

WHERE
insights LEAD TO
answers



Harnessing Computational Informatics In Predictive Toxicology

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Overview



Computational Informatics

Definition and
real-world
Applications

Impact and
Benefits



Predictive Toxicology

Descriptive
toxicology

Mechanistic
toxicology



Cheminformatics

Lead Discovery
and Optimization
ADME Prediction



Bioinformatics

Target
Identification
and Validation



Other services

Biopesticides
risk-assessment

Systematic
review

Automation

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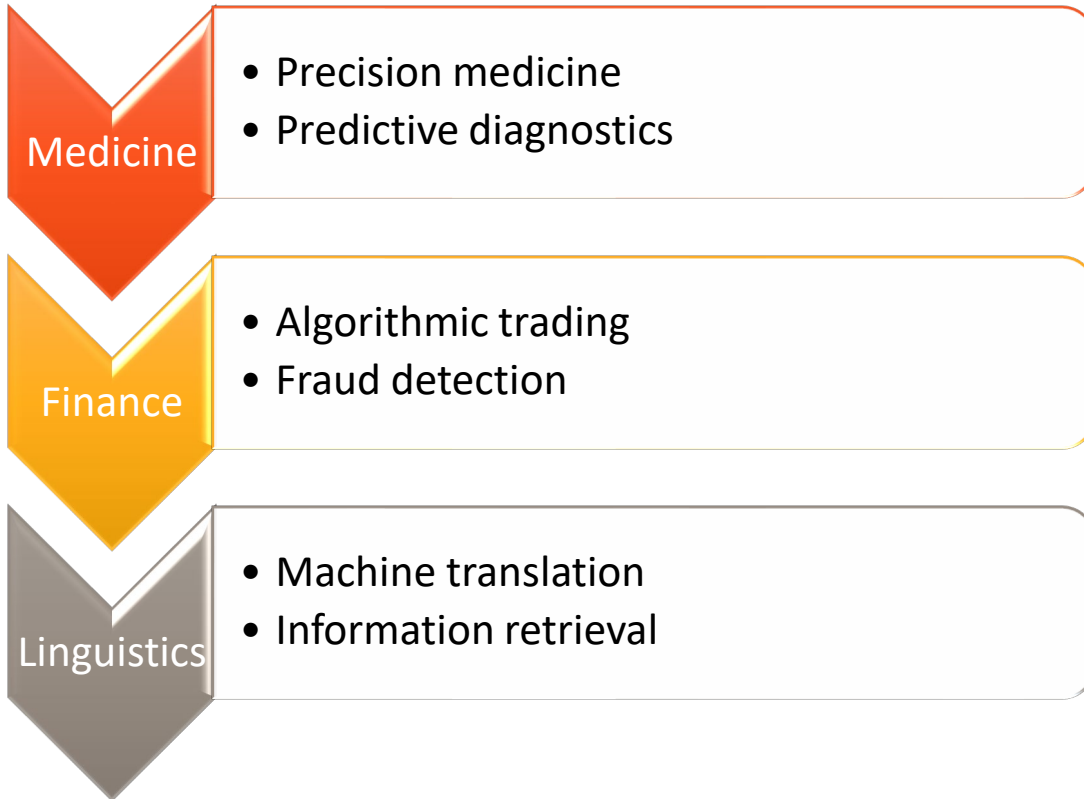
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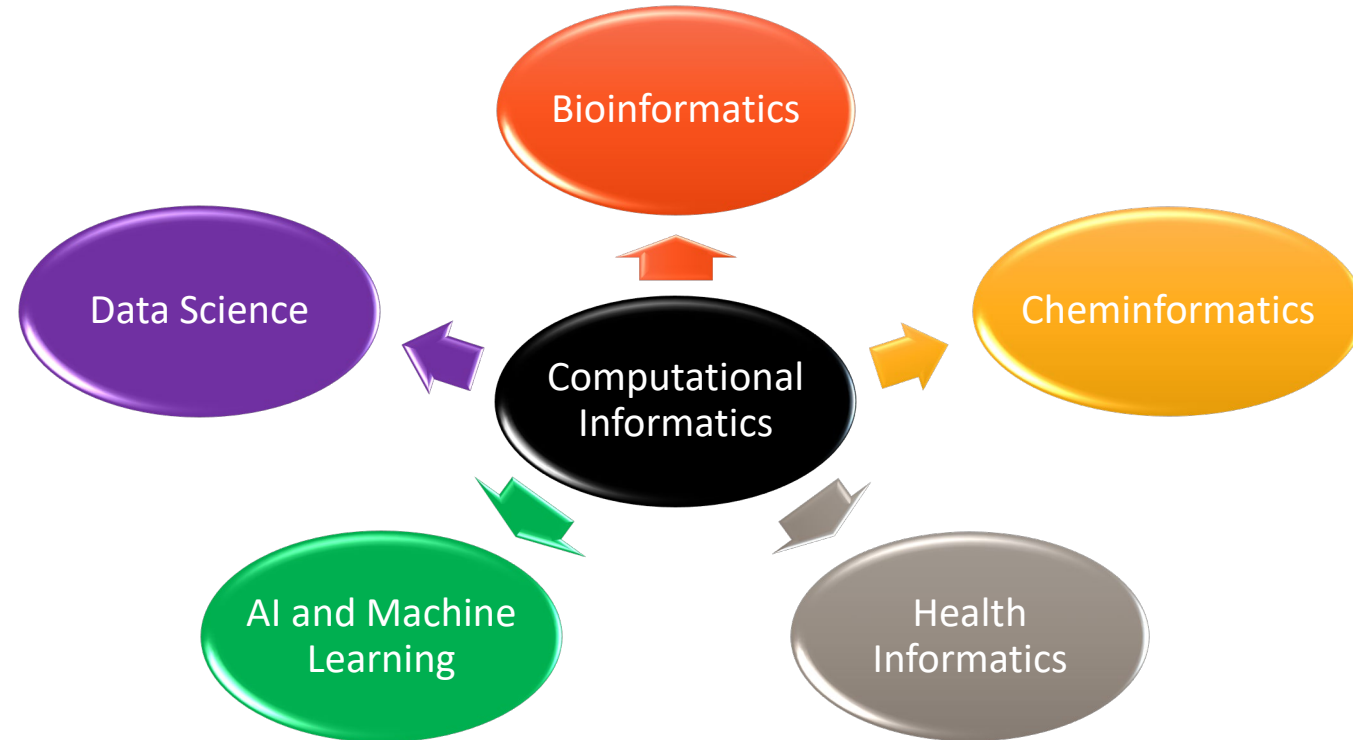
Automation

