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MODERN METHODS OF PHARMACOLOGICAL SCREENING IN EARLY DRUG DISCOVERY

Johannes M. Weber
Department of Experimental Pharmacology,
Berlin Institute of Biomedical Sciences, Germany
johannes.weber@bibs-research.de

Abstract

Early drug discovery increasingly depends on integrated pharmacological screening systems that combine throughput, mechanistic confidence, chemical diversity, human relevance and early developability assessment. This structured review evaluates modern screening methods used to identify and prioritize bioactive compounds before hit-to-lead optimization. The analysis covers high-throughput and quantitative high-throughput screening (HTS/qHTS), target-based and phenotypic strategies, high-content imaging, fragment-based and biophysical screening, artificial-intelligence-assisted virtual screening, secondary pharmacology, early ADME/toxicity assessment, organoids and microphysiological systems. Fifteen international peer-reviewed sources were synthesized within an IMRAD framework. The reviewed evidence shows that scalable biochemical assays remain highly effective for well-validated targets, whereas phenotypic and high-content approaches provide richer information on pathway and cellular responses. Fragment-based screening can efficiently explore chemical space when sensitive biophysical confirmation is available. Artificial intelligence can prioritize very large molecular libraries and support molecular design, but its predictions require prospective experimental validation and careful control of data bias. Organoid and organ-on-chip technologies increase physiological relevance and may improve translational decision-making, although throughput, reproducibility and standardization remain limiting factors. The most robust strategy is therefore a tiered screening cascade integrating assay qualification, orthogonal confirmation, counter-screening, target engagement, selectivity, safety, pharmacokinetics and increasingly human-relevant models. Modern pharmacological screening should be viewed as a decision system rather than a single assay, with evidence quality and reproducibility treated as core pharmacological endpoints.

Keywords: drug discovery; pharmacological screening; high-throughput screening; phenotypic screening; high-content screening; artificial intelligence; organoids; microphysiological systems; ADME/Tox.

1. INTRODUCTION

Pharmacological screening is the experimental and computational process by which chemical or biological entities are evaluated for activity, selectivity, mechanism and developability. In modern drug discovery, screening no longer refers only to testing thousands of compounds against a single molecular target. It now includes a connected set

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of assays and predictive models that begins with target or phenotype definition and extends through hit confirmation, counter-screening, secondary pharmacology and early safety evaluation. The shift reflects a central problem in pharmaceutical research: a compound can be potent in a primary assay and still fail because the assay does not represent disease biology, because the signal is artifactual, because the molecule lacks selectivity, or because its physicochemical and toxicological properties are unsuitable for development (1,2).

Classical high-throughput screening (HTS) made it possible to test large chemical libraries using miniaturized biochemical or cellular assays. Quantitative HTS further improved this paradigm by testing compounds across concentration series rather than at a single concentration, thereby generating concentration-response information during the primary screen and improving the discrimination of active compounds from assay noise (1). At the same time, analyses of approved medicines emphasized the continuing value of phenotypic discovery, particularly when disease-relevant cellular responses cannot be reduced to a single validated target (2).

Current screening technology therefore spans multiple levels of biological organization. Biochemical assays can directly quantify target engagement or enzyme modulation. Cell-based HTS and image-based HCS capture pathway and morphological responses. Phenotypic screens can uncover active compounds without prior knowledge of a molecular target, while computational methods can prioritize candidates from libraries that are far too large to test experimentally. More recent platforms, including organoids and microphysiological systems, aim to preserve tissue architecture, multicellular interactions, flow and organ-specific functions that are absent from conventional two-dimensional culture (3-6).

The rapid expansion of machine learning has added a new layer to pharmacological screening. Algorithms can support virtual screening, molecular generation, image analysis, target identification and toxicity prediction. However, computational ranking does not replace pharmacological validation. Prospective wet-laboratory confirmation, orthogonal assays and careful assessment of model domain remain necessary because model performance is determined by the quality, representativeness and experimental provenance of the training data (7-11).

This article aims to synthesize the major modern methods of pharmacological screening used in early drug discovery, compare their scientific strengths and limitations, and propose an integrated screening cascade that balances throughput, mechanistic interpretability, safety and human relevance.

