



Organoid Response Maps Can Bridge Natural Product Screening and Human Therapeutics by Preserving Tissue Architecture, Heterogeneity, and Patient-Specific Biology

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ABSTRACT

Natural-product screening frequently begins in reductionist systems that efficiently identify activity but poorly preserve the tissue organization, cellular diversity, and patient-specific biology that shape therapeutic response. Human organoids offer an intermediate experimental space in which chemical perturbations can be examined within three-dimensional, disease-relevant models, yet organoid results are often reduced to single viability endpoints and remain disconnected from chemical provenance, spatial phenotype, molecular state, and clinical context. This article develops a proposed organoid response-map translational framework for integrating these dimensions without treating organoid activity as equivalent to mechanism, exposure, or clinical efficacy. The framework positions tissue architecture and heterogeneity, patient and disease identity, natural-product perturbation, imaging and omics, chemical representation, mechanism inference, and human validation as separable evidence layers that should remain linked but not collapsed. Existing studies support the feasibility of patient-derived organoid pharmacotyping, quantitative three-dimensional phenotyping, multimodal analysis, and defined clinical-response associations. Direct natural-product evidence, however, remains comparatively sparse and chemically heterogeneous. Consequently, the proposed response map is intended as an evidence-organizing and hypothesis-prioritizing construct rather than a validated predictive system. Its translational value depends on controlled compound identity and exposure, organoid fidelity, assay standardization, applicability-domain awareness, orthogonal mechanism testing, and prospective comparison with human tissue and clinical outcomes. The framework therefore aims to improve what is preserved, measured, and qualified between natural-product screening and therapeutic interpretation while making uncertainty explicit.

Key Words: Organoids, Natural products, Phenotypic screening, Precision medicine, Multimodal profiling, Translational pharmacology

eIJPPR 2026; 16(4):50-59

HOW TO CITE THIS ARTICLE: Kumar R, Sharma N, Deshmukh A, Kulkarni S, A Nair. Organoid Response Maps Can Bridge Natural Product Screening and Human Therapeutics by Preserving Tissue Architecture, Heterogeneity, and Patient-Specific Biology. Int J Pharm Phytopharmacol Res. 2026;16(4):50-9. <https://doi.org/10.51847/rGAfjALuOz>

INTRODUCTION

Natural-product discovery often moves from chemical isolation or extract fractionation into biochemical, two-

dimensional cellular, or animal assays. These platforms can establish activity efficiently, but each removes or alters dimensions of the human tissue context in which a

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Received: 12 April 2026; **Revised:** 21 July 2026; **Accepted:** 23 July 2026

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candidate must ultimately act. Human organoids now occupy an increasingly important position between reductionist screening and clinical biology because they can retain aspects of tissue organization, disease phenotype, and functional response while remaining experimentally accessible [1]. Their value is therefore not that they reproduce a whole patient, but that they permit pharmacological questions to be asked in a three-dimensional human-derived system whose biological context is richer than that of many conventional screens.

For drug discovery, this added context is both an opportunity and a burden. Organoid systems can expose response heterogeneity, tissue-specific effects, and complex phenotypes that would be invisible in simplified assays, but they also introduce variation in culture conditions, maturation state, matrix composition, image analysis, throughput, and endpoint definition [2]. A translational framework must therefore preserve the additional information organoids generate rather than compressing it into a single “sensitive” or “resistant” label. Recent drug-development scholarship places organoids within a broader trajectory from predictive model systems toward development and validation workflows, while emphasizing unresolved standardization and regulatory questions [3]. Patient-derived tumor organoids similarly provide an experimental bridge between tumor biology and functional precision oncology, but their performance remains dependent on tumor type, sampling, culture fidelity, and the treatment being modeled [4]. These boundaries are especially consequential for natural products, where chemical identity, metabolite formation, solubility, and clinically achievable exposure may be uncertain.

This article therefore proposes an organoid response map: a structured representation in which chemical perturbation is linked to organoid context, three-dimensional phenotype, molecular response, heterogeneity, mechanism evidence, and human-validation status. The purpose is not to replace established pharmacology or clinical validation. It is to prevent loss of biologically informative context as a natural-product signal moves from screening toward therapeutic interpretation.