Computational Informatics Applications

Real-world applications



Drug Discovery



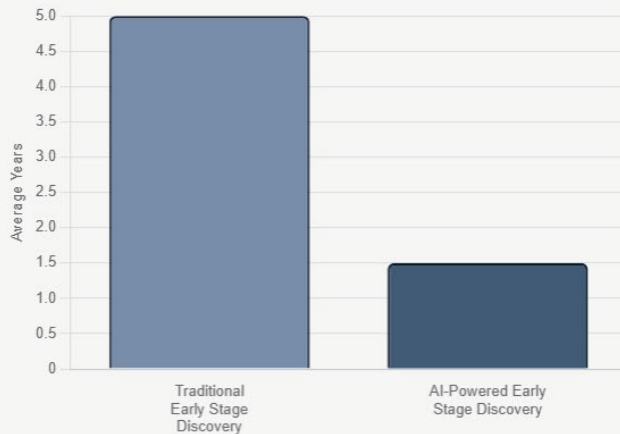
Computational Informatics Impact in Drug Discovery

The Payoff: Quantifying the Leap

The shift to computational methods delivers staggering, measurable improvements in speed and financial efficiency, transforming the economics of drug development.

Accelerated Discovery Timeline

Informatics drastically compresses the initial, most uncertain phase of research.



Massive Cost Reduction

By failing faster and smarter, the financial drain of late-stage failures is significantly reduced.

