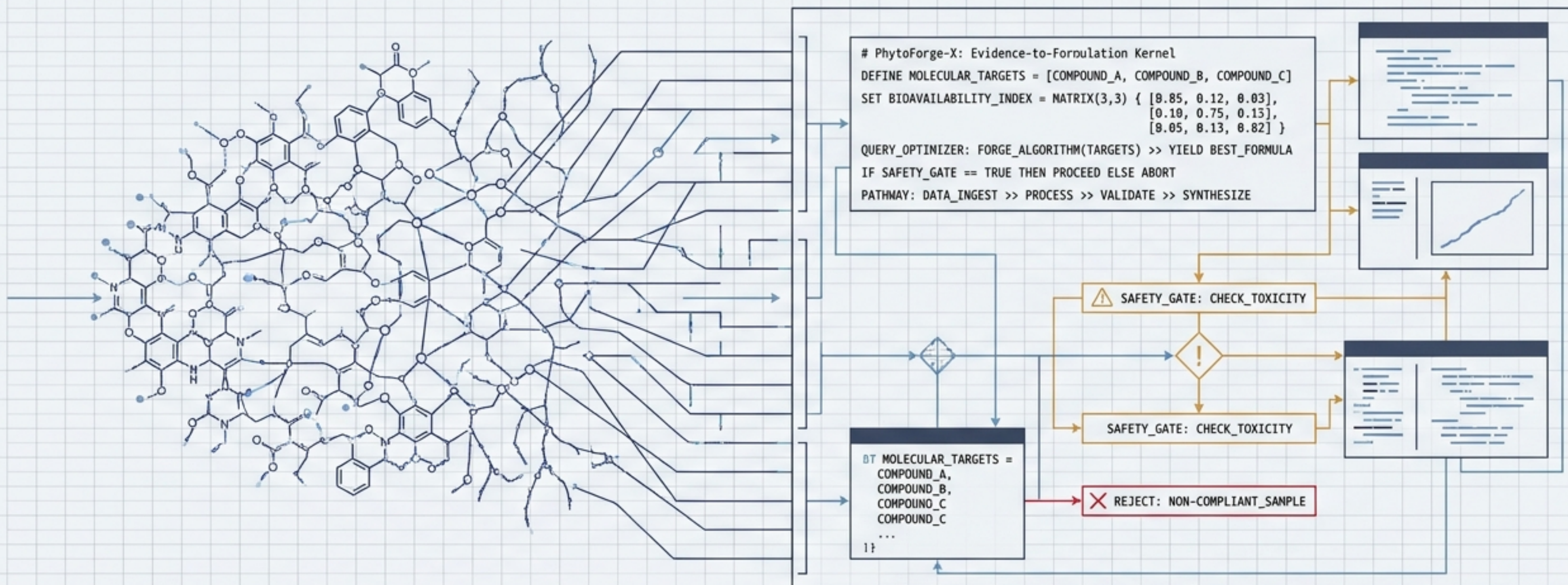
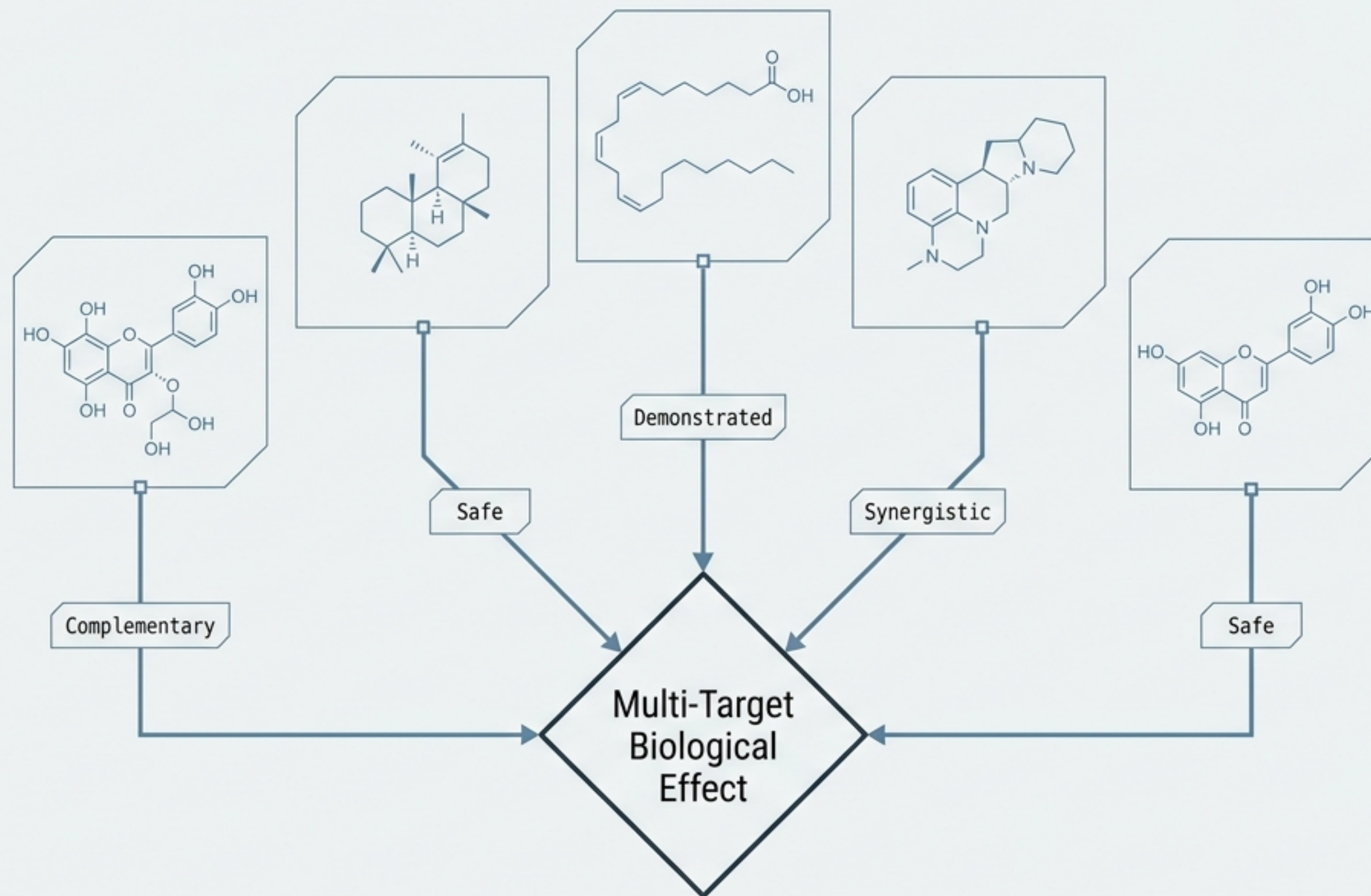




PHYTOFORGE-X™

The Evidence-to-Formulation Research & Optimization Framework

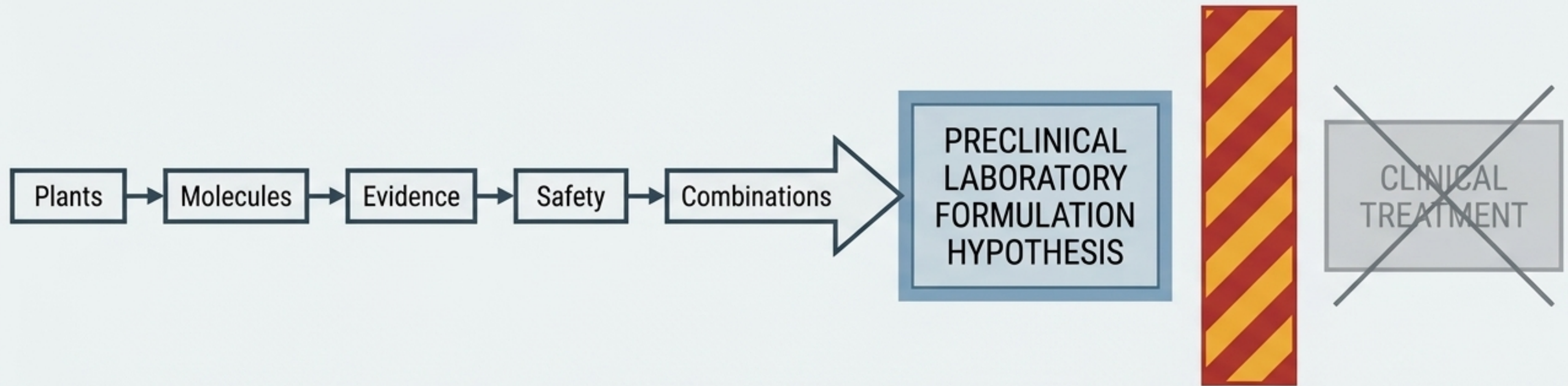
The Core Scientific Principle



The central PHYTOFORGE-X hypothesis is that a rationally selected combination of chemically characterized plant-derived molecules may produce useful multi-target biological effects.

