RUBIX life sciences

RUBIX LS SCIENTIFIC & TECHNICAL WHITE PAPER

Project Panacea and the DCIS-to-Invasive Breast Cancer Translation Path

Advancing a topical breast cancer proof-of-concept toward tissue-confirmed pharmacology in ductal carcinoma in situ — using Ki-67 as the lead pharmacodynamic bridge, ER/PR/HER2 as receptor-context stratifiers, and progression biology as the path toward DCIS-to-invasive translation.

The Rubix LS thesis
Evidence strategy is not something that happens after therapeutic development — it is how therapeutic development becomes translatable. This paper defines the translational evidence architecture for Project Panacea's next credible step.

Program	Project Panacea — investigational topical breast cancer therapeutic
First disease context	Ductal carcinoma in situ (DCIS) to invasive ductal carcinoma (IDC)
Publication	Rubix Life Sciences · June 2026
Classification	Hypothesis-generating translational evidence strategy — not clinical efficacy data

Executive summary

At Rubix LS, Project Panacea is not positioned as a general clinical-operations story. It is a translational breast cancer program built around a specific scientific question: can a topical, local-action therapeutic create measurable biological activity in breast tissue while limiting systemic exposure?

That distinction matters because the first disease context for Panacea is not broad metastatic breast cancer. The clearest translational entry point is ductal carcinoma in situ (DCIS) and the biological bridge from DCIS toward invasive ductal carcinoma. DCIS is heterogeneous: some lesions remain indolent, while others recur or progress toward invasive disease. A DCIS precision-medicine review notes that more than 50% of DCIS will remain indolent and never progress to invasive ductal carcinoma, while emphasizing that none of the common receptor markers can reliably predict recurrence or progression on their own.[1]

For this next phase, Ki-67 should be the lead biological readout because it provides a practical measure of tumor-cell proliferation and has precedent in presurgical breast cancer and DCIS studies. A randomized phase 2 preoperative DCIS trial comparing oral tamoxifen with transdermal 4-hydroxytamoxifen used absolute change in DCIS Ki-67 labeling index as its primary endpoint.[2] That trial did not confirm antiproliferative noninferiority of the gel, but it clarified a critical development lesson for Panacea: topical breast therapy must prove tissue delivery, pharmacodynamic effect, and systemic-exposure advantage together.[2]

> **Preclinical proof-of-concept (20-rat Sprague Dawley DMBA mammary tumor model)**
> Treated tumors were approximately 50–60% smaller in volume than controls by week 4, with several treated animals showing partial or complete remission and no significant systemic toxicity observed. Histology showed extensive necrosis and fibrosis, reduced viable tumor fraction, lower Ki-67, increased cleaved caspase-3, downregulation of phosphorylated Akt, and increased immune-cell presence including CD8+ T cells and macrophages.

The next phase is built around one central translation claim:

> **Panacea is ready to move from tumor-volume proof-of-concept toward tissue-confirmed pharmacology.**

The next studies should not simply ask whether the topical compound shrinks tumors. They should ask whether the compound reaches breast tissue, changes the expected biology, preserves a favorable systemic-exposure profile, and generates a biomarker pattern that can inform DCIS-to-invasive disease translation.

Why DCIS is the right first technical frame

DCIS sits at the boundary between localized disease and invasive transformation. It is defined as a clonal proliferation of breast epithelial cells confined to the mammary duct, but the disease is heterogeneous across morphology, receptor expression, molecular profile, recurrence risk, and progression potential.[1] The problem in DCIS is not simply treatment availability — it is risk discrimination. Many lesions are treated aggressively to prevent recurrence or invasive progression, yet a substantial proportion may never progress. This creates a development opportunity for localized therapy: if a topical intervention can produce a measurable tissue-level effect in biologically active DCIS, it could support a more precise treatment-development pathway.

The DCIS frame gives Panacea a technical development logic

- Localized disease: DCIS is anatomically localized, making it more appropriate for a topical/local-action concept than disseminated disease.
- Measurable biology: Ki-67, ER, PR, HER2, p-Akt, cleaved caspase-3, immune infiltration, and progression markers can be assessed directly in tissue.
- Window-of-opportunity feasibility: Patients scheduled for surgery can receive short presurgical exposure, allowing tissue analysis after excision.
- Progression relevance: DCIS-to-IDC translation can be studied through proliferation, receptor biology, microenvironment changes, ECM remodeling, COX-2, p16, necrosis, and invasive-risk signatures.
- Patient-centered rationale: Local action may be especially meaningful if systemic exposure is reduced without losing tissue-level activity.