\$2.5B

Avg. Traditional R&D Cost

~35%

Potential R&D Cost Reduction

- Zhavoronkov, A. From Start to Phase 1 in 30 Months: AI-Discovered and AI-Designed Anti-Fibrotic Drug Enters Phase I Clinical Trial. 2022 <https://insilico.com/phase1>
- Exscientia, in partnership with Sumitomo Dainippon Pharma, developed a novel small-molecule drug candidate (DSP-1181) for obsessive-compulsive disorder (OCD) in less than 12 months, making it the first AI-designed molecule to enter human clinical trials.

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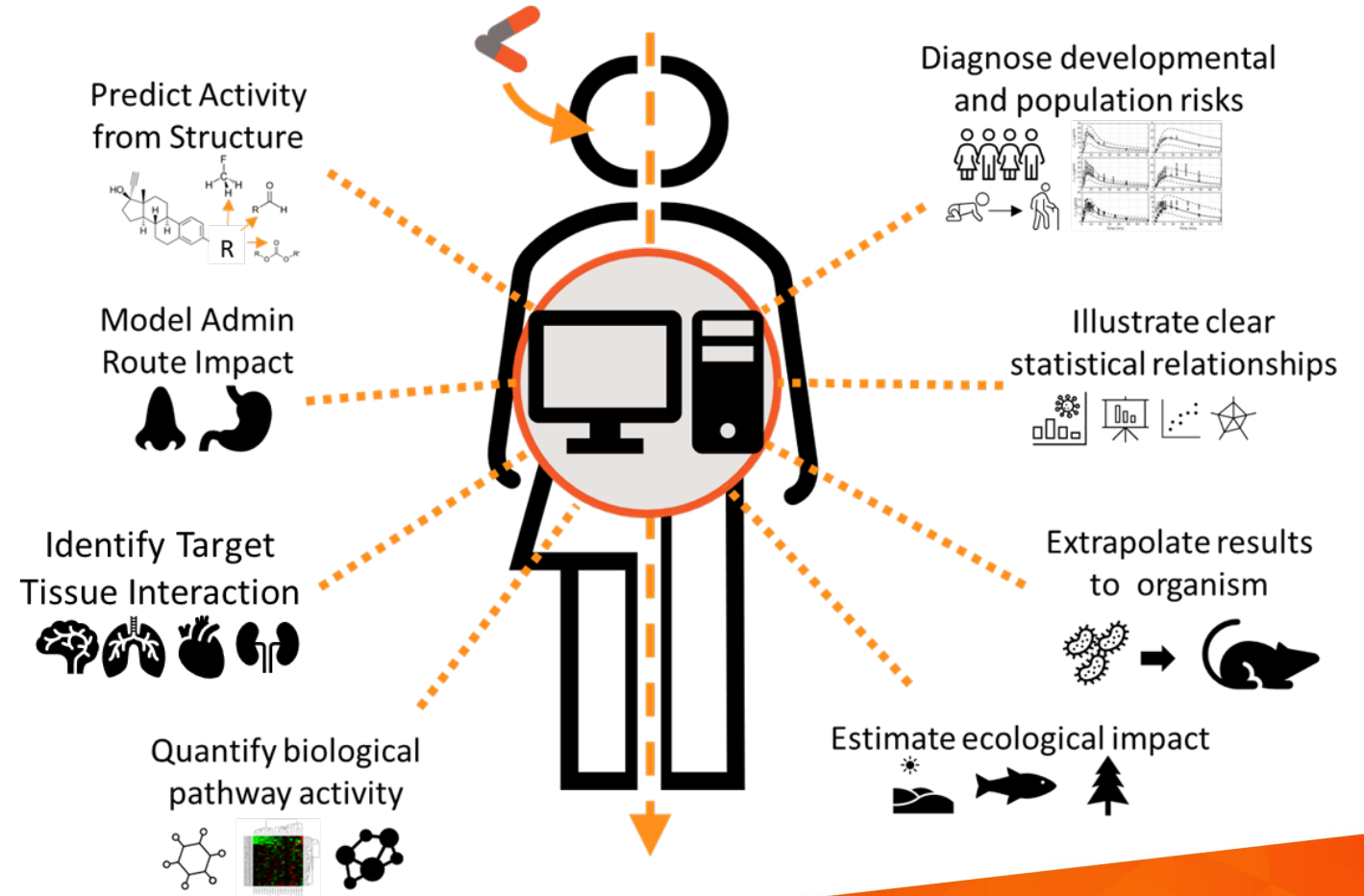
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Predictive Toxicology finds hazards and quantifies risk before trials