- ✓ Experimentally demonstrated mechanisms
- ✓ Compatible exposure characteristics
- ✓ Acceptable laboratory safety profiles
- ✓ Measurable combination synergy

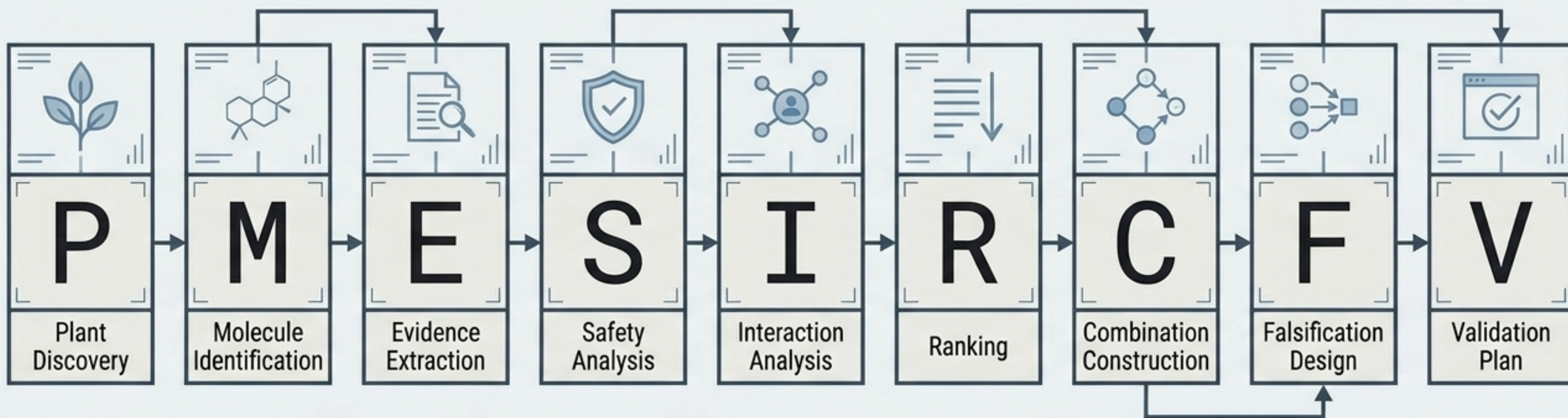
The 'Plants to Pills' Myth vs. Translation Reality



PHYTOFORGE-X Outputs	Strictly Prohibited
▪ Ranked research hypothesis sets ▪ Experimental validation plans ▪ Target mechanism matrices	▪ Human dosing schedules ▪ Recommendations to replace approved medicines ▪ Clinical efficacy claims based on cellular evidence

RULE: No preclinical observation may be promoted to a clinical claim.

The 9-Stage AI Execution Contract



SYSTEM MANDATE: The AI must never jump directly from [plant → pill] without passing through the evidence, safety, pharmacology, and combination-analysis layers.

Information Ingestion & The Universal Query

Data Inputs	
Disease Target:	Glioblastoma
Population:	All
Clinical Translation Allowed:	NO 
Human Dosing Allowed:	NO 

Boolean Architecture

[D ∧ (P1 ∨ P2 ∨ ... Pn)
∧ (M1 ∨ M2 ∨ ... Mn)]

Expanded Target Example: Glioblastoma

D = Glioblastoma

Apoptosis

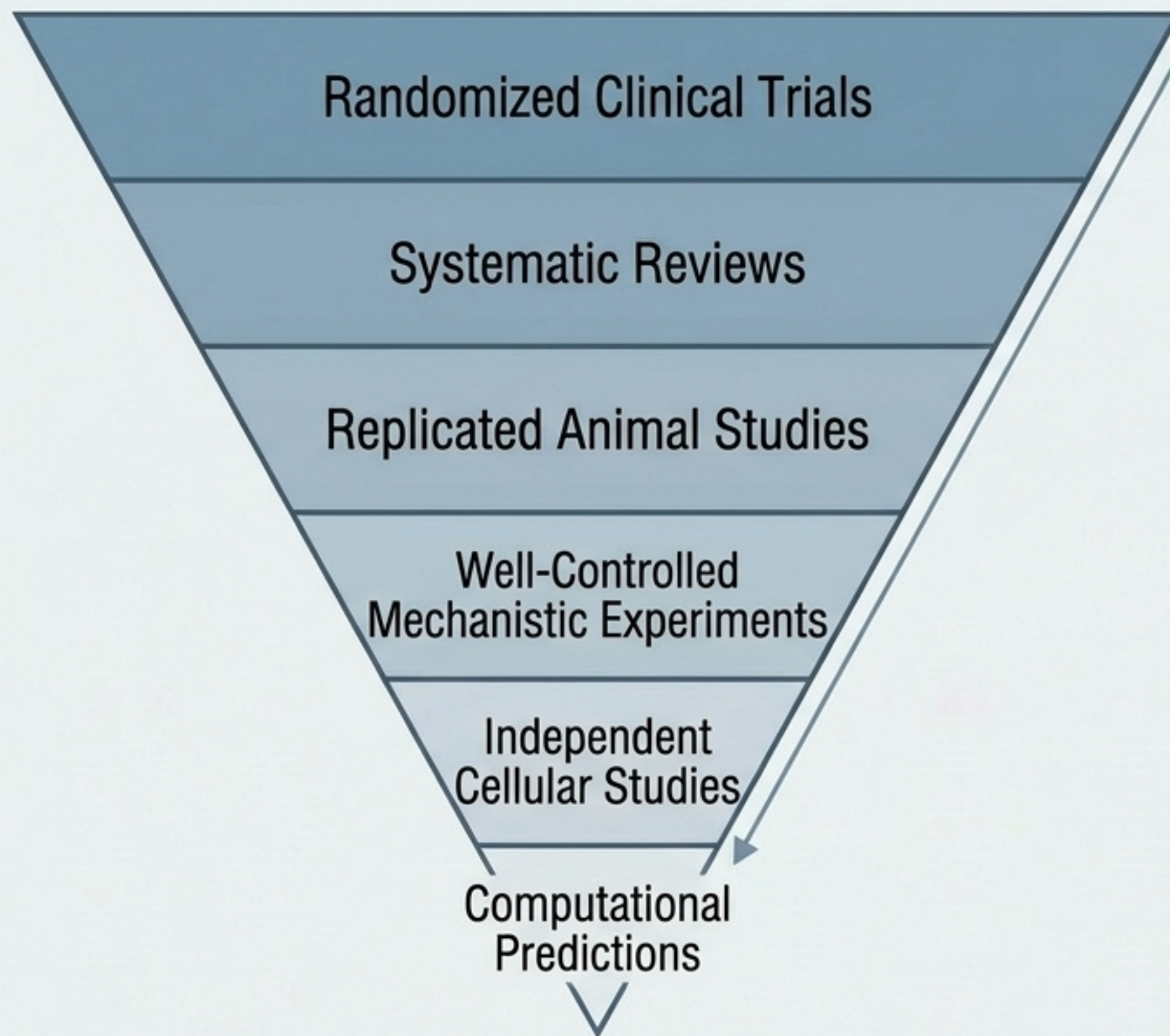
Angiogenesis

Cancer Stem Cells

TMZ Resistance

The AI systematically executes targeted searches across all biologically relevant domains, preventing single-pathway bias.

Source Quality & PRISMA-S Reproducibility



PRISMA-S Mandate

Search methodology is strictly bound by PRISMA-S principles. Full search strings, dates, filters, and result counts are immutably logged for replication.