Organoid architecture and cellular heterogeneity

Three-dimensional architecture is not merely a visual feature of an organoid. In branched pancreatic ductal adenocarcinoma organoids, heterogeneous phenotypic states and plasticity were associated with differential treatment behavior, indicating that response can depend on how cellular states are organized within the model [5]. Architecture should therefore be treated as a measurable response context rather than assumed to be constant across organoids receiving the same perturbation.

Reproducibility is equally important. High-quantity human brain organoid work has shown that complex organoid systems can be produced and quantitatively evaluated for structural and cellular reliability while supporting disease modeling and drug-screening applications [6]. This does not imply that organoid heterogeneity is experimental noise to be eliminated. Instead, technical variability must be distinguished from biological variability so that genuine between-organoid or within-organoid differences remain interpretable.

Living breast-cancer organoid biobanks further demonstrate that patient-derived organoids can retain substantial disease heterogeneity across models [7]. What is preserved is nevertheless selective: culture may enrich or lose particular cell states, and stromal, vascular, and immune components are not automatically reconstructed. Across organoid systems, architecture and cellular heterogeneity are measurable biological variables that can influence or stratify functional behaviour, although their manifestation is tissue- and platform-dependent [5–7].

For the proposed response map, this leads to a strict distinction among organoid identity, architectural state, and perturbation-induced change. A treatment-associated morphology cannot be interpreted without knowing the baseline structure from which it emerged. Likewise, two organoids with similar bulk viability may represent different biological outcomes if one undergoes focal collapse, lineage redistribution, altered branching, or selective survival of a resistant subpopulation. Preserving these distinctions is central to using organoids as translational models rather than enlarged viability assays.

Patient-specific and disease-specific organoid models

The strongest rationale for patient-derived organoids is not simply three-dimensional growth; it is the possibility of maintaining biologically meaningful differences among patients. Individualized brain tumor organoid models have been reported to preserve measured features of patient tumor ecosystems and to support patient-specific therapeutic-response assessment [8]. Such evidence supports using patient identity as an experimental variable, but not assuming that every component of the source tumor or its microenvironment remains intact after culture.

Gastric cancer organoid studies provide a complementary pharmacological perspective. Personalized drug screening in patient-derived gastric organoids has produced heterogeneous treatment responses that could be compared with molecular and clinical information [9]. The translational importance lies in the pattern of differential response, not in any claim that an organoid score is intrinsically a clinical decision rule. Sampling site, previous treatment, establishment success, assay timing,

and the exact regimen being modeled can all alter interpretation.

In advanced pancreatic cancer, organoid pharmacotyping has also been investigated as a functional-precision strategy [10]. This supports the feasibility of complementing molecular profiling with experimentally measured drug response. It does not establish that functional organoid testing improves survival or should override validated biomarkers, pharmacokinetic constraints, or clinical evidence. Within a response-map framework, molecular and functional evidence therefore remain parallel and potentially convergent rather than interchangeable.

Disease-specific biology further constrains transferability. Gastric cancer organoid biobanks preserve important histological and molecular subtype diversity and enable therapeutic screening across disease states [11]. A response observed in one subtype, tissue origin, or culture context cannot be treated as a property of the compound alone. The proposed map consequently retains patient, disease subtype, sampling context, and baseline phenotype alongside the perturbation result. This makes a negative or positive response interpretable as an observation in a defined biological system rather than as an unconditional statement about therapeutic sensitivity.

Natural product perturbation and response profiling

Natural products introduce an additional layer of uncertainty because the tested entity may range from a purified molecule with defined stereochemistry to an extract or fraction containing multiple constituents. Recent literature specifically addressing cancer patient-derived organoids and natural products shows that this is an emerging area rather than a mature translational evidence

base [12]. Organoids can therefore strengthen natural-product screening only if chemical provenance is recorded with the same care as biological provenance.

Direct evidence remains instructive. Luteolin has been evaluated across patient-derived gastric cancer organoids, with heterogeneous antitumor responses accompanied by molecular analyses [13]. This establishes that a defined natural product can be tested in patient-specific organoid systems and linked to molecular observations. It does not establish clinical efficacy, clinically achievable tumor exposure, or a universal mechanism. Concentration in culture, protein binding, stability, metabolism, tissue penetration, and the absence of whole-body disposition remain separate pharmacological questions.