The DCIS-to-IDC frame also avoids overextending the claim. We are not positioning Panacea as a replacement for systemic therapy in metastatic breast cancer. We are positioning it as an investigational local-action therapy developed first where local tissue pharmacology can be tested directly.

The biomarker stack: what we measure and why

The next scientific phase centers on a layered biomarker stack. Ki-67 leads because it is the most direct early readout of antiproliferative effect; ER, PR, and HER2 provide receptor-context stratification; progression biology then determines whether the signal is relevant to DCIS-to-IDC transition.

Biomarker layer	Marker set	Why it matters for Panacea
Lead pharmacodynamic readout	Ki-67	Measures proliferation change after topical exposure; the clearest presurgical tissue endpoint.
Mechanism confirmation	p-Akt, total Akt, cleaved caspase-3	Tests whether the topical active suppresses survival signaling and induces apoptosis in the expected direction.
Receptor context	ER, PR, HER2	Defines whether response patterns differ across hormone-receptor and HER2 expression states.

Biomarker layer	Marker set	Why it matters for Panacea
DCIS recurrence & progression	HER2, Ki-67, intraductal necrosis, p16, COX-2	Connects Panacea response to known high-risk DCIS biology.
Microenvironment & immune	CD8+ T cells, macrophages, NK markers, cytokines	Tests whether topical treatment changes the tumor microenvironment, not only tumor-cell proliferation.
Tissue delivery	Breast-tissue drug concentration, local & systemic exposure	Determines whether topical delivery reaches the intended compartment while limiting systemic exposure.
Translational safety	Dermal tolerability, systemic PK, lab safety, irritation/sensitization	Determines whether the route is clinically viable.

The Ki-67-first strategy is supported by DCIS and presurgical precedent: in the randomized 4-hydroxytamoxifen gel study, Ki-67 labeling index was the primary endpoint and tissue drug concentration a key secondary measure.[2] A separate DCIS recurrence study found HER2 overexpression in 50% of recurrent cases versus 14% of nonrecurrent cases, and low Ki-67 staining in 87% of nonrecurrent versus 50% of recurrent cases.[3] Most DCIS lesions express ER and PR, but ER-negative and PR-negative DCIS are associated with increased grade and local-recurrence risk.[1]

The progression-biology layer is what makes this technically stronger than a simple topical breast-therapy story. DCIS progression has been linked to microenvironmental and extracellular-matrix changes, including lysyl-oxidase-mediated collagen crosslinking, fibrillar collagen, COX-2, VEGF, and MMP-14 biology; an association between invasive progression and co-expression of Ki-67, p16, and COX-2 has been reported although not fully validated.[1] For Panacea, this means Ki-67 should be necessary but not sufficient.

The topical molecule logic

We describe Panacea by disclosed pharmacology rather than chemical identity while the active molecule remains protected for intellectual-property, regulatory, and partner strategy reasons. The disclosed molecule logic is:

- The Panacea active is a topical bioengineered compound intended to halt breast tumor growth and induce tumor-cell death through localized delivery.
- The proof-of-concept package suggests dual activity: inhibition of oncogenic survival signaling and induction of tumor-cell apoptosis.
- Preclinical tissue findings support PI3K-Akt pathway relevance, with downregulation of phosphorylated Akt in treated tumors.
- Tissue findings also support a cell-death signal, with increased cleaved caspase-3 in treated tumors.
- Immune findings suggest possible local microenvironment modulation, including increased CD8+ T-cell and macrophage presence.

This logic is supported by adjacent topical/transdermal breast cancer precedents. Transdermal formestane cream was reported to reduce tumor quantity, size, and volume in DMBA-treated rats, reduce Ki-67, inactivate PI3K-Akt signaling, reduce phosphorylated Akt, and alter tumor immune infiltration including CD8+ T cells, NK cells, and macrophage-related patterns; the study concluded that the cream could penetrate skin and act against breast cancer similarly to the injection formulation.[4] Panacea does not need to overclaim equivalence to any specific prior molecule — these precedents explain the scientific rationale:

> **Topical breast cancer therapy is plausible only when local delivery, local pharmacology, tissue response, and systemic exposure are studied together.**

What the preclinical data establish

Topical delivery produced antitumor activity

In the 20-rat DMBA mammary tumor model, treated tumors were approximately 50–60% smaller than controls by week 4, with several treated animals showing partial or complete remission while control tumors continued to enlarge. This supports continued development but should be framed as proof-of-concept, not clinical evidence.

