (backbone expression, folding QC, nanoparticle formulation, release testing) are standardized and validated once. Vein-to-vaccine target is **6–10 weeks**.

This is the same individualized-product logic that individualized neoantigen cancer vaccines (mRNA-4157, autogene cevumeran) used to clear regulatory and CMC hurdles — applied to a self-food antigen. Critically, the individualized model **travels internationally because the *process* is exported, not a fixed inventory**, and the same engine extends to celiac and other food/auto-antigen disease — a pipeline-in-a-product.

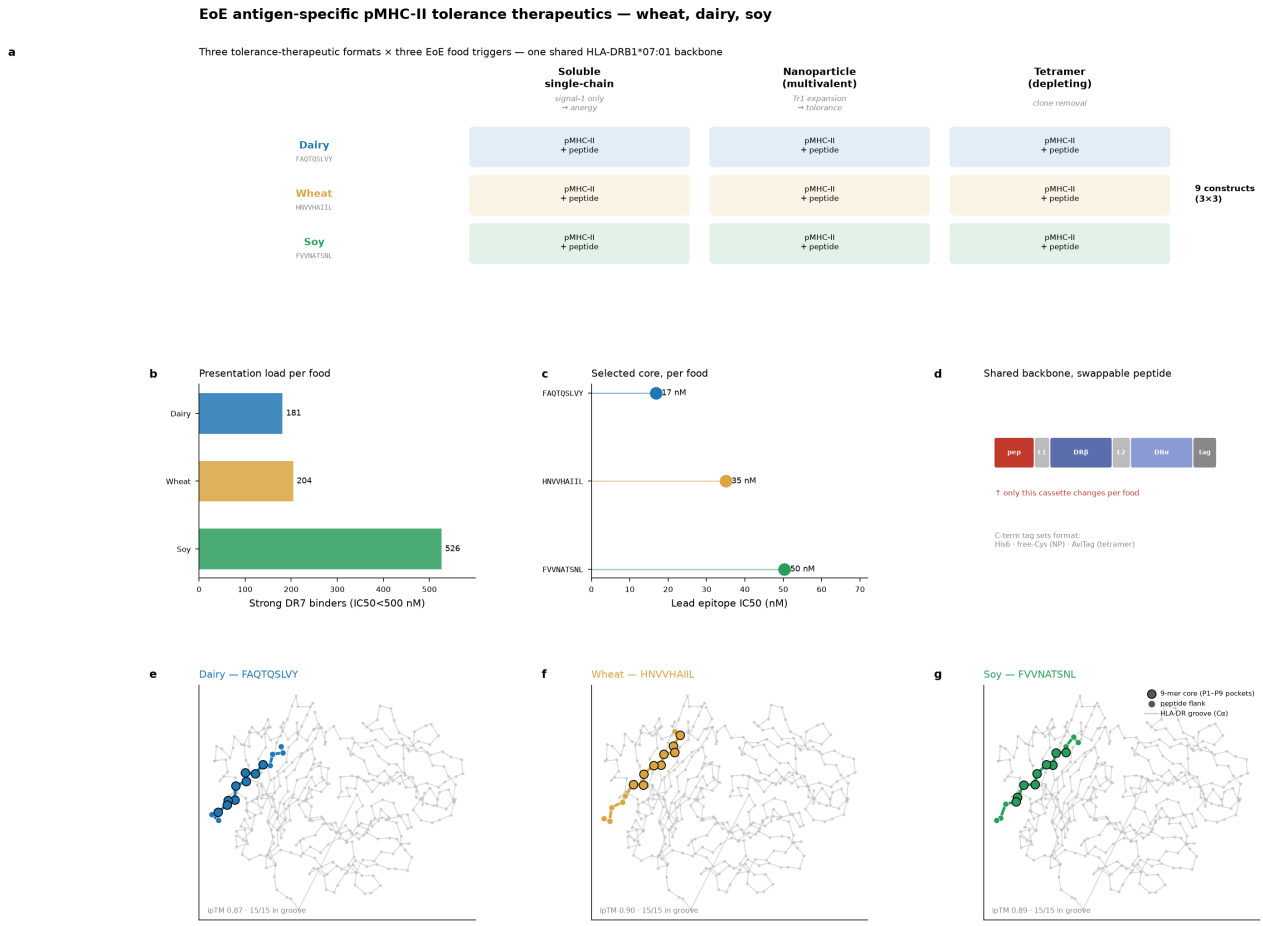


Platform flywheel: every Tier B/C patient generates functional data that converts priors into qualified components → more patients enter Tier A over time.

