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A Promising Mechanism Becomes a Medicine Only When Exposure, Biomarkers, and Clinical Context Converge

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ABSTRACT

Compelling target biology is often treated as the beginning of a translational trajectory, yet mechanistic plausibility does not establish that a therapeutic perturbation reaches the relevant tissue, engages its target under biologically realistic conditions, produces an interpretable pharmacodynamic response, or acts in patients whose disease state remains dependent on that mechanism. This Translational Perspective argues that these evidence layers should be treated as distinct but connected tests rather than interchangeable indicators of progress. Target engagement without adequate site-of-action exposure may be pharmacologically uninformative; a responsive biomarker may lack decision utility if its context of use is undefined; and biomarker-guided selection may fail when disease biology, treatment history, or patient heterogeneity alters the mechanism–response relationship. We therefore develop a proposed mechanism-to-medicine architecture in which translational confidence depends on conditional convergence across target validity, engagement, tissue exposure, pharmacodynamic evidence, biomarker qualification, and clinical context. Discordance is treated as diagnostic information that should trigger reassessment rather than be averaged away. The framework is explicitly non-numeric and does not claim prospective validation. Its purpose is to clarify what has actually been tested, what remains inferential, and when apparently promising programmes require additional evidence rather than stronger mechanistic storytelling.

Keywords: Target engagement, Tissue pharmacokinetics, Pharmacodynamic biomarkers, Biomarker qualification, Patient selection, Translational pharmacology

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INTRODUCTION

Drug development frequently begins with a persuasive mechanistic proposition but fails when evidence collected at later translational levels does not behave as though the same proposition remains true. Portfolio experience has therefore moved beyond target plausibility alone toward coordinated attention to target biology, tissue exposure, safety, patient selection, and other programme-level determinants [1]. A complementary problem is predictive validity: a model can be mechanistically appealing yet still fail to predict the human state for which it is being used [2].

The central argument of this Perspective is that a mechanism becomes therapeutically interpretable only when several questions are kept analytically separate. Is the intended target relevant to the disease? Is the drug engaging that target in the relevant biological environment? Does sufficient unbound or otherwise pharmacologically relevant exposure occur at the site of action? Does target perturbation produce a measurable downstream

response? Is that response a fit-for-purpose biomarker for the intended development decision? Finally, does the mechanism operate in the patients, disease states, treatment histories, and temporal windows actually being studied? These are not successive labels for the same evidence. They are potential points of convergence—and potential sites of falsification.

Mechanistic promise and translational attrition

Historical analyses show that therapeutic mechanisms and indications differ substantially in their development effectiveness, making mechanistic selection itself a consequential source of attrition [3]. Exposure provides a separate constraint. A compound can exhibit attractive potency and selectivity in experimental systems while failing to create the required pharmacological state in the target tissue; tissue exposure and tissue selectivity have therefore been proposed as underweighted contributors to clinical failure [4]. This distinction matters because failure to observe clinical efficacy after inadequate exposure does not constitute a clean falsification of the underlying biological mechanism.

Human genetics can strengthen the prior plausibility of a target, but its role is probabilistic rather than dispositive. Large-scale analyses show that genetic support is associated with increased probabilities of clinical success [5]. Genetic epidemiology also demonstrates why a biomarker associated with disease is not automatically equivalent to a therapeutically actionable target: pleiotropy, the biological consequences of lifelong genetic perturbation, and differences between biomarker modulation and target perturbation can change the interpretation [6]. Direct examples nevertheless exist in which human genetic observations have provided unusually strong routes from target discovery to medicines [7]. Reanalysis of historical pipelines further shows that the magnitude of the genetics–success association depends on how genetic support and target–indication pairs are defined [8]. Taken together, these studies support a shift in prior confidence rather than a deterministic rule that genetically supported mechanisms will succeed [5, 7, 8].

Translational learning must also operate in the opposite direction. Quantitative clinical pharmacology can use human observations to revise assumptions made at the bench rather than treating clinical discordance as an endpoint disconnected from mechanism [9]. Linking genetics with real-world phenotypes can similarly broaden target validation, while retaining the limitations inherent to observational phenotype definition and population structure [10]. Mechanistic promise is therefore strongest when it remains revisable. A mechanism protected from contradictory exposure, engagement, biomarker, or patient evidence is not becoming more credible; it is becoming less falsifiable.