The interpretive problem becomes harder for traditional medicines and chemically complex preparations. Organoid and organ-on-chip approaches are increasingly discussed as platforms for investigating traditional Chinese medicine, but chemical complexity, component interaction, and incomplete standardization constrain attribution [14]. A response map should therefore record whether the perturbation is a purified constituent, characterized mixture, fraction, or incompletely resolved preparation, and should distinguish measured composition from inferred active constituents.

Accordingly, natural-product response profiling should not begin with the question “does the organoid respond?” alone. It should ask what chemical entity reached the model, under what exposure conditions, in which patient-specific architecture, with which phenotypic and molecular consequences, and at what confidence. **Table 1** summarizes the evidence-provenance distinctions that become necessary once organoid response is treated as translational evidence rather than a single assay result.

Table 1. Evidence provenance and confidence requirements for interpreting natural-product responses in patient-derived organoids

Evidence component	What the response map should retain	Evidence-supported basis	Confidence-limiting condition
Chemical provenance	Purified compound, characterized mixture, fraction, or unresolved preparation	Natural-product/organoid evidence requires chemically explicit interpretation	Uncertain composition prevents attribution to a specific constituent
Biological provenance	Patient, disease subtype, sampling context, and baseline organoid state	Patient-derived models demonstrate disease- and patient-dependent responses	Culture selection can alter represented biology
Exposure description	Applied concentration, duration, vehicle or formulation, and relevant stability information	Perturbation experiments require defined experimental exposure	In vitro exposure does not establish human tissue exposure
Response phenotype	Growth, viability, architecture, or another measured functional change	Organoid studies support heterogeneous functional readouts	A response endpoint alone does not establish mechanism
Molecular corroboration	Molecular changes measured alongside phenotype when available	Natural-product organoid experiments demonstrate feasibility of combined profiling	Association does not establish causal target engagement

Translational confidence	Experimental activity separated from mechanistic and clinical interpretation	Proposed synthesis integrating the evidence boundaries above	Clinical efficacy requires independent pharmacokinetic and human validation
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Note: The confidence structure is proposed here. Evidence-derived distinctions arise from the natural-product and patient-derived organoid evidence discussed in the preceding section; no numerical confidence score, universal threshold, or clinical decision boundary is implied.

Imaging, omics, and multimodal response maps

An organoid response map becomes useful only when “response” is decomposed into measurable dimensions. Three-dimensional imaging can convert architecture from a descriptive observation into a quantitative phenotype. Automated multilevel segmentation and cellular-topology analysis have demonstrated that organoid structure can be digitally resolved at multiple scales [15]. For natural-product perturbation, such analysis can separate global growth suppression from spatially heterogeneous effects, altered organization, or selective persistence of particular structures.

Not every response requires labeling or destructive sampling. Label-free photoacoustic imaging has been used to quantify volumetric changes in tumor organoids during drug screening [16]. This provides a complementary view of response dynamics but does not make volume a surrogate for therapeutic efficacy: swelling, necrosis, differentiation, and other biological processes can alter

volume independently of the intended pharmacological mechanism.

A further limitation of well-level averages is that they can hide the distribution of responses among individual organoids. Single-organoid interferometric screening has shown that response can be measured at individual-organoid resolution [17]. The proposed response-map approach therefore treats dispersion, outliers, and subpopulation behavior as potentially informative rather than automatically averaging them away.

Multimodality should be used selectively. Imaging can define architecture and temporal phenotype; molecular profiling can identify transcriptional, epigenetic, or pathway-associated states; and repeated measurement can distinguish baseline heterogeneity from perturbation-induced change. These modalities should not be collapsed into a single confidence score. Instead, each should answer a defined translational question and retain its own uncertainty. **Table 2** summarizes the decision logic for selecting response-map measurements.