5. Scientific Validation — this is not slide-ware

A 9-construct pMHC-II panel across the three dominant EoE food allergens has been designed and GPU-validated:

- **ipTM 0.87–0.90 across the panel; 15/15 designed peptides sit fully in-groove** (full 15-residue engagement of the HLA-DRB1*07:01 binding cleft).
- The **dairy anchor (β-casein aa59–78 on HLA-DRB1*07:01)** is, per our internal design record, supported by a reported tetramer-validated EoE food epitope and a functionally-validated EoE food-reactive TCR (eoeTCR-4) that together establish the pMHC–TCR triad the platform targets. *This literature attribution is carried from the founding brief and is flagged for independent citation verification.*
- **Wheat and soy epitopes are computational priors**; wet-lab functional validation is an explicit, near-term milestone.



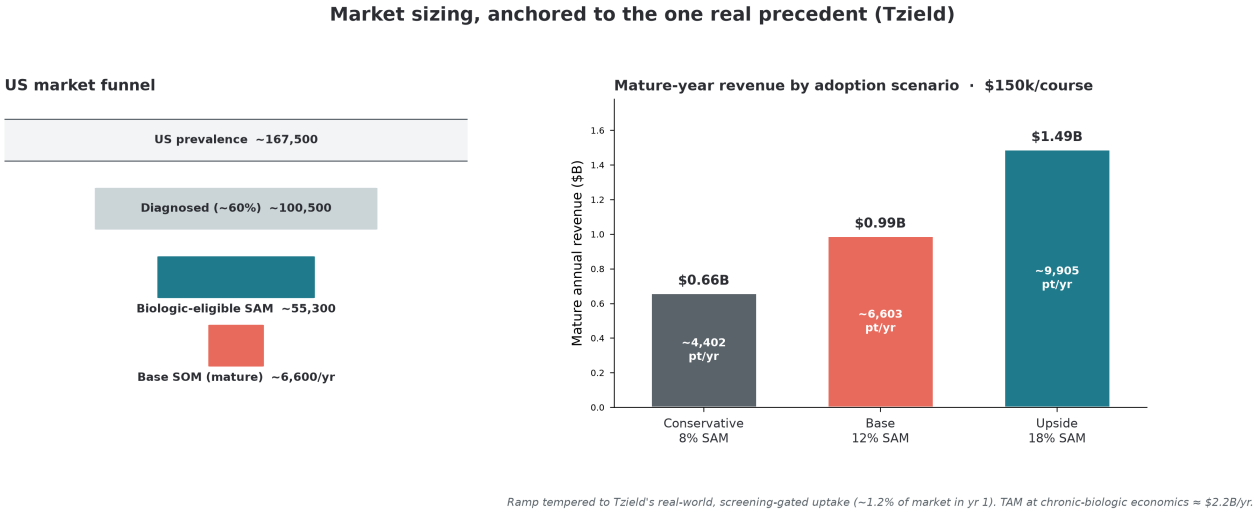
6. Market Analysis

6.1 Sizing (US; EU as expansion)

Layer	Definition	Patients	Basis
Prevalence	US EoE (~1 in 2,000)	**~167,500**	1/2,000 × 335M US
Diagnosed	Clinically diagnosed	**~100,500**	~60% (EoE is under-diagnosed)
SAM — biologic-eligible	Moderate–severe / failing conventional therapy	**~55,300**	~55% of diagnosed

Layer	Definition	Patients	Basis
SOM (mature, base case)	Realistic annual serviceable share	**~6,600 / yr**	~12% of SAM at maturity

- **TAM ≈ $2.2B/yr** if the biologic-eligible pool were treated at ~$40k/yr chronic-biologic pricing (dupilumab-class list economics).
- **Base-case SOM revenue ≈ $1.0B/yr** at maturity (~6,600 patients/yr × $150k one-course price). We present a **scenario range — 8% / 12% / 18% of SAM = $0.66B / $0.99B / $1.49B** — rather than a single point, because the one real precedent (Tzield) shows first-in-class tolerance therapies ramp slowly and are gated by screening infrastructure, not demand.
- **EU roughly doubles** the addressable population; rest-of-world extends further.