Local treatment did not produce an observed systemic toxicity signal

Treated animals remained active with no weight loss or abnormal behavior, feeding, or grooming, and no significant systemic toxicity was observed. This supports the local-action rationale but does not replace GLP toxicology, dermal irritation/sensitization testing, systemic-exposure assessment, or maximal-use evaluation.

Tissue analysis showed reduced proliferation and increased cell death

Treated tumors showed lower Ki-67 index and increased cleaved caspase-3 positivity. This gives Panacea its most important translational bridge: tumor-volume change was supported by tissue pharmacodynamic directionality — the bridge into the window-of-opportunity clinical design.

Mechanistic and microenvironmental findings support deeper profiling

Treated tumors showed p-Akt downregulation and increased immune-cell presence (CD8+ T cells, macrophages). The next phase should not be limited to tumor measurement; it should include pathway and microenvironment assays that determine whether local therapy changes both tumor-intrinsic and tumor-context biology.

In-silico environmental simulation layer

> **Important interpretation guardrail**
> The 100-condition in-silico simulation uses synthetic digital profiles. It is a hypothesis-generating translational planning model — not clinical efficacy evidence, and not human outcome data. All simulation values below are model outputs, not observed patient results, and must not be read as demonstrating that Panacea is validated in humans.

The next technical layer for Panacea is not limited to biological markers alone. We are also modeling how environmental exacerbation, care-context friction, and diverse patient-condition profiles may change the interpretation of topical pharmacology. The biology of DCIS and early breast cancer does not emerge in isolation: heat-sink burden, endocrine-disruptor exposure, nutritional deterioration, occupational exposure, chronic stress, air-quality burden, and care-access friction can create different biological contexts before a patient ever enters a trial.

To pressure-test this, we generated a 100-condition in-silico simulation. These conditions were digitally constructed from known active endpoint and output structures tied to Panacea's proof-of-concept package and internal live-sample endpoint logic. The simulation asks a technical question: under which biological and environmental conditions does tissue-confirmed pharmacology become interpretable?

The simulated set was built from 100% diverse representation by design. No profile was treated as a default reference patient — the purpose was not to rank demographic groups, but to ensure the model does not define “normal” around a non-diverse reference population.