Table 2. Decision criteria for selecting complementary measurements within an organoid response map

Translational question	Preferred measurement class	What it can resolve	Principal interpretive constraint
Did gross structure change?	Quantitative 3D morphology	Shape, branching, topology, spatial organization	Structural change is not inherently beneficial or mechanistic
Did organoid burden change over time?	Label-free volumetric measurement	Non-destructive growth or shrinkage trajectories	Volume is influenced by multiple biological processes
Are responses heterogeneous?	Single-organoid analysis	Response distributions, outliers, resistant subpopulations	Size and assay-specific physical variables require control
Which molecular state accompanies response?	Targeted or omics profiling	Pathway, transcriptional, or regulatory associations	Association alone does not establish causal mechanism
Is the observed change perturbation-specific?	Baseline-plus-treated multimodal comparison	Separation of pre-existing state from induced change	Batch, medium, and sampling effects can mimic treatment differences

Note: The decision logic is proposed here from the analytical distinctions developed in the preceding sections; modalities should be selected according to the biological question rather than accumulated indiscriminately.

These measurement layers are organized visually in **Figure 1** as an uncertainty-aware route from a defined

perturbation to a multidimensional organoid response record.

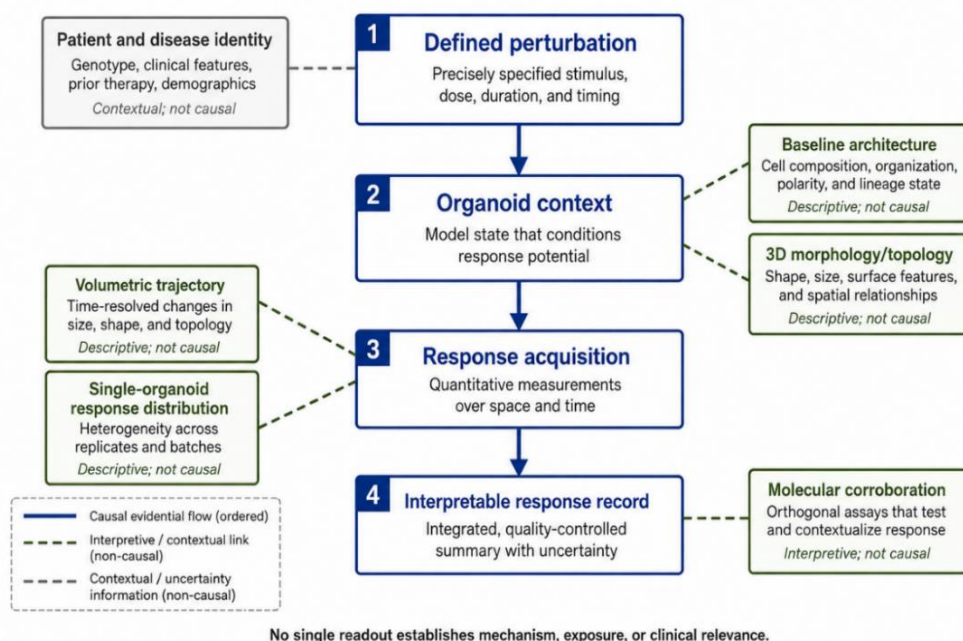


Figure 1. From defined perturbation to a multidimensional organoid response record

Linking chemical structure to organoid phenotype

Organoid phenotypes become more informative when they remain connected to the chemistry that produced them. Morphological profiling already provides high-dimensional representations of cellular perturbation and has become increasingly integrated with deep-learning approaches for drug discovery [18]. Extending that principle to organoids is plausible because organoid images contain architectural information unavailable in conventional monolayers, but the transfer is methodological rather than validated: organoid morphology has its own sources of variability and cannot simply inherit performance estimates from two-dimensional datasets.

Large-scale computational work has shown that chemical structure and phenotypic profiles can contribute complementary information for compound-activity prediction [19]. Within the proposed framework, a natural product should therefore retain both a chemical representation and a response representation. The chemical layer may encode a defined structure, stereochemistry, or characterized mixture; the phenotypic layer records what happened in a particular organoid context. Neither is a substitute for the other.

Applicability domain is critical. Combining chemical fingerprints with morphological information does not guarantee better inference, and model utility can depend on similarity to the training data [20]. Natural products may be especially vulnerable to domain shift because scaffolds, stereochemical complexity, glycosylation, aggregation behavior, or mixture composition can differ from the compounds used to train conventional models.