Why we tempered the SOM. Our earlier model used a single 15%-of-SAM (~8,300/yr) mature share. The market report's Tzield deep-dive — ~1.2% of its market captured in the first full year, a multi-year ramp explicitly gated by the absence of routine screening — argues for presenting a **base case of ~12% with an explicit range**, which is both more defensible and still supports a ~$1B mature revenue line.

6.2 Epidemiology & disease-area context

EoE sits within a family of antigen-specific-tolerance opportunities. **Type 1 diabetes** proved the modality (defined autoantigens, a C-peptide biomarker, TrialNet screening infrastructure, deep advocacy) and produced the field's only approved agent. **Celiac disease** offers the cleanest antigen (gluten; ~90% HLA-DQ2.5) but the hardest endpoint. **EoE combines the strongest commercial whitespace with the hardest antigen-selection problem** — its drivers are plural, patient-variable food allergens (milk, wheat, egg, soy). Solving antigen selection — the project's core scientific task — is exactly what converts the whitespace into a program.

---

7. Competitive Landscape & Whitespace

Every approved and pipeline EoE therapy shares one structural feature: **chronic dosing of a broad, non-antigen-specific mechanism.**

Agent / modality	Company	Mechanism	Dosing	Antigen-specific?	Durable off-therapy?
Dupilumab (Dupixent)	Sanofi/ Regeneron	anti-IL-4Rα	chronic injection	No	No
Budesonide oral susp. (Eohilia)	Takeda	topical corticosteroid	chronic BID	No	No

Agent / modality	Company	Mechanism	Dosing	Antigen-specific?	Durable off-therapy?
Cendakimab	Bristol Myers Squibb	anti-IL-13	chronic	No	No
Tezepelumab	AstraZeneca/ Amgen	anti-TSLP	chronic	No	No
PPIs	generic	acid suppression	chronic	No	No
Elimination diet	—	antigen avoidance	lifelong	antigen-directed, not therapeutic	No (relapse on reintroduction)
TOL-EoE (Project Tolera)	**this roadmap**	**antigen-specific pMHC-II tolerance (Tr1)**	**one course**	**Yes**	**Design goal: yes**

Competitors cluster in the *broad-mechanism / chronic-dosing* quadrant. Tolera occupies the *antigen-specific / one-course* corner alone. And the differentiation is **categorical, not incremental**: a recent pipeline agent was discontinued for EoE after failing to improve the endoscopic reference score despite a measurable mechanistic effect — a reminder that mechanism alone doesn't win, endpoints do, and that even sophisticated cytokine-targeting agents remain palliative.

Every EoE therapy clusters in one corner. Tolera owns the opposite one.

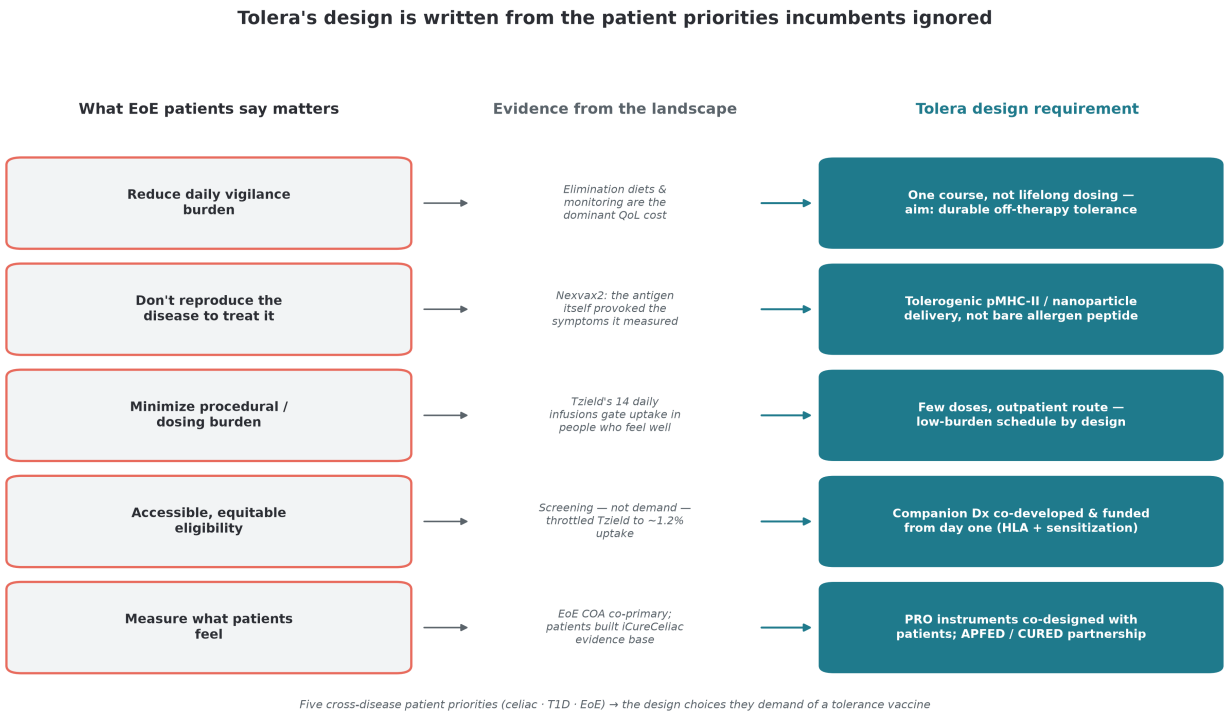
US EoE competitive landscape, 2025–26. Marker size highlights the focal asset. No approved or pipeline agent is antigen-specific or durable off-therapy.