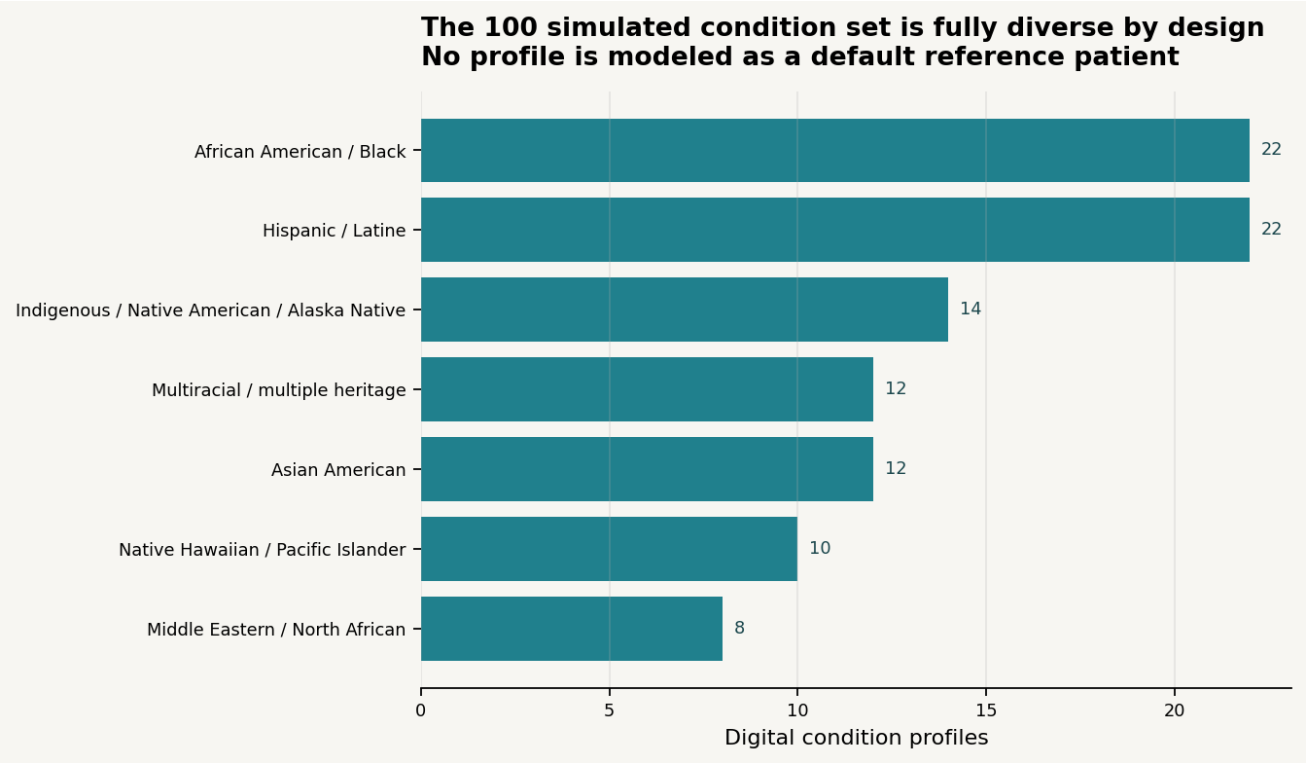

Figure 1. Demographic representation across the 100 simulated Panacea condition profiles. Synthetic digital profiles, designed for diversity — not patient outcomes.

Each digital condition was scored across four layers

Layer	Variables	Why it matters for Panacea
Environmental exacerbation	Heat-sink, air-pollution, endocrine-disruptor, nutritional-deterioration, occupational-exposure, care-access-friction, chronic-stress pressure	Tests whether non-biological pressure changes baseline disease biology, response interpretability, and trial-enrichment strategy.
Baseline disease biology	Ki-67, ER, PR, HER2, p-Akt activation, immune-context index, ECM progression index, apoptosis-readiness index	Connects DCIS and early breast-lesion biology to the expected Panacea response pattern.
Topical delivery behavior	Predicted tissue exposure, predicted systemic exposure, skin-delivery context	Tests whether local action can be separated from systemic exposure.
Pharmacodynamic output	Predicted Ki-67 reduction, p-Akt reduction, cleaved-caspase-3 increase, CD8+ T-cell shift, tissue-confirmed pharmacology score	Converts topical exposure into measurable tissue-response hypotheses.

Simulated mean outputs (model values, not observed outcomes)

0.543 Environmental exacerbation index	**32.7%** Baseline Ki-67	**0.735** Predicted tissue exposure index
0.198 Predicted systemic exposure index	**34.8%** Predicted Ki-67 reduction	**0.585** Tissue-confirmed pharmacology score

The central finding is not that environmental pressure eliminates response — it is that environmental pressure changes interpretation. A Ki-67 reduction in a low-exacerbation profile may reflect direct antiproliferative activity; a similar reduction in a high-exacerbation profile may need to be interpreted alongside inflammation, metabolic stress, microenvironment, access friction, nutrition, and chronic-exposure variables.