Another important development is the convergence of pharmacological screening with biophysical and structural methods. Surface plasmon resonance, differential scanning fluorimetry, nuclear magnetic resonance spectroscopy, native mass spectrometry and related approaches can directly measure ligand binding or changes in target stability. These technologies are especially valuable in fragment-based drug discovery, in which low-molecular-weight compounds often bind with modest affinity but high ligand efficiency. Because fragment signals are weak and prone to false positives, orthogonal confirmation by more than one method is considered essential (15).

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At the same time, screening programs are becoming more automated and information-rich. Robotic liquid handling, acoustic dispensing, miniaturized plates, automated microscopy and integrated laboratory information systems enable large experiments with tighter control of timing and reagent use. However, automation does not eliminate biological or analytical uncertainty. Assay drift, plate-edge effects, batch variation, compound precipitation and detection interference can generate systematic errors at scale. Therefore, modern screening requires quality metrics and control strategies that are planned before library testing begins rather than applied only after suspicious hits are observed.

A final trend is the movement of pharmacokinetic and safety information into the earliest stages of discovery. Instead of selecting compounds solely on potency and addressing absorption, metabolism or off-target liabilities later, contemporary programs increasingly use multiparameter optimization. Potency, selectivity, solubility, permeability, metabolic stability and safety signals are considered together so that medicinal chemistry resources are focused on compounds with a realistic path toward development (7,8).

2. MATERIALS AND METHODS

This work was designed as a structured narrative review using an IMRAD format. International peer-reviewed publications were selected to represent both foundational screening technologies and recent methodological developments. The final evidence set comprised 15 sources published from 2006 through 2026, including methodological articles, reviews and perspectives in pharmacology, drug discovery, chemical biology, microphysiological systems and artificial intelligence.

Sources were prioritized when they addressed one or more of the following domains: quantitative or high-throughput screening, phenotypic and image-based high-content screening, machine-learning or structure-based virtual screening, secondary pharmacology, predictive toxicology, three-dimensional organoids, organ-on-chip or MPS technologies. Emphasis was placed on publications that discussed assay performance, translational relevance, hit confirmation, selectivity, reproducibility or practical integration into discovery pipelines (1-15).

Information was extracted into a comparative framework with four principal dimensions: (i) throughput and scalability; (ii) mechanistic interpretability; (iii) biological and translational relevance; and (iv) major sources of false-positive, false-negative or non-translatable findings. The synthesis did not pool effect sizes because the included sources evaluated heterogeneous technologies rather than a common clinical or experimental endpoint. Accordingly, the Results section presents a qualitative evidence synthesis rather than a meta-analysis.

The review was organized around a screening-cascade concept. Evidence was grouped into primary hit-finding methods, confirmatory and mechanistic methods, developability and safety screens, and human-relevant translational models. Particular attention was given to whether each method generates direct target information, phenotypic information or

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predictive computational evidence, because these evidence types answer different pharmacological questions and are not interchangeable.

No pooled effect size or meta-analytic estimate was calculated because the included publications cover heterogeneous technologies, assay formats and decision endpoints rather than a common clinical outcome. Comparative statements in the Results section therefore represent qualitative synthesis of published methodological evidence. Figures are conceptual diagrams prepared for this review and do not represent experimentally measured superiority of one platform over another.

3. RESULTS

3.1. High-throughput, quantitative and target-based screening

HTS remains the core discovery technology when a validated molecular target and scalable assay are available. Biochemical formats are especially useful for enzymes, receptors and protein-protein interactions because they offer direct mechanistic readouts and can be miniaturized for large chemical libraries. Their main limitation is reductionism: activity against an isolated target does not guarantee target engagement, pathway modulation or a therapeutically useful response in intact cells.

qHTS addresses an important weakness of single-concentration primary screens by generating concentration-response relationships at scale. This helps separate reproducible pharmacology from marginal signals and allows compounds to be classified according to response quality (1). Modern screening cascades frequently combine a sensitive primary assay with orthogonal assays based on a different detection principle. Such confirmation is essential for excluding fluorescence interference, aggregation, redox cycling, nonspecific reactivity and other assay-specific artifacts.

Assay qualification is a prerequisite for both HTS and qHTS. Positive and negative controls should define an adequate signal window, and variability should be monitored across plates, days and reagent lots. Metrics such as the Z-prime factor are commonly used to describe separation between control distributions, but no single statistic can establish biological validity. A technically excellent assay can still be poorly predictive if the target construct, substrate concentration, cell state or detection endpoint does not represent the intended pharmacology.