8. Patient-Centered Differentiation — the voice-first thesis

The single strongest finding of the landscape report is that **programs which understood what patients actually experienced designed better trials** — and that patient voice arrived *too late* in every prior program. No formal patient-experience event (PFDD or equivalent) demonstrably preceded the program it might have shaped; **EoE has no dedicated PFDD at all.**

Because EoE has no dedicated PFDD *and* no pMHC program, Tolera has the rare opportunity to **invert the field's historical sequence** — capturing patient needs, interest, and concerns before designing the trial. The follow-on EoE patient survey is the first instrument of that inversion; partnering with APFED and CURED to convene an EoE externally-led PFDD would formalize it.

Five cross-disease patient priorities map directly onto Tolera design requirements:



Five cross-disease patient priorities (celiac · T1D · EoE) → the design choices they demand of a tolerance vaccine

This is not a soft advantage. Patient voice is already **codified in FDA's EoE guidance** as a symptom-COA co-primary endpoint; a program that co-designs its PRO instruments with patients (the iCureCeliac model) and partners with organized advocacy (APFED, CURED, CEGIR, EUREOS) de-risks recruitment, endpoint selection, and community trust — precisely the axes on which trials succeed or stall.

---

9. Business Model

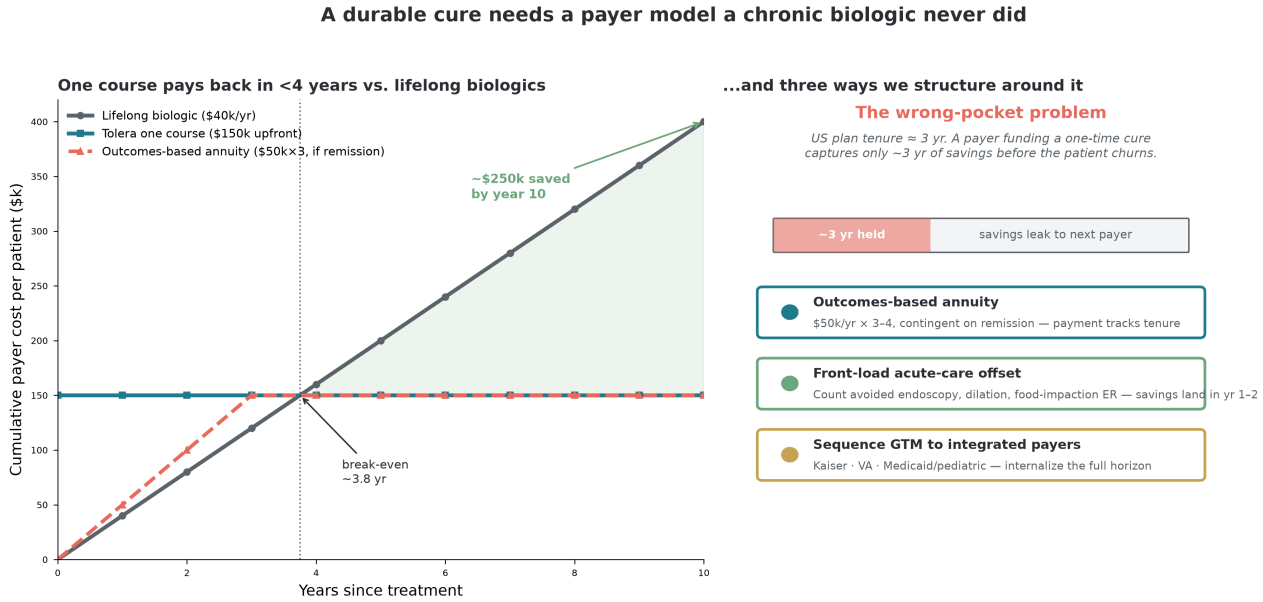
- **Primary:** personalized tolerance vaccine (TOL-EoE), one course, value-based priced (~$150k).
- **Secondary — companion diagnostic:** a blood-based food-trigger + clonotype assay that is *both* the patient-selection gate *and* the objective remission monitor that makes outcomes-based contracting operable. It can generate revenue **earlier and independently** of the therapeutic.
- **Platform optionality:** PACT extended to celiac and other IgE/T-cell food disease; out-licensing of qualified backbones/cassettes.