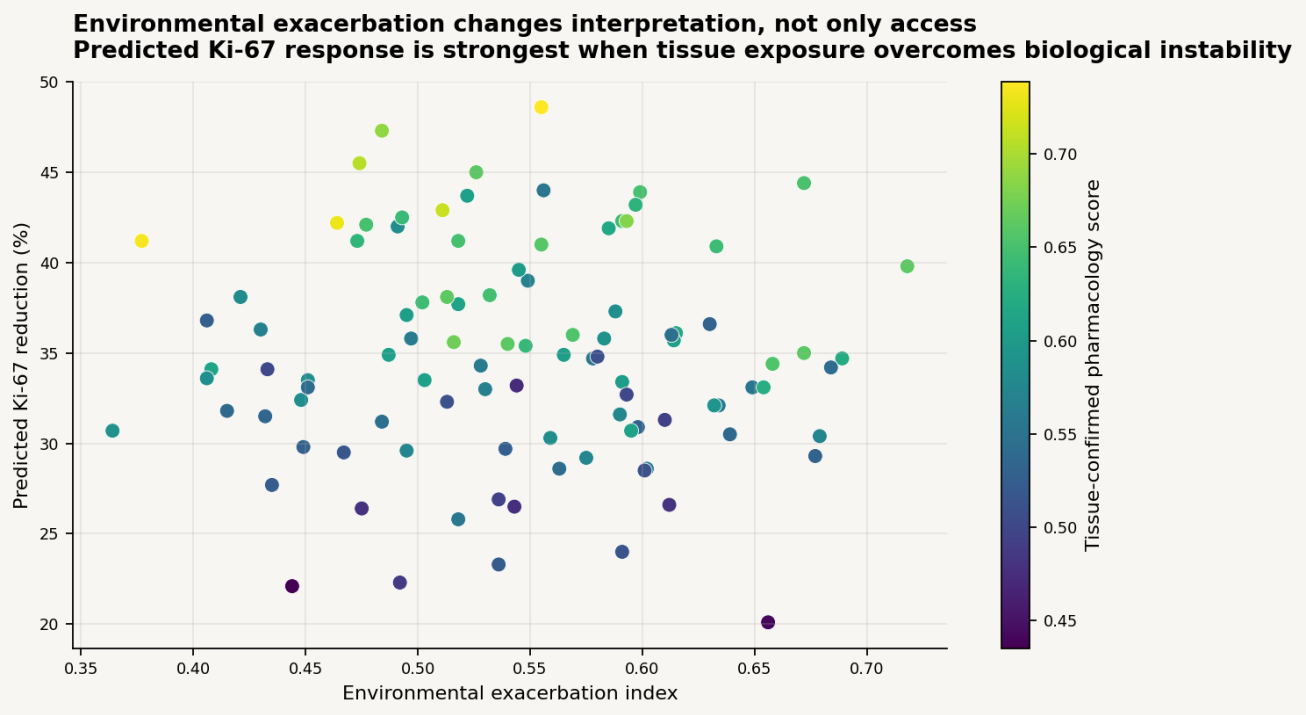

Figure 2. Predicted Ki-67 reduction versus environmental exacerbation index across the 100 simulated conditions, colored by tissue-confirmed pharmacology score. Simulation output — not human efficacy data.

In the simulation, 7 of 100 profiles were classified as high priority for window-study enrichment, 62 as translationally informative monitoring profiles, and 31 as requiring additional characterization or refinement. These are study-design outputs, not clinical eligibility recommendations.