Duplicate Control

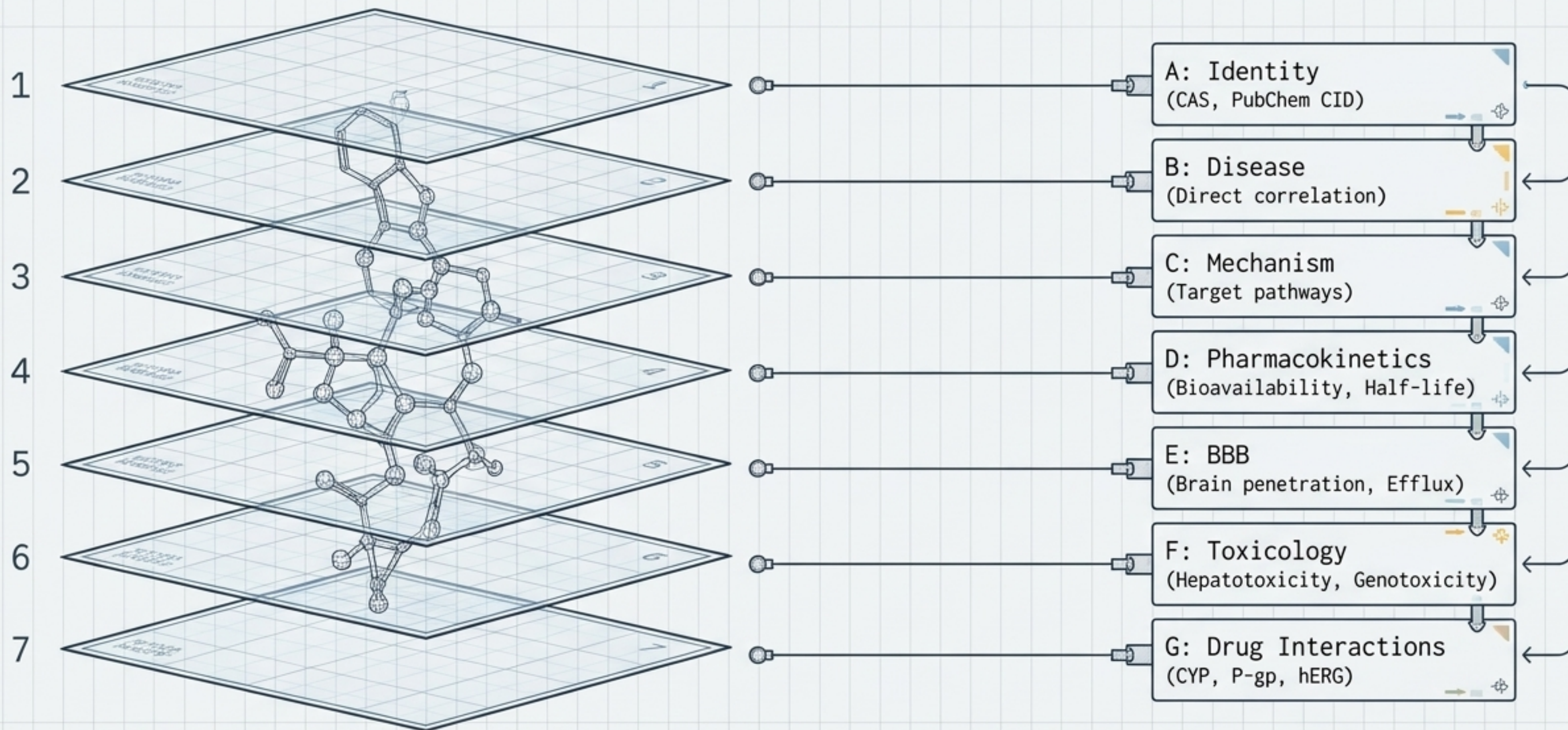
Cross-referencing via DOI, PMID, and Trial ID ensures a single study appearing in multiple databases is never double-counted to inflate evidence.

! RULE

Reviews are discovery tools. Primary research is required to verify specific mechanistic claims.

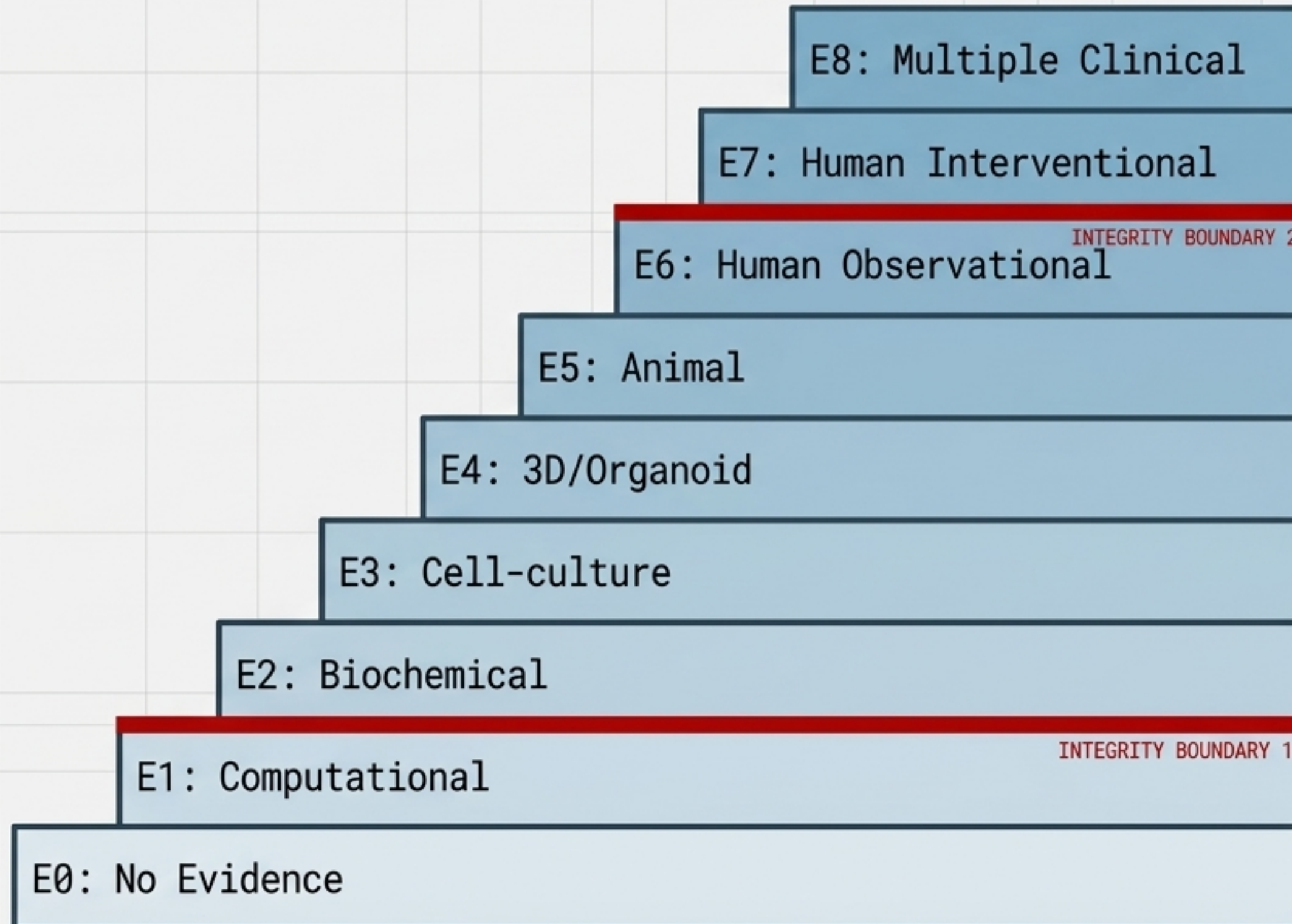


The 7-Layer Stratification System



Every candidate molecule is subjected to an independent diagnostic scan across all seven layers before progression.

The Evidence Hierarchy & Integrity Boundaries



CONFIDENCE SCORE FORMULA

Confidence Score:

$$E_i = w_L L_i + w_M M_i + w_R R_i + w_T T_i + w_C C_i$$

(Literature, Mechanism, Reproducibility, Translation, Clinical)



WARNING

The AI shall never convert
 $E1 \rightarrow E3$ or $E3 \rightarrow E7$ without
supporting evidence.