Chemical structure and perturbational morphology therefore provide complementary but non-equivalent representations, and their value depends on the biological task and applicability domain [18–20]. A chemically similar pair may yield different organoid phenotypes, whereas different structures may converge on a similar morphology through distinct mechanisms. The response map should preserve these discordances because they can identify informative exceptions, trigger mechanistic experiments, and prevent chemical similarity from being mistaken for pharmacological equivalence.

Mechanism inference and therapeutic sensitivity

A response map should support mechanism inference without turning association into causal attribution. Integrated profiling of pancreatic cancer organoids has identified chromatin-accessibility features associated with drug sensitivity [21]. Such relationships can prioritize candidate pathways or state variables, but they do not establish that a measured molecular feature is the causal target of the compound.

Heterogeneity complicates mechanism further. Single-cell-derived colorectal tumor organoid arrays have demonstrated that drug resistance can differ among clonally derived organoid populations [22]. A bulk response may therefore represent selective survival of a subpopulation rather than uniform adaptation. For natural products, this distinction matters because an apparently moderate average effect could conceal strong activity in one state and resistance in another.

Therapeutic sensitivity becomes translationally stronger when functional response is compared with patient

outcome. Recent metastatic colorectal cancer work has linked patient-derived organoid pharmacotyping with treatment response [23]. Even then, the inference remains disease- and regimen-specific and does not convert organoid sensitivity into a universal clinical predictor. The proposed framework therefore grades mechanistic interpretation by evidential convergence. Phenotypic

response supports an effect claim; molecular association supports a mechanism hypothesis; perturbation or rescue can strengthen causal attribution; and patient-linked concordance supports translational relevance. **Table 3** crosswalks these contexts with the methods most appropriate to each question.

Table 3. Context-by-method crosswalk for separating organoid response, mechanism inference, and therapeutic sensitivity

Interpretive context	Most informative method class	Permitted inference	Inference that remains unjustified
Whole-organoid effect	Imaging, growth, viability, volumetric assays	A measured phenotype changed after exposure	The molecular target is known
Response heterogeneity	Single-organoid or clonal analysis	Distinct response states or resistant subpopulations exist	The resistant state is clinically dominant
Molecular association	Transcriptomic, epigenetic, or pathway profiling	A molecular state accompanies sensitivity or resistance	The associated feature is causal
Mechanistic strengthening	Orthogonal perturbation, rescue, target-engagement or convergent assays	A proposed pathway gains causal support	Universal mechanism across tissues and compounds
Translational sensitivity	Patient-linked pharmacotyping	Organoid response corresponds with outcome in a defined context	General clinical predictiveness beyond that context

Note: The crosswalk is a proposed interpretive hierarchy. It deliberately separates assay readout, mechanism evidence, and patient-linked validation so that increasing biological detail is not mistaken for increasing causal certainty.

The organoid response-map translational framework

The proposed organoid response-map framework integrates five evidence bands that should remain connected but analytically separable. First, chemical evidence defines what was tested: molecular identity, composition, provenance, formulation or vehicle, and experimental exposure. Second, biological context records the patient, disease subtype, organoid identity, baseline architecture, and relevant culture conditions. Third, the response phenotype captures time-resolved and heterogeneous structural or functional changes. Fourth, mechanism evidence records molecular associations and the strength of orthogonal causal support. Fifth, human validation records concordance with source tissue, clinically relevant biology, or patient outcome where such evidence exists.

A map should also preserve discordance. If a natural product produces a strong morphological response without molecular corroboration, or a molecular signature without a corresponding functional phenotype, the mismatch is not automatically an analytical failure. It can signal timing differences, assay sensitivity, alternative mechanisms, or context dependence. The proposed framework therefore treats disagreement among layers as information that can

direct the next experiment rather than forcing every modality toward one consensus label.

AI-enabled organoid methods provide a technical basis for handling complex imaging and molecular data, but current literature does not justify treating an integrated algorithm as a clinically validated decision engine [24]. Disease-focused organoid work likewise shows why response interpretation must remain anchored to patient and tumor context rather than abstracted into a compound-only score [25].