Target engagement

Target engagement establishes whether a molecule physically perturbs its intended target under a defined biological condition, but the measurement is highly context dependent. Live-cell kinase profiling has shown that apparent biochemical potency can diverge from intracellular engagement because the cellular environment—including ATP concentration—changes effective binding conditions [11]. Consequently, biochemical activity should not be treated as interchangeable with engagement in intact cells, tissues, or patients.

Engagement must also be specific enough to support the proposed causal interpretation. Chemical-proteomic deconvolution of histone deacetylase inhibitors revealed recurrent interactions with targets outside their conventional annotations, illustrating how an apparently well-characterized pharmacological class can retain unexpected target liabilities [12]. Such findings do not establish that every off-target interaction is harmful, but they do weaken any interpretation that assumes the nominal target is the sole mediator of downstream effects.

Even confirmed engagement remains one evidentiary layer. CeTEAM illustrates that cellular target engagement and downstream phenotypic responses can be measured together while remaining analytically distinguishable [13]. Targeted protein degraders make the same point from a different direction: degradation, neosubstrate recruitment, duration of protein loss, and downstream recovery cannot always be represented adequately by occupancy alone [14]. The relevant question is therefore not simply whether engagement occurred, but whether the measured engagement corresponds to the pharmacological process proposed to connect exposure with biological response.

Tissue exposure

Clinical interpretation becomes fragile when systemic pharmacokinetics are used as a surrogate for exposure at the biological site of action without evidence that the surrogate is valid. In neuroscience development, positron emission tomography can provide direct human information about brain distribution and target occupancy for

suitable tracers and targets [15]. More broadly, tissue pharmacokinetic–pharmacodynamic analyses demonstrate that plasma, total tissue, and pharmacologically relevant local concentrations can diverge across drugs, tissues, and modalities [16].

The problem is spatial as well as quantitative. High-resolution neuropharmacokinetic work has shown regional and subregional differences in unbound antipsychotic exposure across the brain, cautioning against the assumption that a single global tissue concentration necessarily represents local target availability [17]. Membrane transporters create another boundary because influx and efflux processes can reshape exposure according to substrate, tissue, genotype, interacting drugs, and disease context [18].

Local target engagement can also depend on the interaction between delivery and target biology. Physiologically based pharmacokinetic simulations of intra-target microdosing show that the ability to observe engagement depends jointly on pharmacokinetics, affinity, receptor abundance, blood flow, and other tissue properties [19]. For large molecules, mechanistic modeling further indicates that high-affinity target binding can itself reduce interstitial free-drug concentrations, creating feedback between engagement and local exposure rather than a simple one-way sequence from exposure to binding [20]. Translational modeling of bedaquiline and pretomanid similarly illustrates how lesion-level target attainment in tuberculosis can differ from what systemic pharmacokinetics alone would suggest [21]. These predictions are not measured clinical outcomes, but they identify where apparently adequate plasma exposure may leave the decisive tissue question unresolved.

The central exposure problem is therefore better represented as a set of boundary states than as a single concentration threshold. **Table 1** separates those states by asking what evidence would permit an exposure interpretation to stand, what would weaken it, and what development decision remains justified when the boundary is crossed.

Table 1. When systemic pharmacokinetics is insufficient to establish pharmacologically relevant tissue exposure

Translational exposure state	Basis for the exposure interpretation	Prior evidence that must already hold	Observation that weakens the interpretation	Permissible development consequence	Transfer boundary	Unresolved medicine-development question
Systemic exposure only	Plasma exposure is characterized, but direct target-site evidence is absent	Compound identity, dose and systemic PK are credible	Tissue access is unknown or a biological barrier is expected	Treat efficacy failure as mechanistically ambiguous rather than definitive	Plasma-to-tissue transfer must be justified for the specific drug and organ	Was the mechanism actually tested at the site of action?
Site-of-action exposure supported	Local or tissue-relevant drug exposure is measured or strongly constrained	Systemic PK and relevant bioanalytical method are adequate	Local exposure falls below the range needed to interrogate target pharmacology	Reconsider dose, delivery, formulation or molecule before rejecting the target	Measurement applies only to the sampled tissue, compartment and time window	Does adequate local exposure produce engagement?
Spatially heterogeneous access	Exposure differs across regions or subcompartments	Tissue localization method resolves biologically relevant space	Averaged tissue concentration masks poorly exposed target regions	Match exposure evidence to the anatomical location of the target	Regional findings cannot automatically be generalized across organs or species	Is the pharmacologically important subregion sufficiently exposed?
Transport-shaped exposure	Influx or efflux processes materially influence local concentration	Relevant transporter expression and substrate behavior are plausible	Genotype, disease, co-medication or tissue context changes transport	Treat exposure as context dependent and reassess the intended population	Transporter effects are substrate-, tissue- and condition-specific	Will patient context preserve target-site availability?