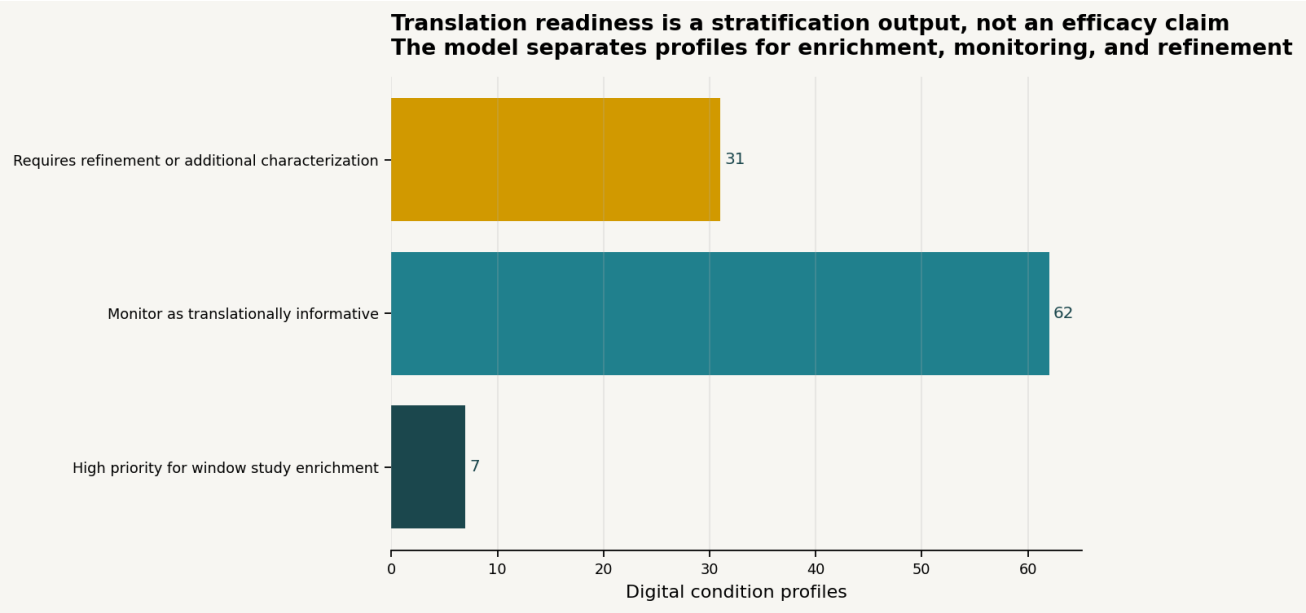

Figure 3. Simulated translation-readiness categories. A stratification output for study design — not an efficacy claim.

The simulation therefore strengthens the technical rationale for a DCIS-first, tissue-confirmed pharmacology strategy. The first human evidence package should not ask whether a topical active "works" in a generic population. It should ask whether Panacea reaches breast tissue, produces Ki-67 reduction, suppresses p-Akt, increases cleaved caspase-3, maintains low systemic exposure, and remains interpretable across biological and environmental condition types.

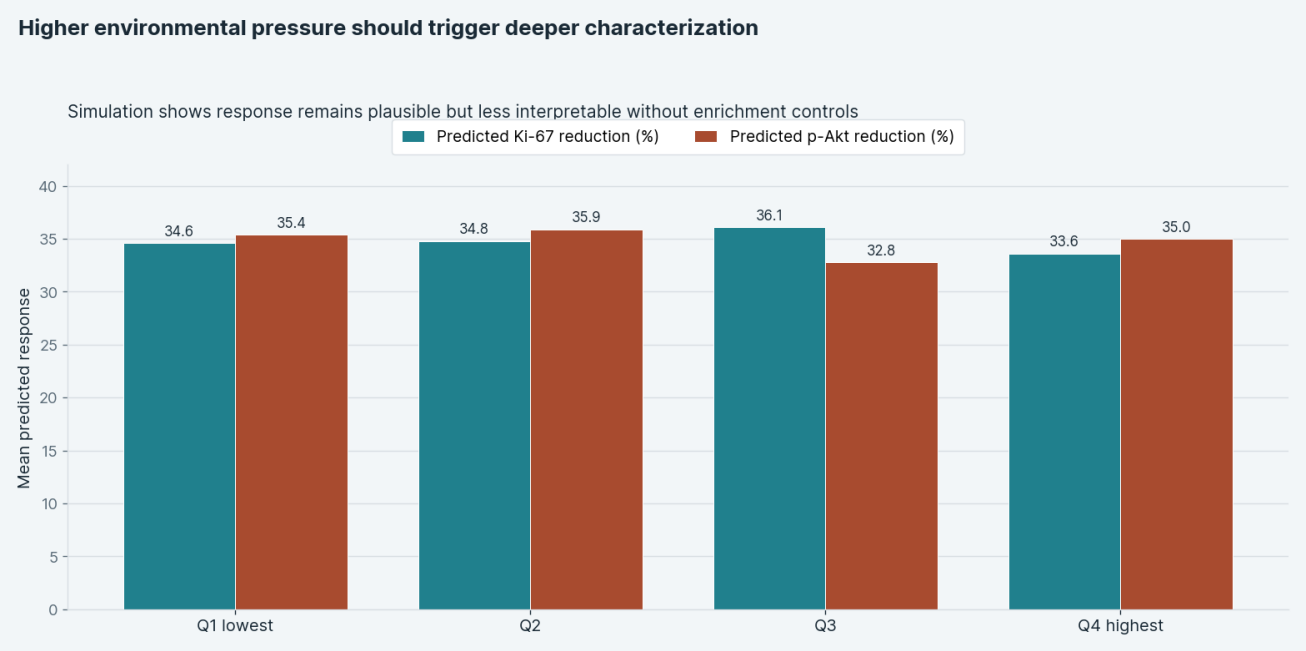

Figure 4. Predicted response distribution by environmental-exacerbation quartile across the simulated set. Hypothesis-generating model output only.