Two revenue lines, sequenced: the diagnostic can generate revenue pre-therapeutic-approval; therapeutic revenue follows Phase 2 / approval.

---

10. Market Access & Reimbursement — the wrong-pocket problem, solved

A durable, one-course therapy priced at ~$150k faces a structural payer problem a chronic biologic does not. US commercial plan tenure averages ~3 years. A payer that funds a one-time cure captures only ~2–3 years of avoided cost before the patient — now in durable remission and cheap to insure — churns to a competitor's book. This is the **wrong-pocket problem** that rationed the Hepatitis C cures and slowed gene-therapy uptake. A healthcare-literate VC will raise it; naming it and showing a strategy for it is a credibility signal.



Our answer is not a louder cost-effectiveness claim — it is to change **whose** money is spent, **when**, and **how the contract is structured**:

1. **Front-load the offset — count acute care, not just biologics.** Avoided surveillance endoscopies, esophageal dilations, and food-impaction ER visits land inside the first 12–24 months, not year 8, moving effective break-even toward the ~3-year tenure window.
2. **Change the contract to track tenure — outcomes-based annuity.** ~$50k/yr for 3–4 years, contingent on documented sustained remission, capped at the headline value; payment stops on relapse (a warranty). Each payer pays roughly in proportion to the tenure it holds — following gene-therapy annuity/ warranty precedents (Zolgensma, Hemgenix).
3. **Sequence go-to-market toward payers who internalize the full horizon.** Land first in **integrated/ capitated systems (Kaiser, VA, large IDNs)**, **Medicaid/CHIP and pediatric EoE** (long tenure; children avoid decades of biologic exposure), and **self-insured employers** (internalize medical + productivity).

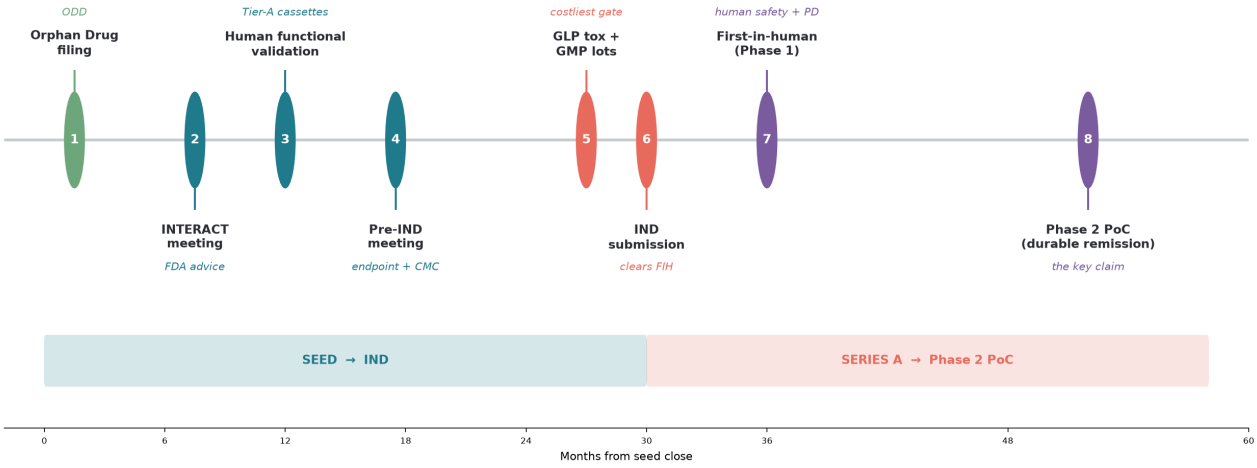
Three contracting models carried into negotiation — outcomes-based annuity, one-time price + outcomes warranty, and front-loaded value model — are presented with their trade-offs rather than pre-committed, matched per channel. Every model except the simplest depends on **documenting sustained remission**, which is a second strategic reason the companion diagnostic is core, not optional.