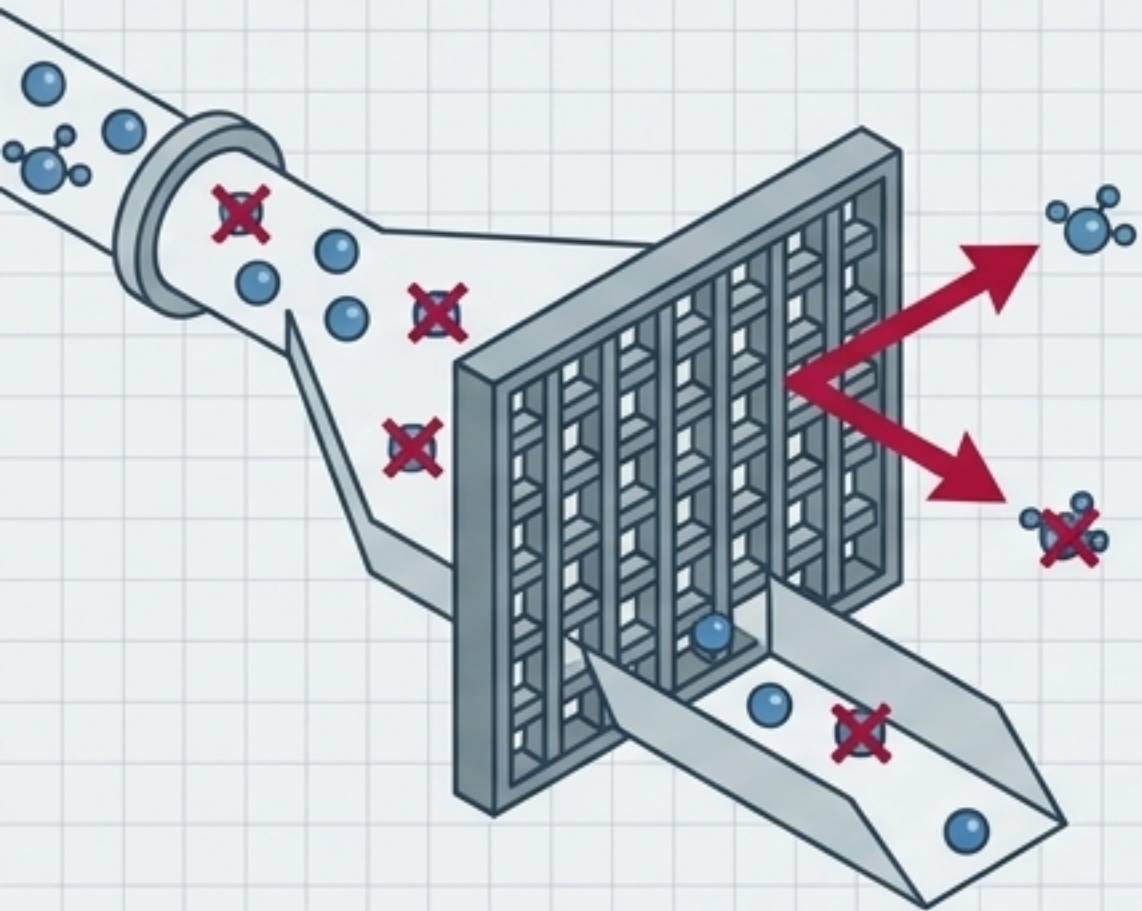
Docking is not proof of
biological activity.

Network pharmacology is not
proof of mechanism.

Association is not causation.



The Contraindication & Safety Engine (Hard Exclusions)



**Absence of
evidence is
not evidence
of safety.**

Hard Exclusion Criteria

- ✗ - Unacceptable toxicity at relevant exposures
- ✗ - Clinically important QT/hERG liability
- ✗ - Severe hepatotoxicity / nephrotoxicity
- ✗ - Inability to distinguish tumor effects from normal-cell toxicity

System Action: Any molecule triggering a Hard Gate is immediately ejected, regardless of its biological efficacy score.



Pharmacokinetics & The BBB Module

$$B_i = w_P P_i + w_T T_i + w_E E_i - w_{Eff} Eff_i$$



Passive Permeability (+)



Transport Evidence (+)



Brain Exposure (+)



Efflux Liability (-)

Context:

For neurological diseases, the AI cannot infer Blood-Brain Barrier (BBB) penetration solely from molecular weight.

Metric Requirements:

Experimental data points demanded include P-glycoprotein/ABCB1, BCRP/ABCG2, and unbound brain concentration ($K_{p,uu}$).

AI-derived estimates must be strictly labelled as predictions, not data.



Tumor Selectivity & Standard Therapy Interactions

Tumor Selectivity

$$SI = \frac{IC50_{normal}}{IC50_{tumor}}$$

A higher SI indicates **experimental selectivity**. However, $SI > 1$ is **not automatically sufficient**. The AI rigorously audits cell type, assay duration, and replicate structure.

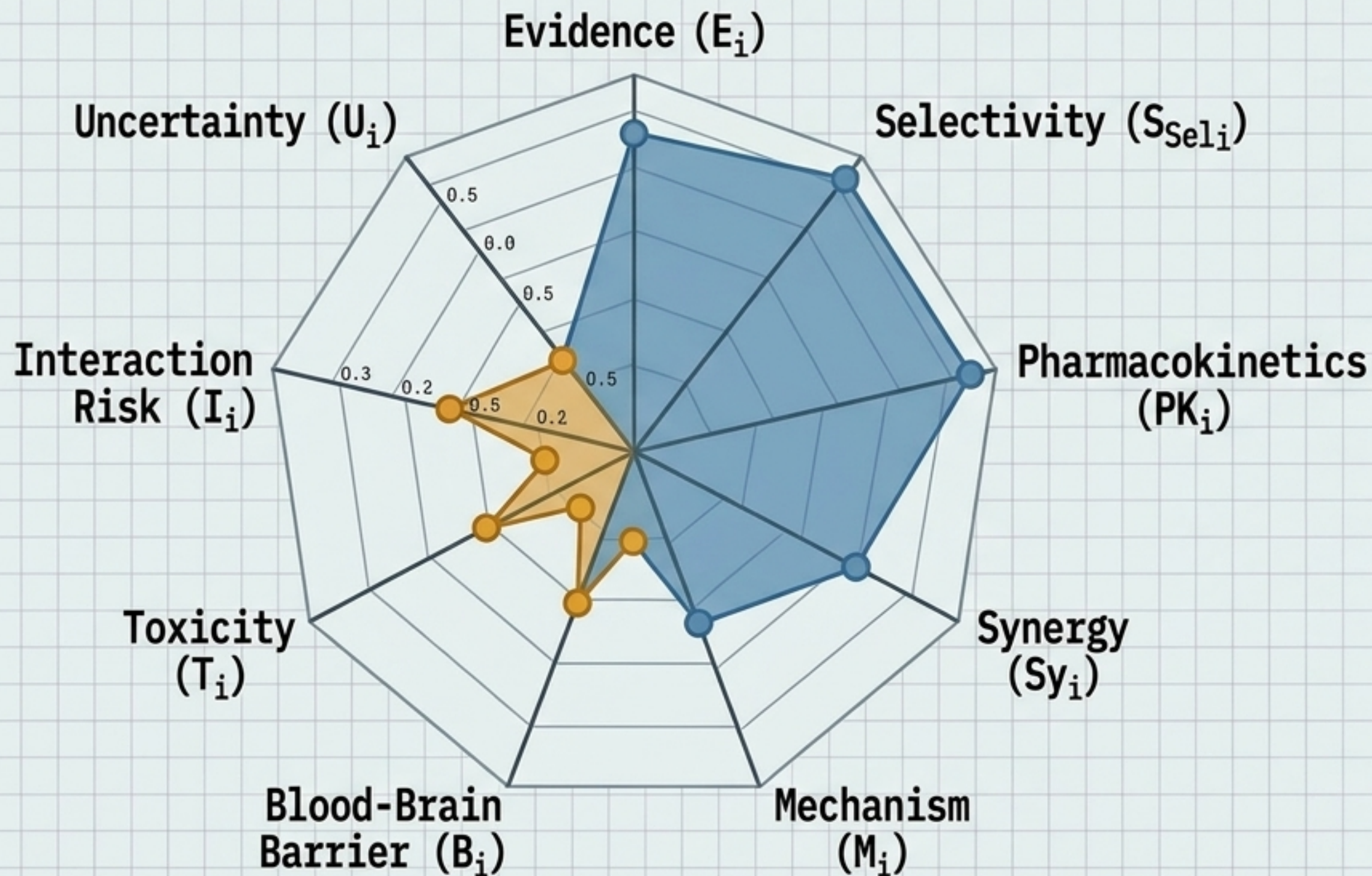
Drug Interaction Matrix

Plant Molecules	Temozolomide	Radiotherapy	Bevacizumab
Candidate A	Synergistic	None identified	Synergistic
Candidate B	Possible	Possible	None identified
Candidate C	Antagonistic	Synergistic	Possible