Binding-shaped local exposure	Target abundance or binding changes free local drug concentration	Binding kinetics and target distribution are sufficiently characterized	Target-mediated depletion or nonlinear disposition separates local from systemic exposure	Couple exposure and engagement models rather than interpreting them independently	Model-derived effects require empirical confirmation in the relevant biological system	Is apparent underexposure caused by delivery failure or by the target interaction itself?
Translationally modeled tissue attainment	Mechanistic model integrates systemic PK with tissue-specific determinants	Model structure is biologically credible and key parameters are supported	Predictions are sensitive to unverified assumptions or fail external checks	Use the model to identify uncertainty and testing priorities, not as proof of efficacy	Prediction remains conditional on model validity and transportability	Which measurement would most directly falsify the predicted tissue state?

These exposure states also interact with engagement, biomarkers, and later patient-level decisions. **Figure 1** therefore places tissue exposure at the centre of a decision-utility field rather than depicting it as an intermediate box in a linear pipeline.

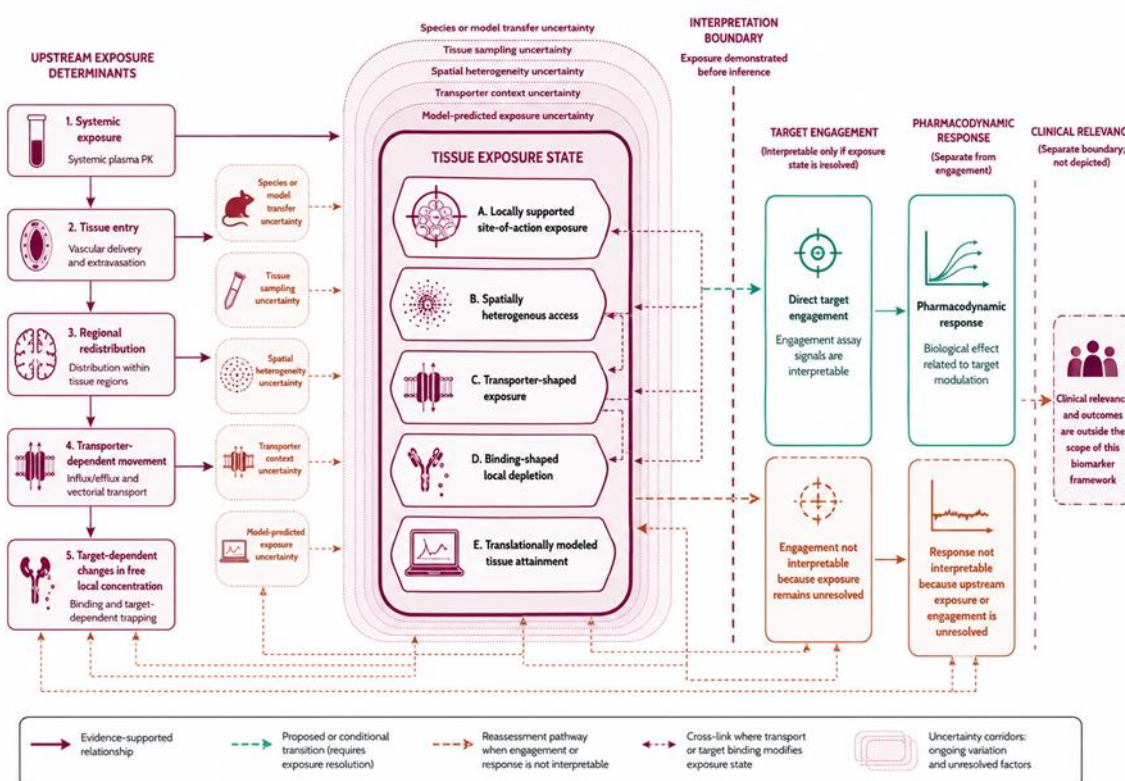


Figure 1. Tissue Exposure Determines Whether Target Engagement Can Carry Translational Meaning

Pharmacodynamic biomarkers

A pharmacodynamic biomarker becomes valuable when it reduces uncertainty about a defined pharmacological question. Regulatory experience with biosimilar development illustrates that a sufficiently sensitive PD biomarker can, in a suitable context, provide more direct evidence of pharmacological similarity than a comparatively insensitive clinical efficacy endpoint [22, 23]. That principle does not mean that any changing laboratory measure qualifies. The biomarker must respond over an informative range, relate plausibly to the mechanism under study, and be measured with enough analytical reliability to support the intended decision.