11. Regulatory Strategy

An EoE pMHC vaccine follows a trail blazed by Tzield (T1D), KAN-101 (celiac), and dupilumab (EoE), and inherits the same central tension: credentialing a disease-modifying, immune-mediated mechanism to a regulator whose muscle memory is built around symptom relief.

- **Designations:** Orphan Drug (if the target population is defined narrowly enough) → Fast Track (the realistic near-term entry, as granted to KAN-101) → Breakthrough (on early biomarker/histologic signal, as Tzield achieved) → test **RMAT** early rather than assuming it.
- **Endpoints:** FDA's EoE guidance mandates **co-primary endpoints — a validated patient-reported dysphagia measure (DSQ-type COA)** ***and*** **histologic response**. This dual bar is clearable (dupilumab, 2022) but operationally demanding, and materially harder for an antigen-specific mechanism whose histologic/immunologic change may lag or lead symptom resolution. We will engage FDA early on whether **histologic remission can serve as a registration-enabling surrogate under Accelerated Approval** with dysphagia confirmation as a post-marketing requirement — borrowing Tzield's disease-modification logic while respecting EoE's guidance.
- **A platform IND, not one per patient** — on the individualized-product framework validated by neoantigen vaccines.
- **Companion diagnostic as a regulatory precondition:** because a pMHC-restricted vaccine is inherently genotype-dependent, the diagnostic must be co-developed and co-reviewed, with the timeline running *parallel* to clinical development.

Regulatory & value-inflection timeline — a single platform IND, not one per patient



12. What It Would Cost & Where the Money Would Go

These are scoping estimates for the work the roadmap describes — an order-of-magnitude budget for reaching each milestone, not a financing plan.

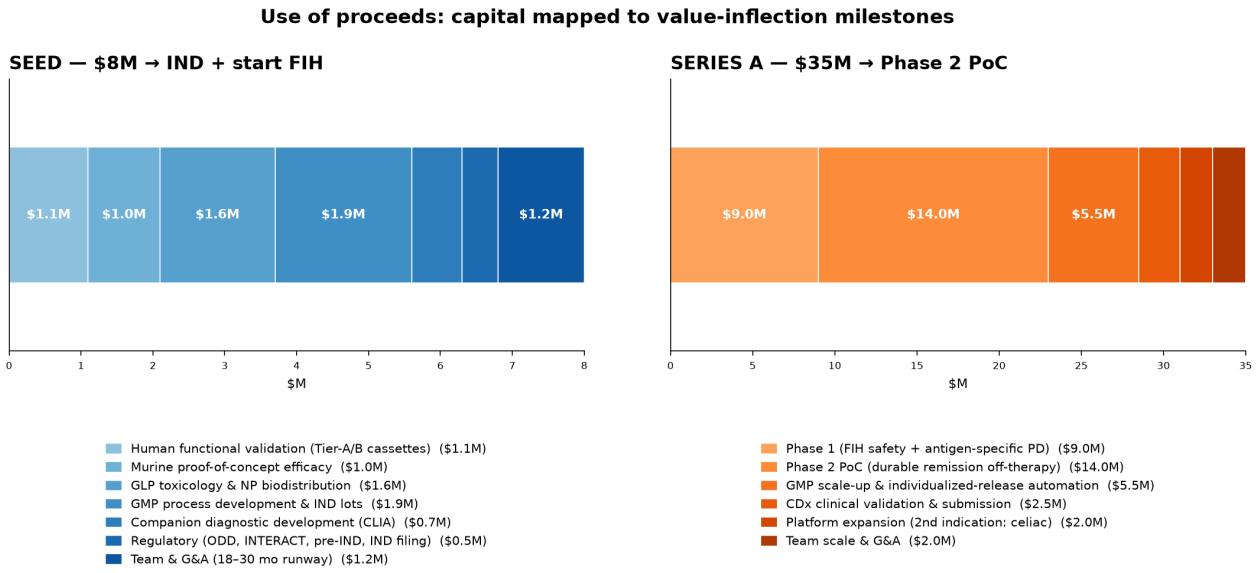
12.1 Phase to IND — ~$8M (→ cleared IND + start first-in-human; ~18–30 mo)