RULE: Any strong antagonism with a required standard therapy triggers a **Hard Exclusion**.



$$R_i = w_E E_i + w_B B_i + w_{Me} M_i + w_{Sel} S_{Sel_i} + w_{PK} PK_i + w_{Sy} Sy_i - w_T - w_T T_i - w_I I_i - w_U U_i$$



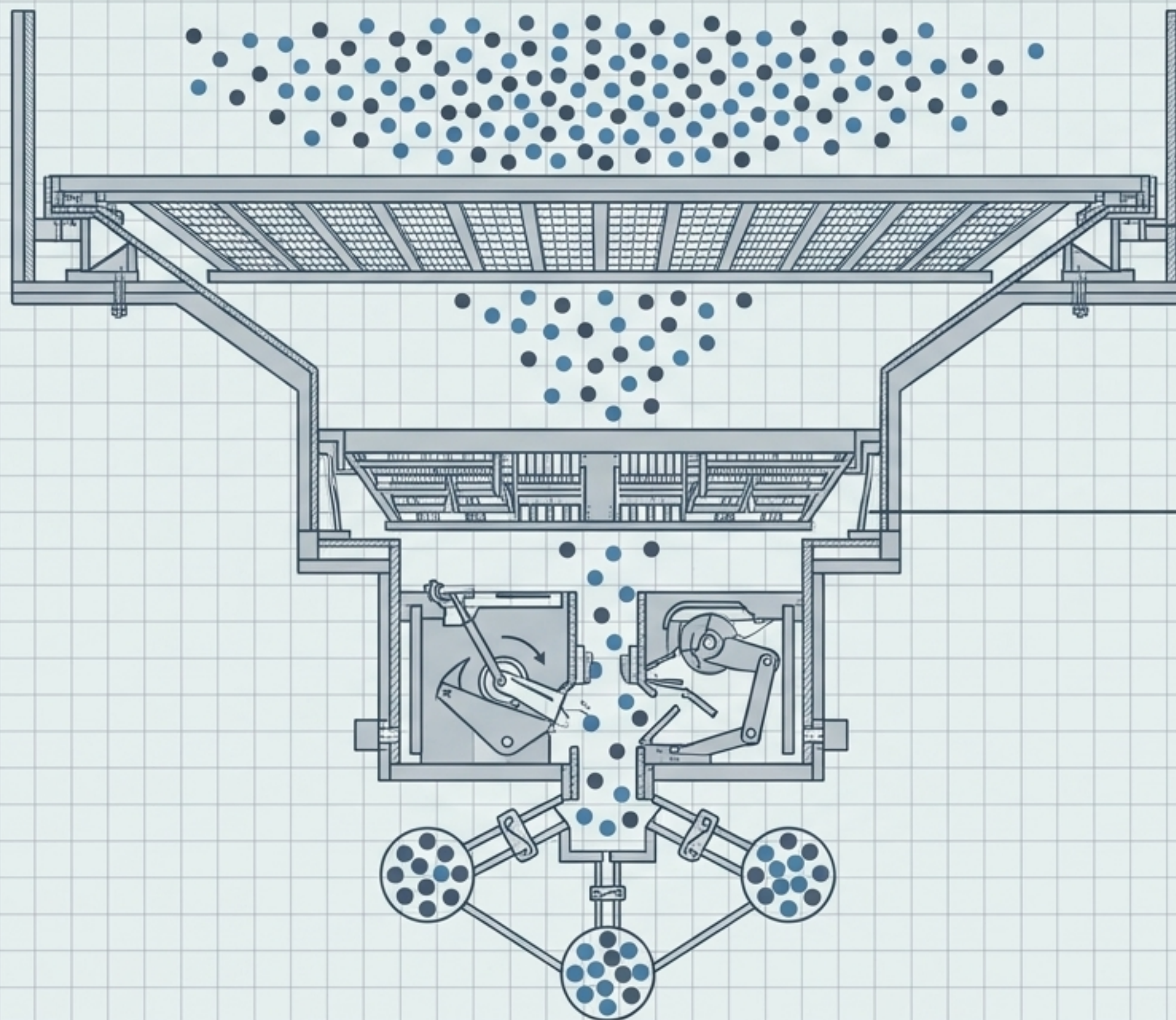
Insight

A high score does not signify the "best treatment." It signifies high research priority under declared mathematical assumptions.

All weights are explicitly documented to prevent AI manipulation.



The 100 → 20 → 10 → 5 Funnel Architecture



Stage 1 (100): Broad Discovery

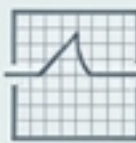
Verification, Tox, PK

Stage 2 (20): Evidence, Identity,
PK, and Preliminary Safety
Verification

Replication & Interactions

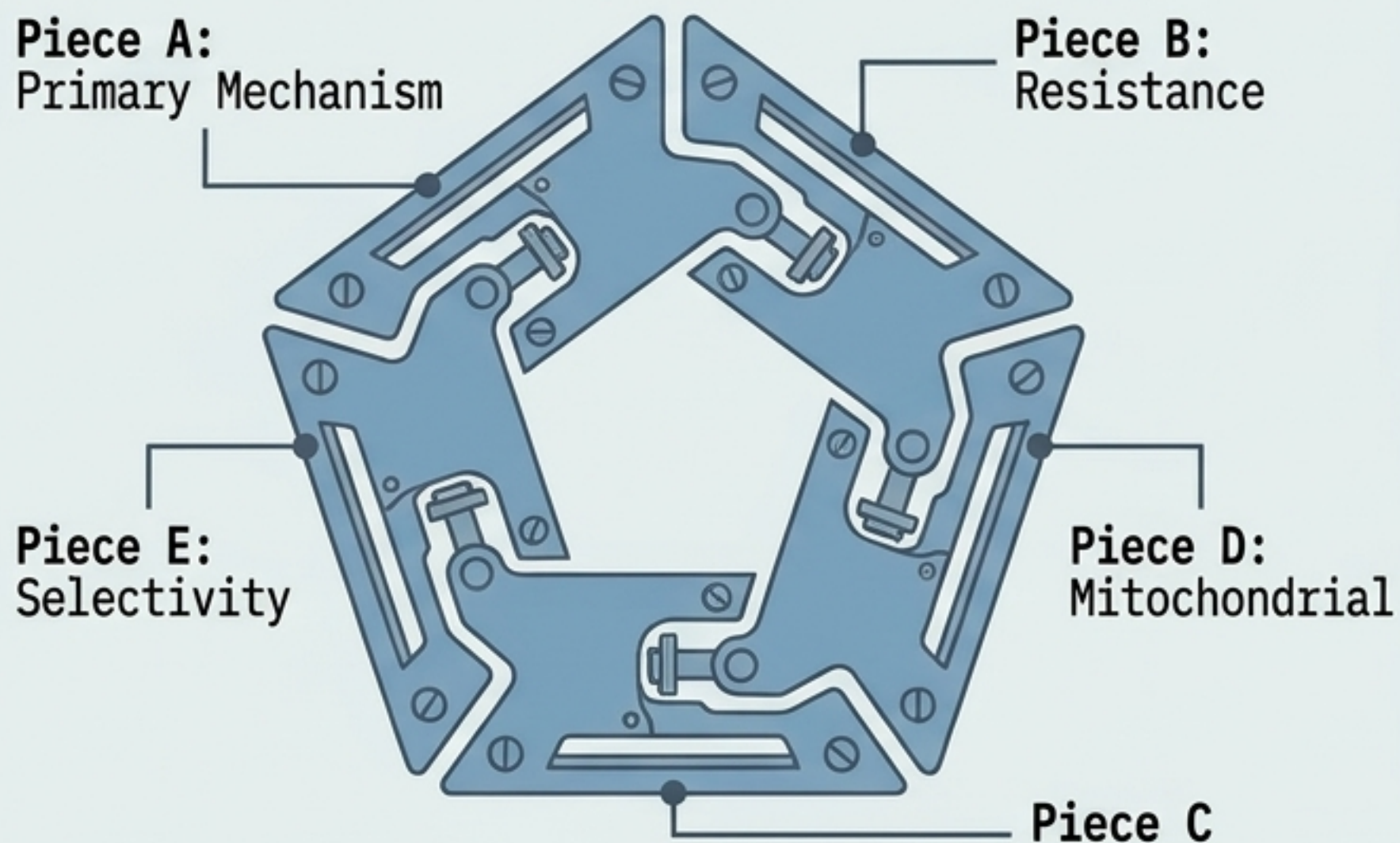
Stage 3 (10): Independent
Replication, Interaction
Analysis, and Resistance Biology