The framework therefore uses evidence progression rather than score accumulation. Functional organoid results can contribute to a decision hierarchy only when their intended use and validation level are explicit [26]. Translation from bench to bedside similarly requires staged evaluation rather than direct promotion of an active in vitro signal into a therapeutic claim [27]. A response map is consequently best viewed as an auditable record of converging and conflicting evidence.

Table 4 identifies failure modes that can distort that record and the mitigation logic required before interpretation. **Figure 2** then represents the complete framework as interlocking evidence bands whose continuity is interrupted by explicit boundary conditions.

Table 4. Failure modes that can distort organoid response maps and the corresponding mitigation logic

Failure mode	How interpretation is distorted	Mitigation within the proposed framework	Residual boundary
Ambiguous chemical identity	Phenotype cannot be attributed confidently	Record provenance, composition, preparation, and exposure	Complex mixtures may remain only partially resolved

Baseline organoid mismatch	Treatment change is confused with pre-existing state	Capture baseline architecture, disease context, and identity	Culture may still select particular states
Single-endpoint compression	Distinct biological responses appear equivalent	Retain complementary structural, functional, and molecular dimensions	Added modalities also add noise and missingness
Mechanism over-attribution	Association is presented as causal target evidence	Require orthogonal perturbation, rescue, engagement, or convergence	Some mechanisms remain unresolved
Clinical over-transfer	Ex vivo sensitivity is treated as therapeutic efficacy	Separate organoid activity from human exposure and patient validation	Concordance may remain regimen- and disease-specific

Note: Failure modes and mitigation logic are proposed as safeguards for interpretation; they are not validated scoring rules or regulatory criteria.

Figure 2 shows how the framework maintains continuity across evidence types while making its principal failure boundaries visible.

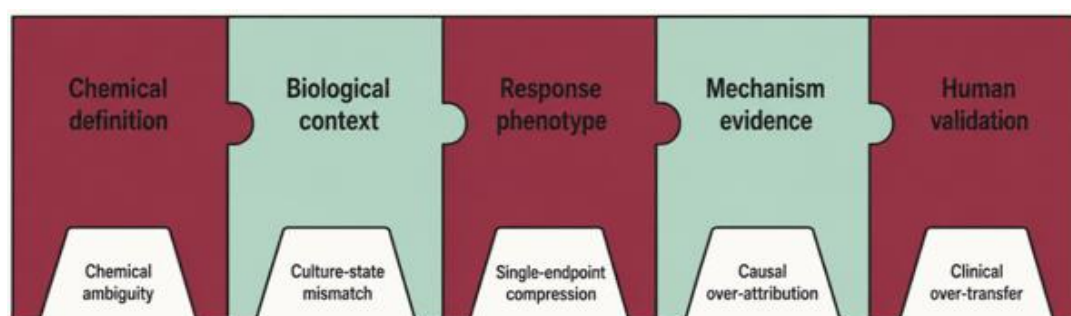


Figure 2. Interlocking evidence bands for an uncertainty-bounded organoid response map

Validation against human tissue and clinical biology

The translational value of an organoid response map ultimately depends on comparison with biology outside the organoid itself. Patient-derived organoids from metastatic gastrointestinal cancers have reproduced clinically relevant treatment-response patterns in defined settings [28]. Such studies establish that organoid pharmacology can correspond with human response, but they do not establish universal accuracy across diseases, regimens, sampling procedures, or assay platforms.

Metastatic colorectal cancer studies further show that predictive performance can vary by treatment context [29]. This is important for natural products because even a reproducible organoid phenotype cannot substitute for evidence that the active chemical species reaches the relevant human tissue at an appropriate exposure. Pharmacokinetics, metabolism, protein binding, formulation, and tolerability remain outside the organoid unless explicitly modeled.

Prospective pancreatic cancer work has also reported correlations between organoid sensitivity and therapeutic response [30]. The strongest defensible conclusion is therefore conditional: organoid-clinical response associations have been demonstrated in defined gastrointestinal and pancreatic cancer settings, but their performance remains disease-, treatment-, and study-design-dependent [28–30].