Category	$M	What it funds
Human functional validation (Tier-A/B cassettes)	1.1	Computational priors → validated cassettes
Murine proof-of-concept efficacy	1.0	In vivo tolerance/efficacy signal
GLP toxicology & NP biodistribution	1.6	Safety package for FIH

Category	$M	What it funds
GMP process development & IND lots	1.9	Individualized-manufacturing control strategy
Companion diagnostic development (CLIA)	0.7	Patient-selection assay + standalone product
Regulatory (ODD, INTERACT, pre-IND, IND)	0.5	Designations + FDA alignment + filing
Team & G&A	1.2	Core scientific + ops team, runway
Total	**8.0**	**Cleared IND + first-in-human dosing**

12.2 Phase to clinical PoC — ~$35M (→ Phase 2 proof-of-concept)

Category	$M
Phase 1 (FIH safety + antigen-specific PD)	9.0
Phase 2 PoC (durable remission off-therapy)	14.0
GMP scale-up & individualized-release automation	5.5
CDx clinical validation & submission	2.5
Platform expansion (2nd indication: celiac)	2.0
Team scale & G&A	2.0
Total	**35.0**



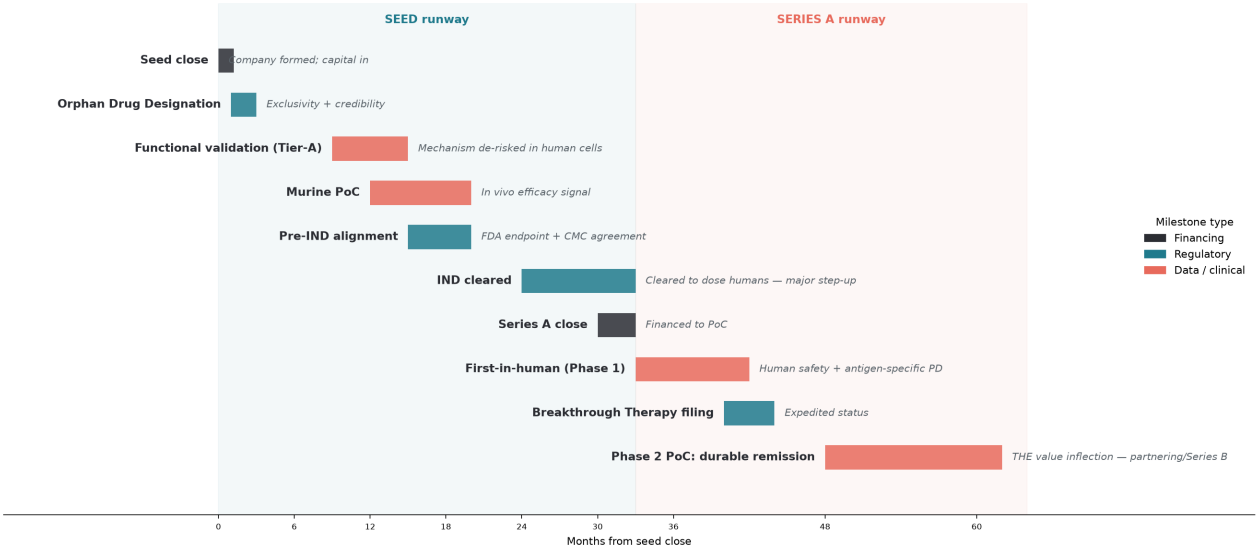
12.3 Why this would be worth building

- **Category-defining approach** in a ~$2.2B unmet-need market with no antigen-specific competitor.
- **A platform, not a single molecule** — multiple shots on goal from one engine.
- **Capital-efficient path to inflection** — ~$8M to IND/FIH, ~$43M cumulative to a Phase 2 PoC that would justify a dedicated organization and partnering.
- **Two potential value lines** — therapeutic + companion diagnostic.
- **A precedent for the value at stake:** Tzield — a first-in-class tolerance asset — drew a **$2.9B Sanofi acquisition (2023)** on the strength of a single delay-of-onset indication, at a course price (~$194k) above the one modeled here.