Miniaturization increases throughput by reducing reagent and compound consumption, but smaller assay volumes can magnify evaporation, adsorption and dispensing errors. For this reason, acoustic dispensing and automated liquid handling are frequently paired with plate randomization, reference compounds and spatial quality-control analysis. These operational elements are not merely engineering details: they directly affect apparent potency, reproducibility and the false-positive rate of a pharmacological screen.

3.2. Phenotypic and high-content screening

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Phenotypic screening identifies compounds by their ability to alter a disease-relevant cellular or organismal phenotype rather than by predefined activity at a single target. Historical analyses have shown that phenotypic strategies contributed substantially to first-in-class small-molecule discovery, supporting their value when disease biology is incompletely understood (2). The modern form of phenotypic screening increasingly incorporates genetically defined cell models, patient-derived cells, three-dimensional cultures and multi-omic or imaging readouts (6).

Image-based HCS expands a simple viability or reporter assay into a multiparametric description of cellular state. Automated microscopy can quantify morphology, localization, organelle features, cell-cycle patterns and population heterogeneity. Machine-learning methods can then convert high-dimensional images into phenotypic fingerprints that support mechanism-of-action inference or compound clustering (3,4). The main challenges are assay complexity, batch effects, segmentation errors, data dimensionality and the risk that a visually rich phenotype is not causally linked to clinical benefit.

Cell-painting and related morphological profiling strategies illustrate how image-based screening can function as a broad pharmacological fingerprint rather than a single-endpoint assay. Multiparametric features can be used to group compounds with similar biological effects, identify unexpected pathway activity and select mechanistically diverse representatives for follow-up. The principal challenge is interpretation: high-dimensional similarity may indicate a shared mechanism, a shared stress response or simply a technical confound, so mechanistic hypotheses still require direct experiments (3,4).

Phenotypic screening also creates a target-identification problem. Once a compound produces a reproducible disease-relevant phenotype, researchers may use resistant mutants, CRISPR perturbation, affinity-based proteomics, transcriptomics, metabolomics or chemical-genetic interaction data to determine the causal target or pathway. This target-deconvolution phase can be resource intensive, but it can reveal previously unrecognized disease biology and may preserve mechanisms that would have been missed by target-first discovery (2,5).

Table 1. Comparison of major pharmacological screening approaches in early drug discovery

Method	Throughput	Interpretability	Biological relevance	Principal strength	Key limitation
Biochemical HTS / qHTS	Very high	High for defined target	Low-moderate	Fast, scalable, direct target pharmacology	Reductionist biology; assay artifacts
Cell-based HTS	High	Moderate-high	Moderate	Pathway context; permeability implicit	Cell-line dependence; indirect mechanism

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Phenotypic screening	Moderate-high	Initially low-moderate	Moderate-high	Disease-relevant responses; target-agnostic discovery	Target deconvolution; complex hit validation
High-content imaging	Moderate	Moderate	High	Multiparametric phenotypes; heterogeneity	Data complexity; imaging and analysis burden
AI / virtual screening	Extremely high in silico	Model-dependent	Model-dependent	Prioritizes huge chemical spaces; reduces wet-lab burden	Dataset bias; scoring error; requires prospective validation
Organoids	Low-moderate	Moderate	High	Human 3D architecture and multicellular biology	Variability; cost; standardization and throughput
Organ-on-chip / MPS	Low	Moderate-high	Very high	Flow, tissue interfaces, organ-level functions	Engineering complexity; limited harmonization

3.3. Artificial intelligence and virtual screening

Computational screening has moved from a supporting role to a major front-end strategy for reducing the experimental search space. Structure-based virtual screening ranks molecules according to predicted complementarity with a target binding site, whereas ligand-based machine-learning models infer activity from known chemical-biological relationships. Generative models can propose new molecular structures subject to potency or property constraints (7,11).

Recent AI-accelerated virtual screening platforms demonstrate that very large chemical spaces can be searched and experimentally testable hits can be obtained, but these studies also reinforce the need for prospective validation and structural confirmation (8). In practice, the highest value of AI is achieved when predictions are embedded in an iterative design-make-test-learn cycle. Model uncertainty, applicability domain and training-set bias

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should be monitored explicitly rather than treating a prediction score as an experimental endpoint.