Empirical comparison is therefore essential. Randomized work with IL-5 antagonists demonstrates how dose-ranging data can be used to characterize pharmacodynamic responses within a defined pathway [24, 25]. The specific biomarkers and pharmacological systems differ, which is precisely the point: decision utility is not an

intrinsic property of the word “biomarker.” It arises from the relation among drug, mechanism, dose, assay, time course, biological compartment, population, and context of use.

For mechanism-to-medicine reasoning, a PD response should answer a narrower question than clinical efficacy. If exposure is adequate and target engagement has been demonstrated, a mechanistically proximal response can support the conclusion that target perturbation propagated into downstream biology. It cannot, by itself, establish that the change is beneficial, durable, disease modifying, or clinically meaningful. Conversely, lack of a PD response is difficult to interpret if the assay is insensitive or if upstream exposure and engagement have not already been secured.

Biomarker qualification

Biomarker qualification formalizes this context dependence. Analysis of European Medicines Agency qualification procedures shows that biomarker properties, assay validation, and the definition of context of use are recurrent evidentiary issues, and that qualification is a demanding process rather than an automatic consequence of biological plausibility [26]. Qualification should therefore not be conflated with discovery of an association or demonstration that an analyte changes after treatment.

From an industry perspective, biomarker development is most useful when evidence generation is aligned prospectively with the role the biomarker is intended to perform [27]. Public–private qualification programmes likewise illustrate the value of generating common evidentiary resources where no single development programme can efficiently establish the required foundation alone [28]. These precedents support a useful distinction for the present framework: measurement validity asks whether the biomarker can be measured reliably; biological validity asks what the signal represents; decision validity asks whether that evidence is sufficient for the intended development action. This three-part distinction is proposed here as an organizing device, not as a new regulatory qualification standard.

Patient selection and disease context

Even a coherent exposure–engagement–PD sequence can lose meaning if the disease or patient context no longer depends on the mechanism being perturbed. European regulatory dossiers show that biomarkers are used for patient selection in multiple ways and that candidate definitions may change as evidence is translated into an approved indication [29]. US oncology approvals similarly demonstrate the increasing importance of biomarker-defined populations while also showing that not every effective therapy requires a biomarker-restricted indication [30]. Patient selection is therefore neither universally necessary nor merely an optional enrichment technique. Its relevance depends on how strongly mechanism, disease state, and treatment response are coupled.

Patient context also includes variables that are not reducible to a single molecular marker. Intrinsic and extrinsic factors can alter pharmacokinetics, pharmacodynamics, tolerability, adherence, and exposure to interacting environmental or treatment conditions [31]. These factors should not be treated as deterministic demographic labels; rather, they define conditions under which a previously supported exposure–response relationship may change.

Mechanistic integration becomes particularly important when dose–response behavior is non-monotonic. Semimechanistic modeling of epcoritamab linked systemic pharmacokinetics, biodistribution, CD3×CD20 trimer formation, pharmacodynamic observations, and clinical information to support dose selection [32]. The example is product- and mechanism-specific, but it demonstrates why maximal systemic exposure or maximal nominal target occupancy cannot always serve as the development objective. The clinically relevant question is whether the selected patient and dose create the biological configuration required for productive pharmacology.

The decision problem is clearer when patient-selection cases are represented as states rather than as a list of biomarkers. **Table 2** distinguishes what can be concluded at each state, what remains unresolved, and what observation should force reassessment.

Table 2. Patient-selection states that determine whether biomarker evidence can guide a mechanism-based development decision