13. Milestones & Value Inflection

Milestone	~Month	De-risking delivered
Effort resourced	0	Work begins; team assembled
Orphan Drug Designation	1–3	Exclusivity + early credibility
Functional validation (Tier-A)	9–15	Mechanism de-risked in human cells
Murine PoC	12–20	In vivo efficacy signal
Pre-IND alignment	15–20	FDA endpoint + CMC agreement
IND cleared	24–33	**Cleared to dose humans — major value step-up**
Clinical-phase resourced	30–33	Funded through PoC
First-in-human (Phase 1)	33–42	Human safety + antigen-specific PD
Breakthrough Therapy filing	40–44	Expedited status
Phase 2 PoC: durable remission	48–62	**The key inflection — where a dedicated organization and partnering make sense**

Value-inflection timeline: each milestone tagged with the de-risking it delivers



14. Who Developed This

Ruth-Anne Pai, PhD — PhD Scientist & Advisor, bridging science and advocacy, and a person living with EoE. Developed the Project Tolera roadmap and the PACT platform concept during the "Built with Claude: Life Sciences Hackathon" (July 2026). The patient-scientist perspective is a design input throughout, not a disclaimer: it shapes which patient priorities lead, which endpoints matter, and how the community would be engaged.

Contact — advising@ruthannepai.com · ruthannepai.com · linkedin.com/in/ruth-anne-pai Hackathon: Built with Claude: Life Sciences, July 2026

Realizing this roadmap would require a dedicated scientific and operations team — a Head of CMC, a regulatory lead, and a clinical/translational lead among the first key roles (scoped in the budget above).

15. Risks & Mitigations

Risk	Severity	Mitigation
Antigen heterogeneity — no single dominant EoE allergen	High	Omics-driven epitope prioritization; personalized/multi-allergen pMHC; start with milk/wheat-dominant subset
Anaphylaxis / reactogenicity from allergen exposure	High	Tolerogenic delivery (pMHC NP), dose-escalation, early exclusion of high-anaphylaxis-risk patients
No validated tolerance PD biomarker for EoE	High	Biomarker-first development; esophageal histology + allergen-specific T-cell assays
pMHC modality clinically unproven anywhere	Med–High	De-risk via Navacim/celiac-NP read-across; strong preclinical package
Symptom-COA co-primary is demanding (FDA EoE guidance)	Medium	Early COA strategy; PRO co-designed with patients; pursue histologic surrogate under Accelerated Approval
Slow adoption / screening bottleneck (Tzield precedent)	Medium	Companion-diagnostic + patient-org access partnership from day one; coverage-navigation program budgeted
Wrong-pocket / payer churn on a durable therapy	Medium	Outcomes-based annuity; front-loaded acute-care offset; sequence GTM to integrated/capitated payers
Small addressable early-disease population	Medium	Health-economic case built on preventing fibrostenosis/endoscopy burden

16. Where This Goes Next

This roadmap shows that a personalized pMHC-II tolerance vaccine for EoE is scientifically credible today, commercially rational, and — critically — designable by a citizen-scientist with the right tools in a single week. The nearest and most valuable next step is turning validated in-silico designs into **human-validated, IND-enabling data**: the ~$8M phase that carries the concept to a **cleared IND and first-in-human dosing**, with the companion diagnostic developed alongside. A subsequent ~$35M would reach the Phase 2 durable-remission proof-of-concept — the point at which the science would warrant a dedicated organization to carry it to patients.

If this roadmap is useful to you — as a researcher, clinician, patient-advocate, funder, or potential biotech partner — please reach out: **advising@ruthannepai.com** · ruthannepai.com · linkedin.com/in/ruth-anne-pai.

This is an independent research roadmap, not a company prospectus or an offer to invest. Dollar and market figures are illustrative planning assumptions grounded in public data; they are not guidance and would be refined with FDA interactions, manufacturing quotes, and clinical-site costs. All non-dairy epitope activity remains a computational prior pending wet-lab validation. The food-trigger assay concept is patented (Hill/Spergel) — a freedom-to-operate / licensing consideration for anyone taking this forward. Not medical advice.