Virtual screening can be divided broadly into ligand-based and structure-based approaches. Ligand-based models learn relationships between molecular descriptors or learned chemical representations and known activity, whereas structure-based approaches use target structures to estimate molecular complementarity and binding poses. Deep learning has expanded both approaches through graph neural networks, protein-language models and learned scoring functions, while generative models can propose new structures under multi-objective constraints (6,11,12).

The central limitation of AI-assisted screening is that predictive performance within a retrospective benchmark does not guarantee prospective pharmacological success. Chemical datasets can contain scaffold imbalance, assay artifacts, inconsistent activity labels and hidden duplication. Models can therefore learn correlations that do not generalize to new chemical series. Prospective experimental testing, temporal validation and chemically realistic train-test splits are necessary when AI scores are used to select compounds for synthesis or purchase (6,11).

AI is increasingly valuable after rather than only before the wet-laboratory screen. Machine-learning models can integrate concentration-response data, imaging phenotypes, physicochemical properties, off-target panels and ADME/Tox measurements to support compound ranking. This closed-loop use of experimental evidence is more defensible than treating an in silico score as an independent proof of efficacy because new data continuously constrain and update the model.

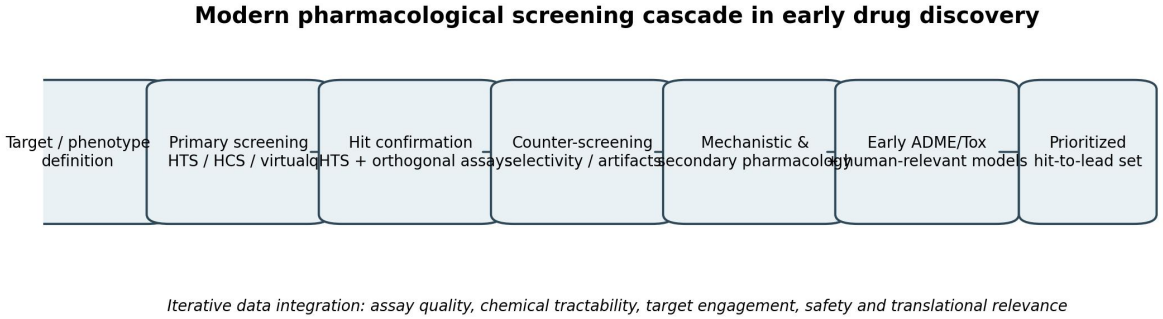


Figure 1. Integrated modern screening cascade from biological question to a prioritized hit-to-lead set.

3.4. Fragment-based and biophysical screening

Fragment-based drug discovery (FBDD) screens relatively small libraries of low-molecular-weight compounds and searches for weak but efficient interactions with a target.

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Because fragments occupy chemical space differently from conventional lead-like molecules, a library of hundreds or a few thousand fragments can provide broad structural diversity. The approach is particularly useful for difficult targets when high-affinity ligands are not already known (15).

Fragment hits are commonly detected by sensitive biophysical techniques such as nuclear magnetic resonance spectroscopy, surface plasmon resonance, thermal-shift methods or X-ray crystallography. The low affinities typical of fragments make rigorous confirmation essential. Aggregation, nonspecific binding and unusually high compound concentrations can produce misleading signals, so orthogonal methods and direct structural evidence are valuable whenever feasible (15).

FBDD differs from conventional HTS not only in library size but also in the downstream medicinal-chemistry strategy. A validated fragment is usually grown, linked or merged to improve affinity while preserving favorable ligand efficiency and physicochemical properties. The method therefore connects screening tightly with structural biology and iterative chemistry. It is best viewed as a complementary hit-generation strategy rather than a replacement for HTS or phenotypic screening.

3.5. Secondary pharmacology and early safety screening

Primary potency is only one dimension of hit quality. Secondary pharmacology evaluates activity at unintended targets that may explain adverse or beneficial effects. Industry practice increasingly applies panels of receptors, ion channels, enzymes and transporters before advanced development, with interpretation based on exposure margins and target-specific safety knowledge (9). This step is particularly important when a potent series also interacts with pharmacologically sensitive targets such as cardiac ion channels or central nervous system receptors.