Decision state	Target-engagement information available	Biomarker readout	Disease and patient context	Unresolved uncertainty	Permissible action	Observation that triggers reassessment
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Mechanism-enriched context with concordant pharmacology	Engagement supported in the relevant biological setting	Mechanistically coherent PD change	Selected population retains the pathway or target dependency of interest	Clinical consequence and durability remain uncertain	Advance the mechanistic hypothesis while testing clinically meaningful outcomes	Clinical response diverges despite sustained exposure, engagement, and PD activity
Biomarker-defined population with unresolved site exposure	Engagement may be measurable in an accessible compartment but not at the disease site	Selection marker is present; downstream PD evidence is incomplete	Disease classification supports the target hypothesis	Whether the therapeutic reaches and perturbs the relevant compartment	Resolve tissue exposure before attributing nonresponse to target biology	Direct or improved exposure evidence contradicts the original assumption
Adequate engagement with weak downstream response	Direct engagement is established	PD signal is absent, small, inconsistent, or assay dependent	Population appears mechanistically plausible	Whether engagement is functionally consequential	Reassess biomarker sensitivity, pathway redundancy, dose duration, and mechanistic assumptions	A validated proximal biomarker remains negative despite sustained engagement
Pharmacodynamic response with immature context of use	Engagement and a downstream change are observed	Reproducible PD response	Relationship to selection, prognosis, or clinical benefit is not established	Decision meaning of the biomarker	Use the signal as pharmacological evidence, not as a surrogate for benefit	The biomarker fails to discriminate relevant doses, populations, or outcomes
Heterogeneous mechanism across the intended population	Engagement differs or is incompletely characterized across subgroups	Biomarker pattern varies with disease state or patient factors	Target dependency is not uniform	Which subgroup preserves the mechanism-response relation	Refine biological stratification and prospectively test the revised hypothesis	Stratification fails to improve mechanistic coherence or creates unexplained discordance
No justified selection requirement	Engagement and PD evidence are sufficiently consistent across studied patients	No validated predictive stratifier is necessary for the intended decision	Mechanism appears broadly relevant within the defined indication	Whether later heterogeneity will emerge	Avoid imposing an unsupported biomarker restriction	New evidence identifies clinically important response heterogeneity

Patient selection therefore sits inside, rather than downstream from, translational pharmacology. **Figure 2** represents this relationship as a decision field with feedback channels: biomarker-defined selection changes the population in which exposure, engagement, and response are interpreted, while discordant human evidence feeds back to the mechanistic assumptions that motivated selection.

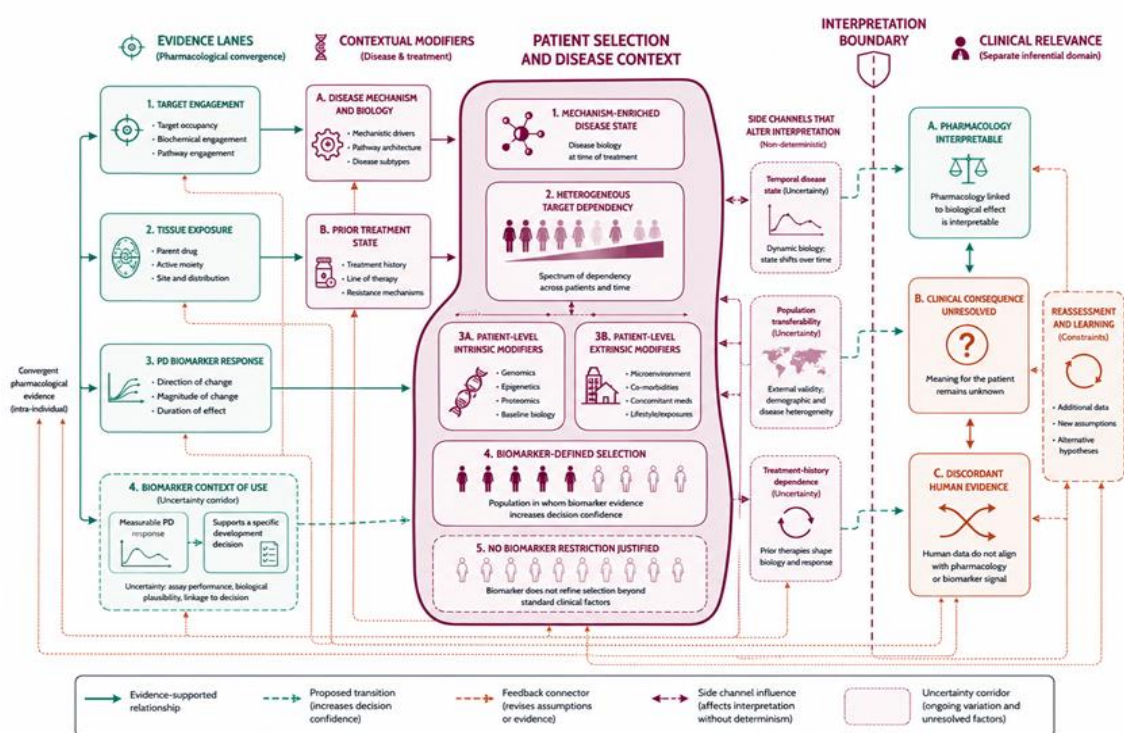


Figure 2. Clinical Context Determines When Biomarker Convergence Is Decision-Relevant

Convergence versus discordance across evidence layers

Convergence has value only when each layer answers a different question. Adequate plasma exposure cannot substitute for target-site exposure, target engagement cannot substitute for downstream pharmacology, and a pharmacodynamic response cannot substitute for clinical relevance. The informative case is therefore not a chain in which one positive result validates the next, but a pattern in which independently interpretable observations remain mutually compatible.