Stage 4 (5): Construction of
complementary, deliberately
differentiated laboratory
combinations



Mechanistic Coverage & The Redundancy Penalty

The Assembly Logic: Mechanistic Coverage



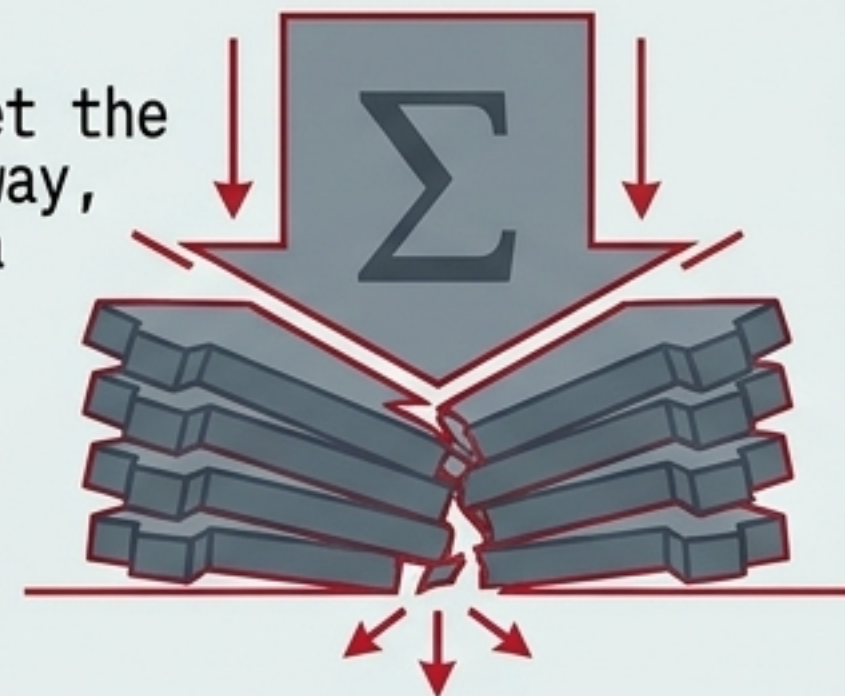
Combinations must cover complementary functional roles. The engine does not simply pick the five highest-scoring molecules.

The Redundancy Penalty

$$P_R = \sum \max(0, N_j - N_{\text{target},j})$$

The Penalty:

If too many candidates target the exact same pathway, the AI applies a penalty.



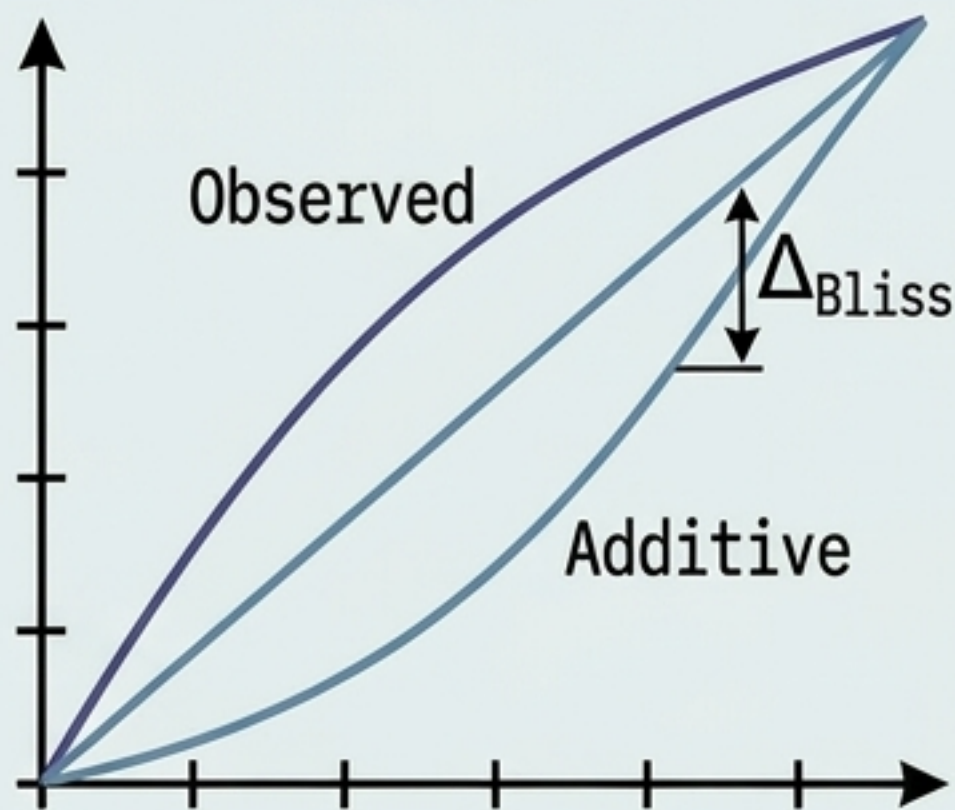
The Penalty: If too many candidates target the exact same pathway, the AI applies a mathematical penalty. A multi-target combination cannot secretly be a collection of identical modulators.



Combination-Synergy Mathematics

RULE: The AI shall not assume that combining positive molecules produces a positive combination.