Computational and experimental toxicity prediction is likewise moving earlier in discovery. Data-driven approaches can estimate liabilities such as hepatotoxicity, cardiotoxicity, mutagenicity or general cytotoxicity before extensive animal studies, but the diversity of toxicity mechanisms limits universal model performance (10). Therefore, predictive toxicology is most useful as a prioritization tool followed by mechanistically appropriate confirmatory assays.

3.6. Organoids and microphysiological systems

Human organoids and MPS technologies represent a major attempt to close the gap between scalable screening and human physiology. Organoids can reproduce aspects of tissue organization and cell diversity, while organ-on-chip systems add controlled flow, tissue interfaces, mechanical forces and interconnected compartments. These features are relevant for pharmacodynamic responses as well as absorption, distribution, metabolism and toxicity (5,12-15).

Reviews published in 2025-2026 emphasize both the opportunity and the unresolved technical barriers. Organoid assays are becoming compatible with screening and machine-

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learning-assisted image analysis, but inter-batch variability, maturation state, matrix dependence and limited standardization remain important. MPS platforms can model gut, liver, kidney and other organ functions, yet widespread routine use requires reproducibility, reference compounds, interoperable readouts and clearer links between in vitro exposure and human dose (13-15).

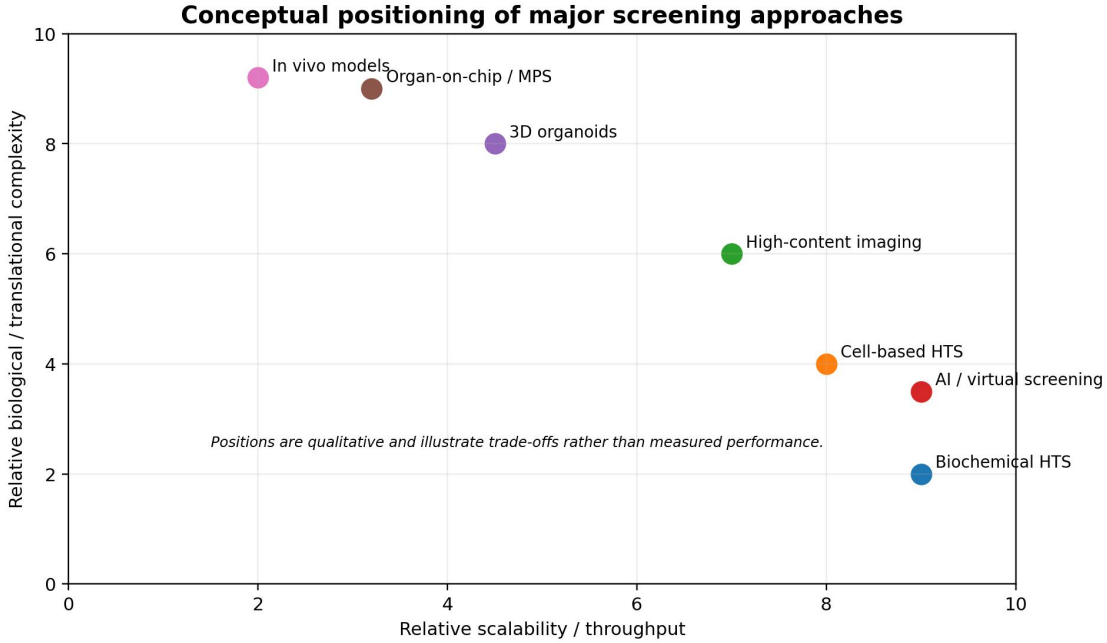


Figure 2. Conceptual trade-off between screening scalability and biological complexity. Positions are qualitative, not measured performance values.

3.7. Automation, miniaturization and integrated data quality

Modern screening programs rely on automation to maintain throughput and reproducibility across thousands to millions of experimental operations. Robotic plate handling, automated incubators, acoustic compound transfer and real-time data capture reduce manual variability and make complex schedules possible. Nevertheless, automated error can propagate more efficiently than manual error, which makes control placement, plate maps, instrument calibration and audit trails essential components of pharmacological quality.