What happens next: the evidence gates

The next phase is framed as a sequence of evidence gates.

Pre-IND evidence package

The pre-IND package should establish what has been shown, what remains uncertain, and which questions must be aligned before human testing — summarizing the DMBA proof-of-concept data, tumor-volume and remission observations, histology (necrosis, fibrosis, viable tumor fraction), IHC (Ki-67, cleaved caspase-3, p-Akt), immune profiling (CD8+ T cells, macrophages), formulation composition and stability, proposed clinical route and dosing rationale, the nonclinical safety plan, and a proposed first-in-human design. The posture should be disciplined: the goal is not to seek agreement that Panacea works clinically, but to align on the evidence required to test local delivery, safety, tissue exposure, and early pharmacodynamic activity responsibly.

GLP dermal toxicology

The topical route requires safety evidence distinct from systemic oncology development. Key questions include dermal irritation under repeat exposure, sensitization risk, local tissue damage unrelated to antitumor effect, systemic exposure under repeated dosing, organ-level toxicity under exaggerated use, and the vehicle's contribution to irritation, penetration variability, and systemic exposure — linked to the maximal-use strategy.

CMC scale-up

CMC is part of the science, not an administrative step. A topical breast therapy depends on formulation reproducibility: if batch-to-batch variation changes penetration, local exposure, stability, or active concentration, the biological interpretation becomes unstable. Key questions span reproducible active concentration, physical/chemical stability, nanocarrier/enhancer consistency at scale, storage effects on penetration and potency, GMP clinical-grade manufacture, dose-control format, and patient acceptability (odor, texture, drying time, residue, adherence). For a topical oncology candidate, formulation is part of pharmacology.

Maximal Usage Trial (MUsT)

The MUsT should test systemic exposure under conditions approximating the highest reasonable clinical use: plasma concentration at maximal application, accumulation under repeated dosing, systemic exposure versus projected therapeutic tissue exposure, systemic metabolite detection, and safety signals under maximal use. This is where Panacea can strengthen the local-action claim by measuring the relationship between local tissue exposure and systemic plasma exposure rather than simply asserting it.

Pre-surgical window-of-opportunity study

This is the central first human biology study. The recommended first clinical context is patients with DCIS scheduled for surgery, with selection based on safety, ethical appropriateness, lesion accessibility, and standard-of-care timing, allowing short presurgical exposure followed by tissue analysis after excision.

Primary objectives

- Assess safety and local tolerability
- Measure drug concentration in breast tissue
- Measure systemic plasma exposure
- Assess change in Ki-67 from baseline biopsy to surgical specimen

Secondary & exploratory

- p-Akt modulation; cleaved caspase-3 / apoptosis
- ER/PR/HER2-stratified response; p16, COX-2
- Necrosis and histologic response
- CD8+ T-cell and macrophage infiltration
- Imaging-pathology correlation; patient-reported tolerability

This study should not be overpowered or overclaimed as an efficacy trial. It should be designed as a tissue-confirmation study: does the topical compound reach the lesion, produce the expected biological effect, and maintain a favorable systemic-exposure profile?

DCIS-to-IDC translation: a staged strategy

Stage one — DCIS tissue pharmacology

The first question is whether Panacea can produce measurable local biological change in DCIS. Ki-67 reduction leads this stage because it is practical, interpretable, and precedent-supported. The 4-hydroxytamoxifen DCIS study showed why Ki-67 plus tissue concentration matters: topical therapy may reduce systemic effects, but inadequate tissue pharmacology can limit antiproliferative performance.[2]

Stage two — high-risk DCIS biology

The second question is whether Panacea's biological effect is stronger or more clinically relevant in high-risk DCIS features. Priority subgroups include high Ki-67 DCIS; HER2-expressing or high-grade DCIS; ER-negative or PR-negative DCIS; DCIS with intraductal necrosis; DCIS with p16/COX-2/Ki-67 co-expression patterns; and DCIS with progression-associated stromal or ECM features. This stage should remain exploratory — it should not claim that Panacea prevents invasion, but ask whether it changes biomarkers associated with proliferation, recurrence, or progression risk.