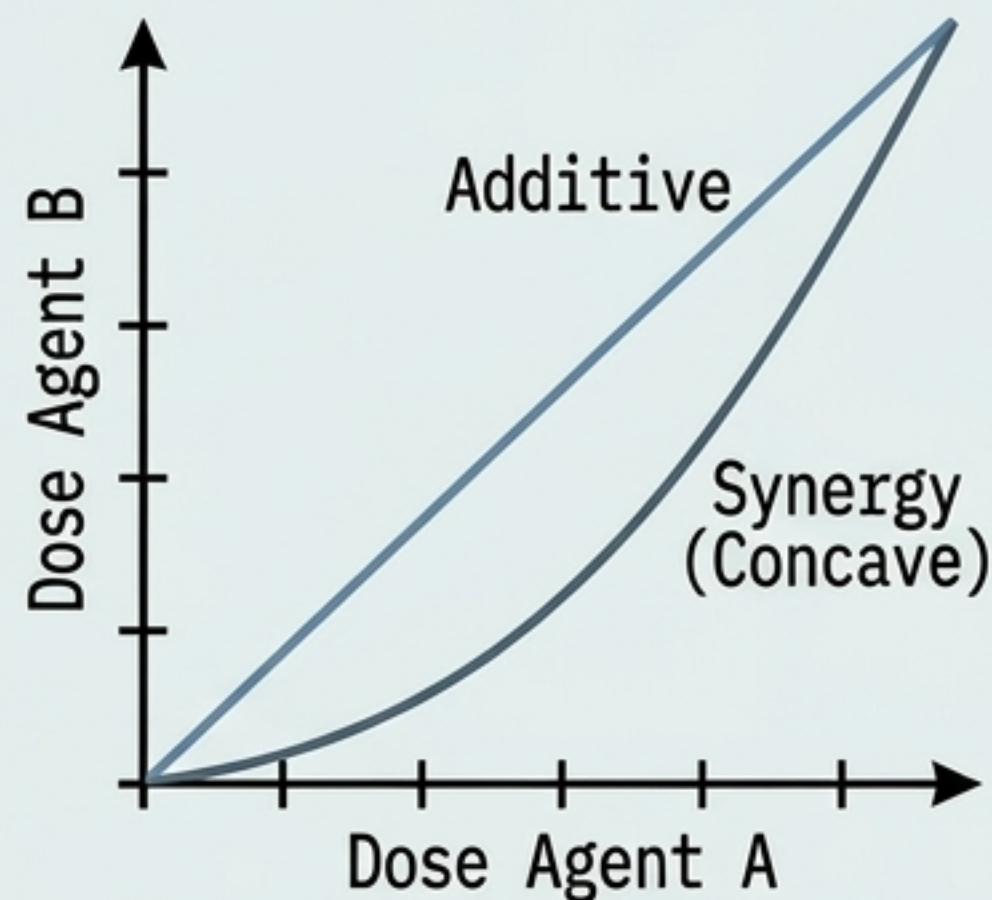
Bliss Independence



Highest Single Agent



Loewe Additivity

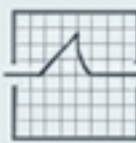


$\Delta_{\text{Bliss}} > 0 \rightarrow \text{Synergy}$

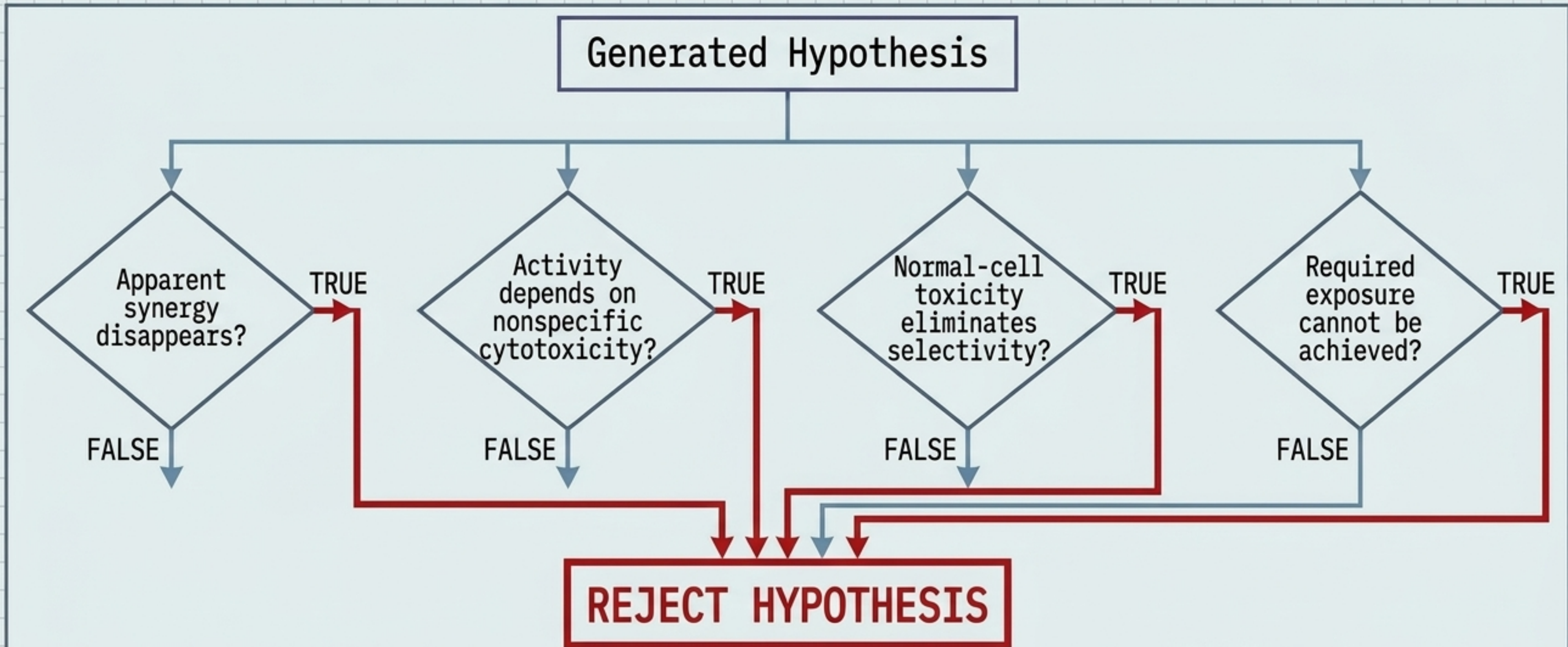
$\Delta_{\text{Bliss}} = 0 \rightarrow \text{Independence}$

$\Delta_{\text{Bliss}} < 0 \rightarrow \text{Antagonism}$

Multi-Model Analysis: For two agents, multiple synergy frameworks are executed when data permits.



The Falsification Engine

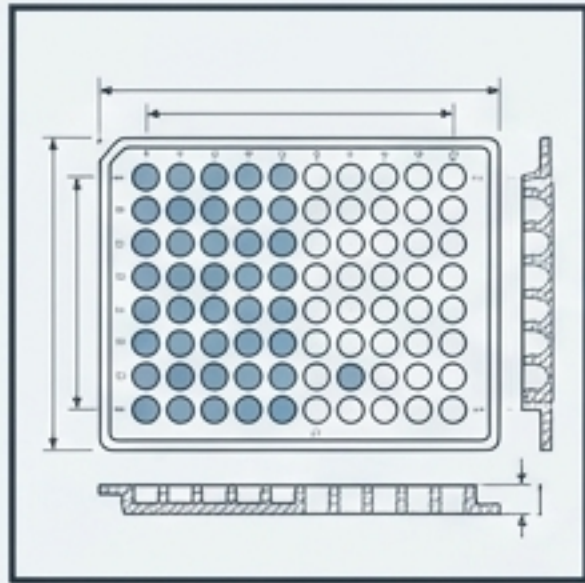


The Philosophical Core: The objective is not to prove the hypothesis.
The objective is to determine whether the hypothesis survives attempted falsification.



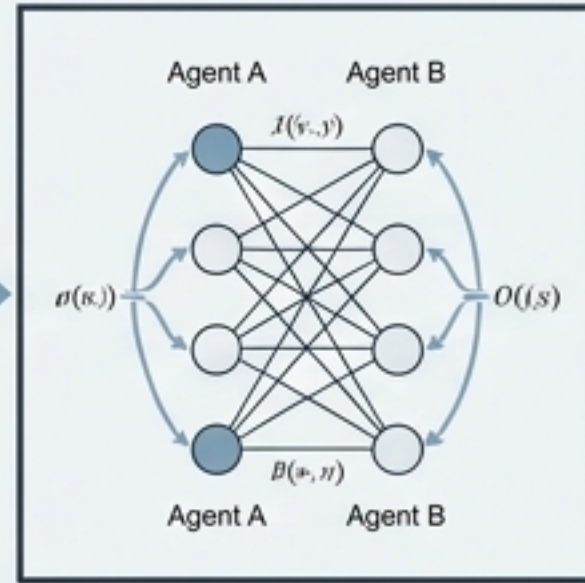
The 5-Panel Laboratory Validation Design