Miniaturization into 384- and 1536-well formats can substantially reduce reagent consumption and increase throughput. The pharmacological benefit is greatest when miniaturization preserves the same biology as the larger assay. Changes in surface-to-volume ratio, cell density, gas exchange and mixing can alter apparent responses, so the miniaturized format should be re-qualified rather than assumed to be equivalent to its parent assay.

Data integration is becoming a separate screening capability. A single compound may generate biochemical potency, cellular efficacy, morphology, selectivity, physicochemical,

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metabolic and toxicity measurements. Decision systems that retain the provenance and uncertainty of each measurement are preferable to a single composite score whose assumptions are hidden. Multiparameter ranking should therefore be transparent, revisable and linked to the biological objective of the project.

Table 2. Recommended modern screening cascade and decision criteria

Stage	Representative readout	Decision question
1. Assay qualification	Z-prime / signal window, controls, reproducibility	Is the assay stable enough to screen?
2. Primary screen	Activity threshold, concentration-response where feasible	Which compounds show reproducible pharmacological activity?
3. Orthogonal confirmation	Different detection principle or assay format	Is the signal independent of the primary assay technology?
4. Counter-screening	Interference, aggregation, nonspecific toxicity, related targets	Is the activity specific and chemically credible?
5. Mechanistic profiling	Target engagement, pathway biomarkers, phenotypic fingerprints	Does the compound act through a plausible mechanism?
6. Secondary pharmacology	Off-target panel and selectivity margins	Are important unintended pharmacological liabilities present?
7. Early ADME/Tox	Solubility, permeability, metabolism, safety alerts	Is the hit developable enough to justify optimization?
8. Human-relevant validation	Organoids, MPS, patient-derived models when appropriate	Does activity persist in a more translational system?

Table 3. Key quality controls and failure modes in modern pharmacological screening

Control / metric	Primary purpose	Typical failure detected	Practical response
Positive and negative controls	Define assay window and biological	Reagent failure, loss of dynamic range	Re-qualify assay; investigate reagent

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	responsiveness		or cell quality
Reference compound	Track expected pharmacology across runs	Potency drift, lot-to-lot variation	Trend potency and efficacy; set acceptance ranges
Orthogonal assay	Confirm activity using a different detection principle	Reporter interference, technology-specific artifacts	Advance only cross-confirmed pharmacology
Counter-screen	Test interference or undesired related activity	Aggregation, autofluorescence, nonspecific cytotoxicity	Remove artifacts or redesign chemical series
Replicate / concentration-response	Assess reproducibility and pharmacological shape	Single-point noise, unstable effects	Require reproducible concentration-dependent activity
Spatial plate QC	Detect location-dependent bias	Edge effects, dispensing gradients, evaporation	Randomize positions; correct process conditions
Prospective model validation	Test computational predictions on unseen compounds	Dataset leakage, overfitting, domain failure	Retrain or restrict model applicability domain

4. DISCUSSION

The reviewed evidence supports a central conclusion: modern pharmacological screening is most effective when viewed as a cascade rather than a single assay. Each method answers a different question. Target-based HTS asks whether a compound modulates a defined molecular entity; phenotypic screening asks whether it changes a biologically meaningful state; HCS asks how the cellular state changes across multiple features; virtual screening asks which compounds deserve experimental testing; secondary pharmacology asks what else the compound may do; and organoid or MPS assays ask whether activity remains detectable in a system that more closely resembles human tissue.

This complementarity also explains why throughput alone is an incomplete measure of screening quality. A highly scalable assay can efficiently produce large numbers of hits that later disappear when tested in a relevant biological context. Conversely, a complex organoid model can be biologically informative but unsuitable for primary screening

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because of cost, variability and limited plate-scale throughput. An efficient workflow therefore uses simple, robust assays to reduce the chemical space and reserves more complex models for confirmation and prioritization.

AI and machine learning should be interpreted within the same framework. Their practical advantage is not that they eliminate experiments, but that they can increase the information gained per experiment. Structure prediction, virtual screening, image analysis and toxicity models can guide compound selection and reveal patterns that are difficult to detect manually. Nevertheless, prospective validation remains essential, particularly when models are applied to new target classes or chemical regions not represented in training data (7,8,10,11).