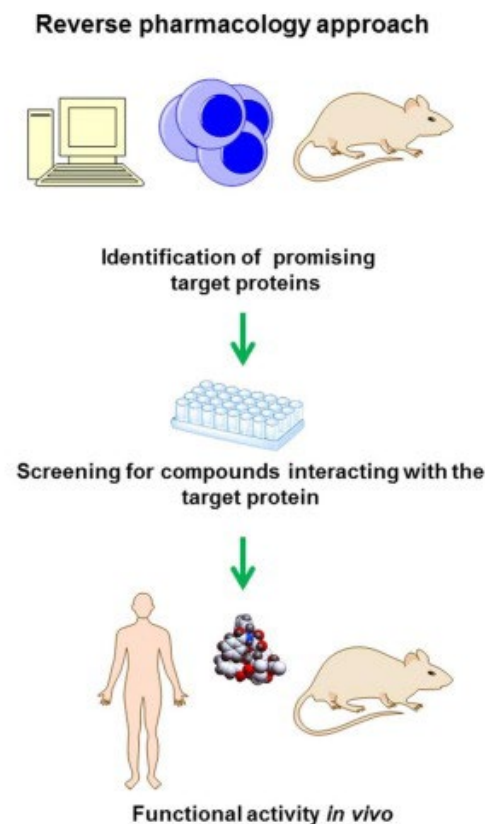
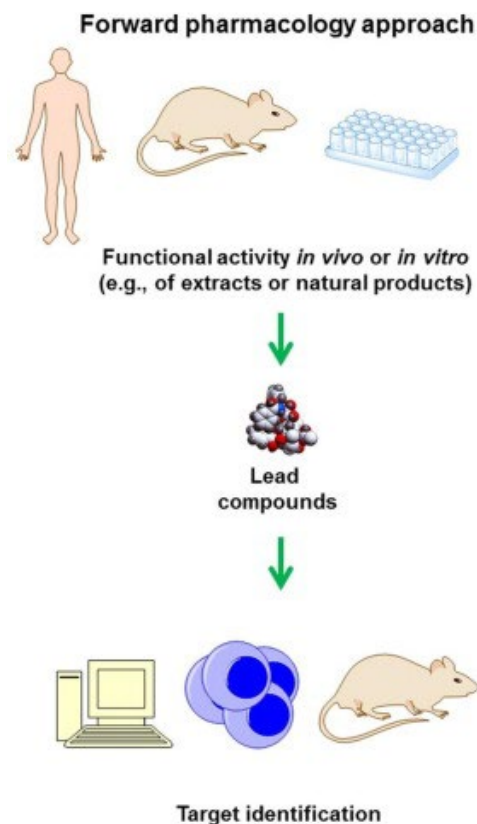
- Quantifies biology to estimate risk and hazard before testing using in vitro and/or in silico data
- Characterizes chemical behavior when in vivo data aren't available or before experimentation to improve confidence



Drug Discovery

Throwing darts at a wall and painting a target where they land. You find a compound that works, then figure out its target

The discovery of penicillin by Alexander Fleming.



Picking a target and then throwing darts at it. You know the target, then find a compound that hits it.

The development of Gleevec (imatinib) for chronic myelogenous leukemia (CML). Researchers knew that a specific mutated protein, BCR-ABL, was the cause of CML.

Swinney DC, Anthony J (Jul 2011). "How were new medicines discovered?". *Nature Reviews. Drug Discovery*. **10** (7): 507–19

Predictive Toxicology

THE EVOLUTION OF TOXICOLOGY: From Observation to Prediction

DESCRIPTIVE TOXICOLOGY

(The Classical “Forward” Approach)