Discordance is equally informative. Comparable PD-1 target engagement can be quantified for different antibodies without establishing equivalent downstream efficacy [33]. A mismatch between engagement and response may reflect insufficient tissue exposure, pathway redundancy, assay insensitivity, disease-state heterogeneity, or an incorrect mechanistic model. The proposed architecture therefore treats discordance as a reassessment trigger rather than noise to be averaged away.

Time adds another boundary. Early engagement may be transient, a pharmacodynamic response may lag, and clinical consequence may emerge after both have changed. **Table 3** organizes these states without assigning numerical weights or thresholds.

Table 3. Temporal Evidence States That Distinguish Convergence from Unresolved or Misleading Agreement

Translational state	Biomarker readout	Clinical relevance	Prior evidence required	Failure criterion	Decision consequence	Article-level test
Early pharmacological convergence	Proximal change follows verified exposure and engagement	Not yet established	Site exposure and engagement are credible	Biomarker fails despite adequate upstream evidence	Reassess biomarker or mechanism	Does the response follow the intended perturbation?
Persistent mechanistic convergence	Reproducible response persists across the relevant window	Plausible but still unproven	Assay validity and context of use are adequate	Response decouples from engagement or dose	Reassess pathway dependence	Is the same mechanism still operating over time?
Delayed clinical divergence	PD evidence remains coherent while	Discordant	Population and disease	Human outcome remains	Reopen patient-selection and	Was the correct clinical context tested?

	clinical outcome does not		context are justified	inconsistent with the mechanistic prediction	disease assumptions	
Apparent convergence under unresolved exposure	Biomarker and systemic PK appear favorable	Ambiguous	Local exposure is not established	Direct tissue evidence contradicts the surrogate	Do not interpret the mechanism as clinically tested	Did the drug reach the biological site that matters?
Recovered convergence after reassessment	Revised exposure, assay, or selection assumptions restore coherence	Requires new confirmation	Cause of prior discordance is testable	Revised explanation fails prospectively	Stop or reformulate the hypothesis	Did reassessment produce a falsifiable improvement rather than a retrospective story?

A mechanism-to-medicine decision architecture

The article's proposed architecture is deliberately non-numeric. Model-informed drug development shows how quantitative models can support dose selection, trial design, and regulatory decisions when they are fit for purpose [34]. Model-based meta-analysis similarly demonstrates how dose, population, endpoint, and time-course evidence can be integrated without pretending that every input is equally informative [35].

The proposed decision rule is non-compensatory for essential layers. Strong target biology should not rescue absent site exposure; a sensitive biomarker should not rescue unverified engagement; and biomarker-defined enrichment should not rescue a disease mechanism that no longer explains response. Positive evidence increases confidence only when the necessary upstream interpretation remains intact. Discordant evidence should return the programme to the earliest unresolved layer capable of explaining the discrepancy.

Falsification and stop criteria

A translational programme should distinguish “the mechanism failed” from “the mechanism was never adequately tested.” Inadequate tissue exposure, uncertain target engagement, or an uninformative biomarker belong to the second category. Persistent discordance after those conditions have been addressed belongs increasingly to the first.

The proposed stop logic is therefore sequential but not mechanically linear. First establish that the relevant biological compartment was exposed; then determine whether the intended target was perturbed in the appropriate mode; then test whether downstream biology changed with an assay capable of detecting that change; finally ask whether the selected disease context and patient population preserve the mechanism–outcome relationship. Repeated reinterpretation without a new falsifiable prediction should itself be considered evidence against continuation.

CONCLUSION

A promising mechanism becomes a medicine only when the evidence surrounding it remains coherent across the biological levels that matter. Exposure, engagement, pharmacodynamic biomarkers, qualification, and clinical context answer different questions and should not be collapsed into one narrative of “proof.” The proposed architecture is not a validated scoring system. Its value is stricter: it makes unresolved assumptions visible, treats discordance as evidence, and defines where additional testing should stop supporting a story and start challenging it.

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