Assay quality management remains a major determinant of success. False positives can arise from reporter interference, colloidal aggregation, cytotoxicity, reactive chemistry or systematic imaging errors. False negatives can result from poor cell permeability, unstable reagents, inappropriate assay timing or insufficient biological context. Orthogonal confirmation and counter-screening are therefore not administrative steps but core pharmacological experiments that test whether an observed signal is reproducible, target-relevant and chemically interpretable.

A second implication is that hit rate should not be confused with screen quality. A high hit rate can indicate rich pharmacology, but it can also reflect nonspecific compounds, an overly permissive threshold or a biologically unstable assay. Conversely, a low hit rate may be appropriate for a difficult target if the detected compounds are reproducible, selective and chemically tractable. Screening performance is therefore better evaluated by the quality of confirmed, actionable chemical matter than by the number of primary actives.

The same principle applies to model complexity. More physiological models are not automatically better for every decision. Complex organoids and MPS platforms may offer high human relevance but can reduce throughput, increase variability and make causal interpretation difficult. A rational cascade uses simple models to answer simple mechanistic questions and reserves complex models for questions that genuinely require multicellular organization, tissue interfaces, flow or human-specific metabolism (9,10,13,14).

Fragment-based screening adds another form of complementarity. It is particularly valuable when structural information is available and when conventional libraries do not produce high-quality hits. However, weak fragment affinity means that confirmation standards must be unusually strict. The requirement for orthogonal biophysics and structural validation illustrates a general rule of early drug discovery: the weaker or more indirect the initial signal, the stronger the confirmation strategy should be (15).

From an organizational perspective, modern screening is increasingly multidisciplinary. Assay biologists, pharmacologists, computational scientists, medicinal chemists, DMPK scientists, toxicologists and automation engineers contribute evidence to the same decision. The value of a screening platform therefore depends not only on instrumentation but also on how rapidly contradictory evidence can be recognized and reconciled. Integrated project governance can prevent optimization around a single favorable endpoint while liabilities accumulate elsewhere.

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For future research, three priorities are particularly important. First, prospective benchmarking should compare emerging AI and human-relevant systems against clearly defined decision outcomes rather than retrospective datasets alone. Second, standard reference compounds and interoperable data formats are needed to improve cross-laboratory reproducibility of organoid and MPS screens. Third, screening workflows should report uncertainty and failure modes explicitly, allowing negative evidence to guide compound selection rather than being hidden by composite ranking algorithms.

The growing adoption of human-relevant models has important implications for early discovery. Organoids and MPS are particularly promising for mechanisms that depend on tissue architecture, metabolism, intercellular signaling or barrier function. Their strongest near-term use may be as a later screening tier for a smaller number of prioritized compounds rather than as universal replacements for conventional HTS. Standardization, automation, reference controls and quantitative exposure modeling will determine how rapidly these systems become routine components of regulated drug development (12-15).

For OAK-oriented scientific reporting, it is also important to separate conceptual comparisons from empirical measurements. The figures in this review summarize the relative roles and trade-offs of screening technologies; they do not claim universal numerical performance. Actual screening campaigns should report assay-specific validation parameters, chemical library composition, hit-selection rules, replicate strategy, concentration ranges, confirmatory methods and predefined criteria for progression.

5. CONCLUSION

Modern pharmacological screening in early drug discovery has evolved from isolated high-throughput assays into integrated, data-rich decision systems. qHTS improves quantitative characterization of primary activity; phenotypic and high-content approaches capture pathway and cellular complexity; AI and virtual screening expand searchable chemical space; secondary pharmacology and predictive toxicology expose early liabilities; and organoids and MPS increase human biological relevance.

The most defensible strategy is a tiered cascade in which screening methods are selected according to the scientific question and linked by orthogonal confirmation. Robust assay validation, artifact control, selectivity profiling and early developability assessment should occur before substantial resources are committed to lead optimization. Future progress will depend less on any single technology than on the disciplined integration of experimental pharmacology, computational prediction and human-relevant model systems.

Future progress is likely to come from closed-loop systems in which computation, automated experimentation and human-relevant biology continuously inform one another. AI can prioritize compounds and interpret high-dimensional data, while experiments provide the prospective evidence required to recalibrate the models. In this framework, the purpose of screening is not simply to find active molecules but to reduce uncertainty efficiently until a compound has sufficient mechanistic, pharmacological and developability evidence to justify further optimization.

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