Individual Agents



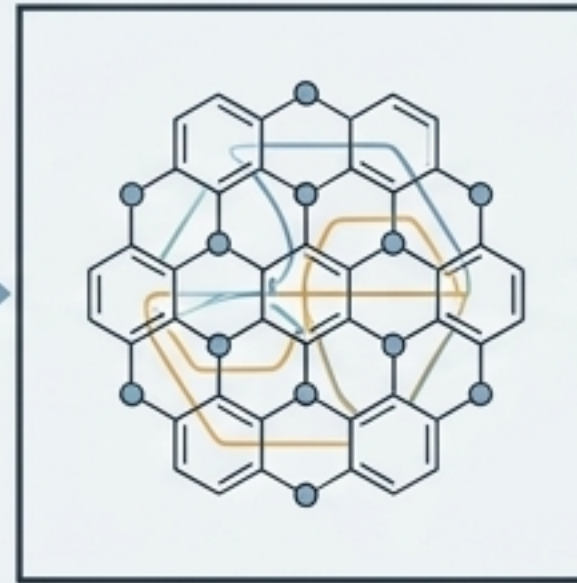
Target engagement,
normal-cell
toxicity

Pairwise Combinations



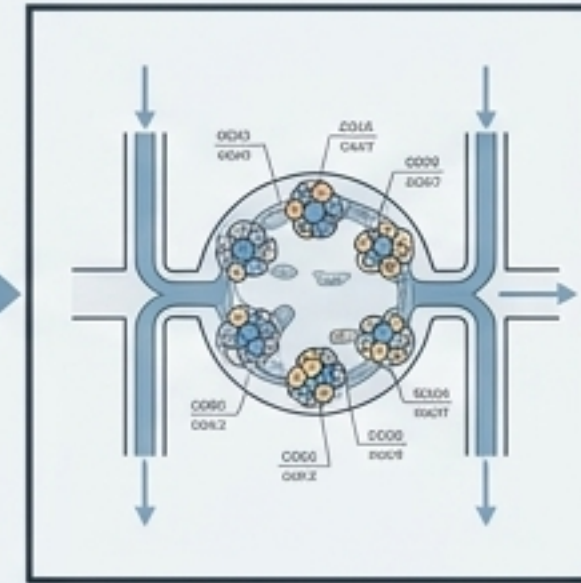
Evaluating
 $n(n-1)/2$
combinations

Higher-Order Combinations



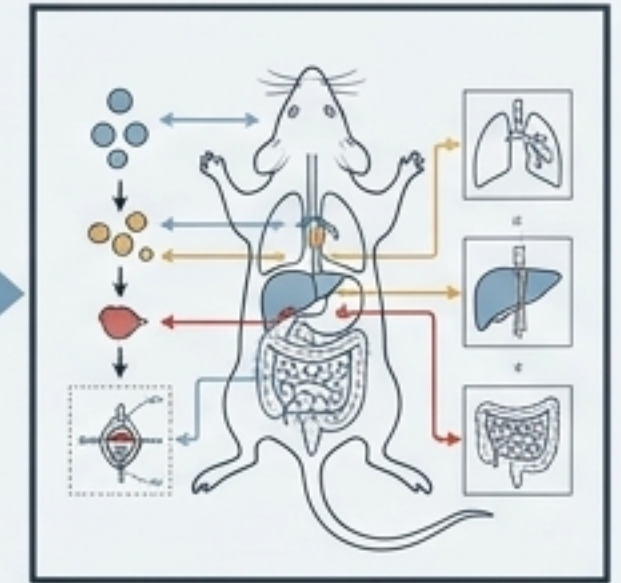
Only if pairwise
succeeds

Disease-Relevant Models



Patient-derived
cells, 3D cultures,
microenvironments

Translational Preclinical Models



Final in-vivo
laboratory
evaluation



The Final Output Deliverable

Mandatory transparency of the initial discovery pool.

100-Molecule Master Grid

ID	Molecule	Plant	Targets	Evidence	BBB	PK	Toxicity	Interaction
001	Berberine	Berberis vulgaris	AMPK, NF-kB	High, PMID:302	✓	Mod	Low	CYP3A4
002	Curcumin	Curcuma longa	COX-2, TNFα	Very High, PMID:450	✗	Low	V.Low	P-gp
003	Resveratrol	Vitis vinifera	SIRT1, FOXO	Medium, PMID:210	✓	Mod	Low	CYP2C9
004	###	Vitis vinifera	###	High, PMID:302	✗	✓	■■■■.....	###
005	###	Resveparol	###	High, PMID:450	✗	Low	■■■■■...	P-gp
006	###	Camus mavepatone	###	High, PMID:302	✓	Mod	Low	CYP3A4
007	###	Vincus berberine	###	High, PMID:300	✗	Low	■■■■.....	P-gp
008	###	Curcuma longa	###	High, PMID:302	✓	Low	■■■■■...	CYP3A4
009	###	Sosmaratcmt	###	High, PMID:210	✓	Low	■■■■■■..	P-gp

The 24-Point Report Highlights

- ☐ PRISMA-style study flow
- ☐ Contraindication matrices
- ☐ Mathematical synergy frameworks
- ☐ Falsification criteria
- ☐ Complete PMID/DOI verification tables

The AI must hand over an exhaustive data package, not just a recommendation.

The Immutable Scientific Integrity Rules

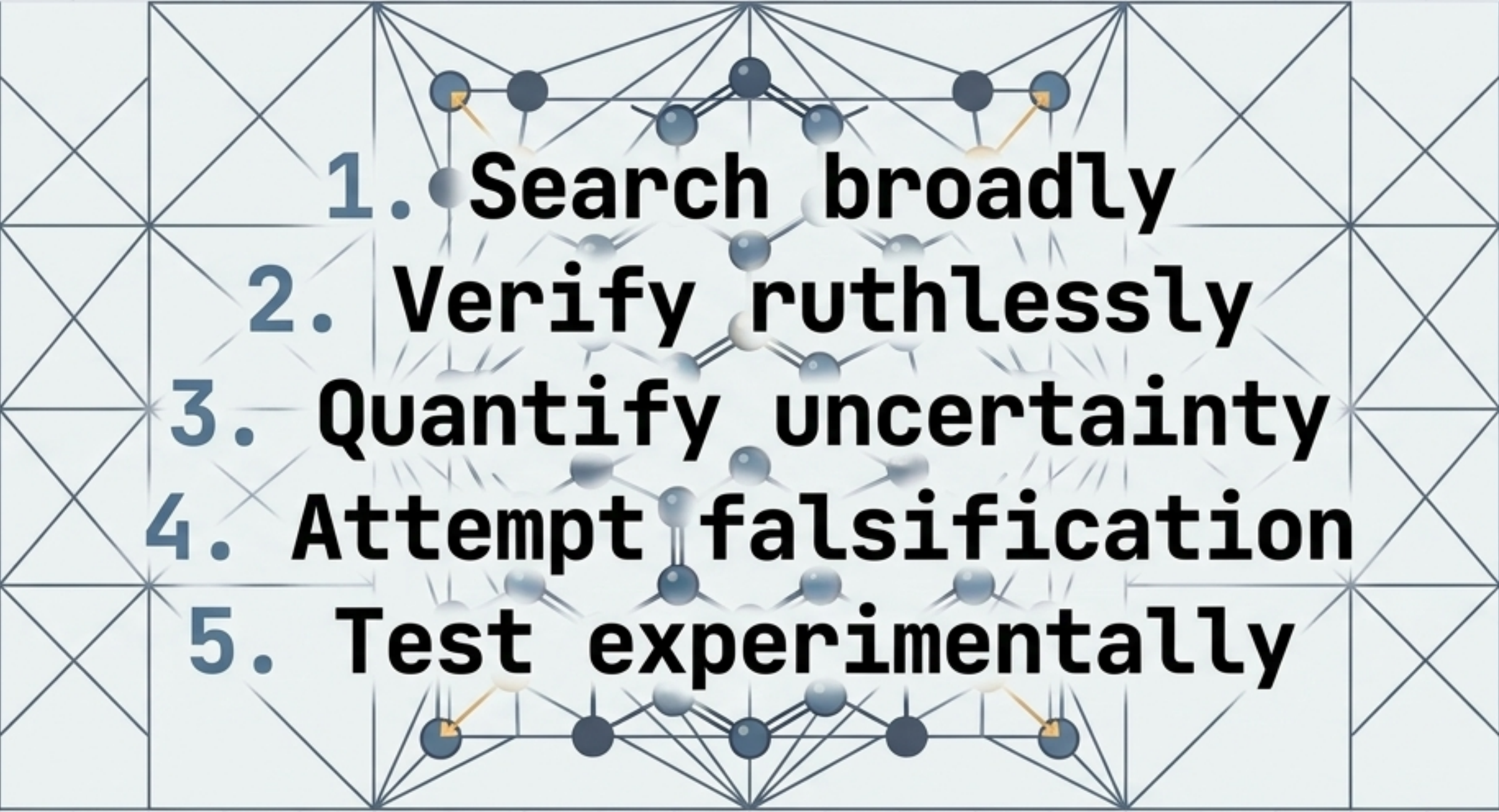
Standard AI Practices		The PHYTOFORGE-X Mandate	
Docking equals validation	→	Never equate docking with experimental validation.	 
Silence implies safety	?	Never claim 'safe' solely because toxicity was not found.	 
Highlight positive studies	→	Always preserve negative findings and quantify uncertainty.	 
Predict human efficacy	?	Never equate animal efficacy with human efficacy.	 

Revision 1.0

Approved by: PHYTOFORGE-X Committee



The PHYTOFORGE-X Philosophy

- 
- 1. Search broadly**
 - 2. Verify ruthlessly**
 - 3. Quantify uncertainty**
 - 4. Attempt falsification**
 - 5. Test experimentally**

PhytoIntelligence Evidence-to-Formulation Research Framework.