Stage three — early invasive ductal carcinoma adjacency

Only after DCIS tissue pharmacology is established should the program explore translation into early IDC, where disease remains localized and presurgical exposure can measure tissue pharmacology without delaying definitive therapy. Questions include whether topical exposure reaches invasive tumor tissue, whether Ki-67 is reduced in early IDC, whether receptor subtype modifies response, and whether topical therapy can serve as adjunctive, neoadjuvant-window, or local-control support. The limitation remains explicit: once disease is systemic or metastatic, local topical therapy cannot be assumed to replace systemic therapy.

Our role in the next phase

This white paper belongs under Rubix LS because our role is not merely operational — we are defining the translational evidence strategy that makes the next Panacea step credible. Our role includes designing the DCIS-to-IDC evidence logic; defining biomarker endpoints and tissue-analysis priorities; translating preclinical signals into clinical pharmacodynamic endpoints; connecting patient-demographic and real-world evidence to disease-context selection; building the pre-surgical window-of-opportunity framework; supporting pre-IND briefing strategy; and helping define which breast cancer subtypes should be studied next.

> We are not positioning Rubix LS as a CRO. We are positioning Rubix LS as the **evidence architecture partner** that helps determine what should be tested, in whom, with which tissue endpoints, and under which translational assumptions before execution scales.

Recommended next technical outputs

Output	Purpose	Owner logic
Panacea biomarker evidence map	Align Ki-67, ER/PR/HER2, p-Akt, cleaved caspase-3, p16, COX-2, necrosis, and immune markers to DCIS-to-IDC translation	Rubix LS-led
In-silico environmental simulation report	Extend the 100-condition digital model into a repeatable framework linking environmental exacerbation, tissue exposure, and pharmacodynamic response	Rubix LS-led
Pre-IND scientific briefing outline	Define regulatory discussion around nonclinical data, topical route, tissue/systemic exposure, and first-in-human design	Rubix LS w/ TheraSyn Bio
GLP dermal toxicology plan	Define local tolerability and systemic safety package	TheraSyn Bio-led, Rubix LS input
CMC & formulation-readiness memo	Connect formulation stability, penetration, dosing, and patient usability	TheraSyn Bio-led
MUsT concept sheet	Define maximal-use systemic-exposure assessment	Joint
DCIS window-of-opportunity protocol synopsis	Define first human tissue-pharmacology study	Rubix LS-led
DCIS-to-IDC translational extension memo	Define which early invasive breast cancer contexts could follow DCIS	Rubix LS-led

The technical thesis

We are advancing a topical breast cancer proof-of-concept toward tissue-confirmed pharmacology in DCIS — using Ki-67 as the lead pharmacodynamic bridge, ER/PR/HER2 as receptor-context stratifiers, and progression biology as the path toward DCIS-to-invasive breast cancer translation.

The simulation layer expands that thesis. We are not only asking whether a topical active can change breast tissue biology — we are asking whether the interpretation of that change is altered by environmental exacerbation, nutritional deterioration, heat-sink burden, exposure pressure, care-access friction, and chronic stress.

The near-term goal is not to claim clinical efficacy. The near-term goal is to show that the topical active:

- Reaches breast tissue
- Produces measurable biological change
- Reduces proliferation
- Supports apoptosis or survival-pathway suppression
- Maintains low systemic exposure
- Demonstrates local tolerability
- Generates a biomarker pattern that justifies deeper DCIS and early invasive breast cancer study
- Remains interpretable across biologically and environmentally characterized patient-condition profiles

That is the next credible step for Project Panacea. It is also the right Rubix LS story: evidence strategy is not something that happens after therapeutic development — it is how therapeutic development becomes translatable.

About Rubix LS

Rubix LS is a clinical research and evidence-generation company — a Health Outcomes Architect building clinical research on the evidence that has been missing. Better evidence starts with better data.

Sources

All claims drawn from external literature are cited below with full clickable URLs. Simulation outputs and preclinical proof-of-concept observations referenced in this paper are internal Rubix LS / Project Panacea materials and are hypothesis-generating, not clinical efficacy evidence.

1. DCIS precision-medicine review — heterogeneity, indolent fraction, and receptor marker limitations (The American Journal of Pathology).
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