For the proposed framework, validation should proceed in layers: source-tissue fidelity, reproducibility across independent organoid preparations, external replication, pharmacologically credible exposure, and patient-linked outcome when a clinical claim is intended. Discordance should not automatically be treated as model failure; it may identify missing host metabolism, immune effects, stromal interactions, treatment scheduling, or sampling bias. Prospective testing should therefore be designed not only to confirm concordance but also to characterize when and why the response map fails.

Scalability, standardization, and boundary conditions

A translational map is useful only if its measurements can be reproduced at a scale compatible with screening. High-throughput tumor-organoid workflows increasingly combine miniaturization, automation, microfluidics, and standardized analysis, but greater throughput can trade biological resolution for operational simplicity [31]. Natural-product programs add further pressure because fraction libraries, dose series, combination experiments, and repeated imaging can expand experimental dimensionality rapidly.

Standardization must begin before measurement. Detailed protocols for establishing patient-derived cancer organoids show that tissue processing, culture conditions, assay timing, and drug-screen execution can be systematically controlled [32]. Standardization, however, should not be

confused with imposing one universal protocol. Tissue-specific requirements may be biologically necessary, and an over-standardized system could suppress the very heterogeneity the model is intended to preserve.

Culture medium is a particularly important boundary condition because it can alter apparent therapeutic-response behavior in gastrointestinal organoids [33]. Medium, matrix, passage, seeding density, organoid size, and baseline growth state should therefore travel with response data as experimental context rather than being relegated to technical footnotes.

Standardization should likewise distinguish invariant metadata from adaptable biology. Chemical identity, dose, exposure duration, passage, acquisition settings, and analysis provenance should be consistently recorded, whereas tissue-specific media or differentiation conditions may legitimately differ when required to preserve the intended biology. This distinction prevents reproducibility from becoming an argument for biologically inappropriate uniformity across organoid systems.

Scalability should consequently be judged by reproducibility of biologically meaningful measurements, not by wells processed per day alone. A scalable response-map platform would need predefined quality control, chemical and biological metadata, batch tracking, image-analysis validation, missing-data handling, and explicit applicability domains. Cross-site studies should test whether the same perturbation produces comparable response patterns under harmonized procedures before any response-map signature is treated as transferable.

Limitations

Organoids remain selective reconstructions of tissue biology. In lung cancer, establishment of pure tumor organoids can be compromised by overgrowth of nonmalignant epithelium, directly demonstrating that an apparently successful culture may misrepresent the intended disease material [34]. Identity and purity therefore require verification before pharmacological response is interpreted.

Reproducibility also depends on tissue acquisition, matrix, media, growth-factor conditions, culture duration, and laboratory practice. Work focused on primary liver-cancer organoids illustrates how these variables can constrain cross-study comparability [35]. Comparable issues are likely to differ in magnitude across tissues rather than obey one universal correction.

The proposed framework has additional limitations. Most direct clinical-validation evidence comes from oncology, and direct natural-product/PDO studies remain sparse. Many candidate natural products undergo metabolism or distribution processes absent from isolated organoids. Immune, neural, stromal, endocrine, vascular, and

microbiome interactions may be incomplete or missing. Multimodal measurements can also increase dimensionality faster than biological interpretability. Finally, response maps may reveal correlations that are reproducible yet mechanistically wrong. Their value therefore depends on explicit uncertainty, orthogonal validation, and willingness to reject a compelling map when human pharmacology contradicts it.

CONCLUSION

Organoid response maps offer a way to preserve information that is commonly lost between natural-product screening and therapeutic interpretation. Their distinctive value lies not in producing another composite score, but in keeping chemical identity, patient and disease context, three-dimensional phenotype, response heterogeneity, molecular evidence, and human validation connected while preventing one layer from substituting for another.

The framework proposed here is deliberately evidential rather than predictive. Organoid activity does not establish human exposure; morphological change does not establish mechanism; molecular association does not prove causality; and patient-linked concordance in one disease does not guarantee transferability elsewhere. Natural products intensify these constraints because chemical complexity, metabolism, formulation, and achievable exposure can remain uncertain even when organoid responses are reproducible.

A useful response map should therefore make confidence and failure boundaries as visible as positive signals. Its future value will depend on chemically controlled perturbations, reproducible organoid models, multimodal but question-driven measurements, orthogonal mechanism testing, and prospective validation against human tissue and clinical biology.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

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