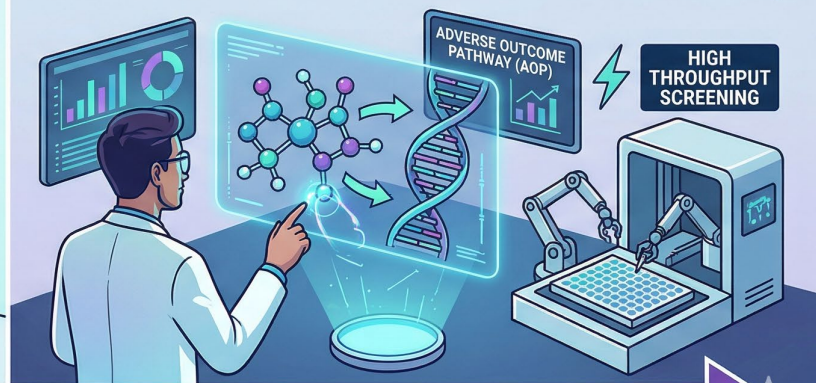
- **Starting Point: Apical Endpoint** (e.g., observe liver damage)
- **Primary Model: In Vivo** (Animal Testing, like mice/rats)
- **Data Type: Qualitative & Observational** (Focus on final outcome)
- **Focus: “What happened?”**: Assessing physical effects
- **Throughput: Low Throughput** (Time-consuming, costly) ⏳



PREDICTIVE TOXICOLOGY

(The Modern “Reverse” Approach)

- **Starting Point: Molecular Initiating Event** (e.g., receptor binding)
- **Primary Model: In Vitro & In Silico** (Cell assays, computational models)
- **Data Type: Quantitative & Mechanistic** (Understanding pathways)
- **Focus: “Will it cause an effect?”**: Assessing risk and mechanism
- **Throughput: High Throughput** (Screen thousands of compounds) ⚡



FIELD EVOLUTION

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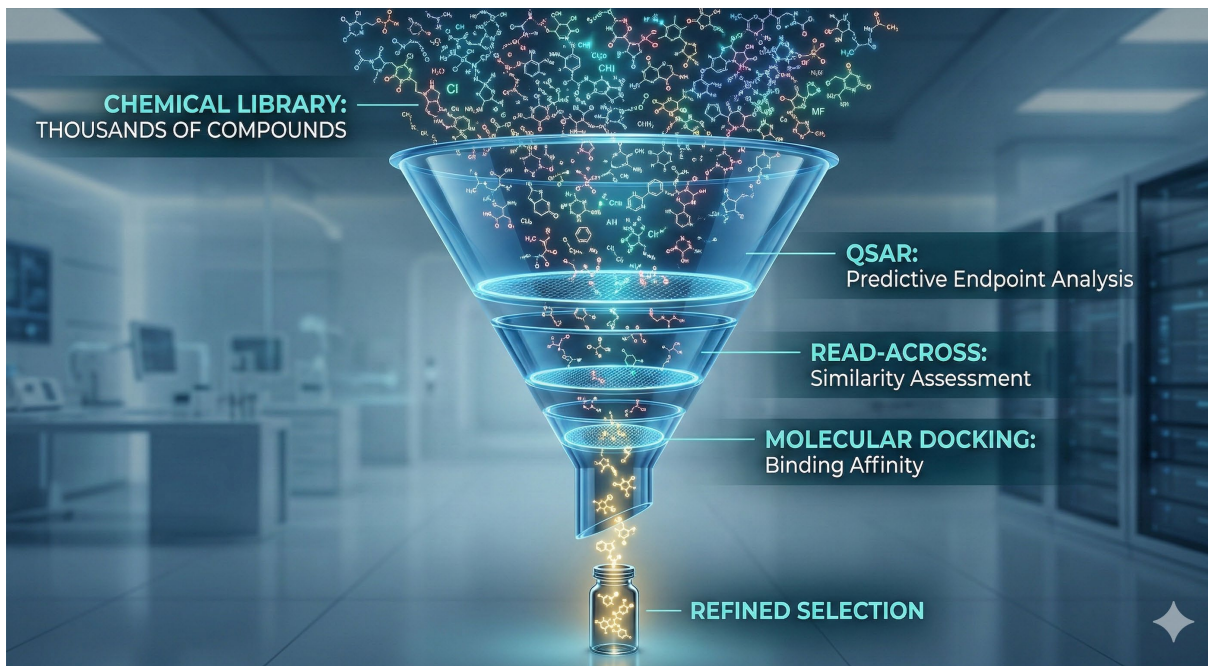
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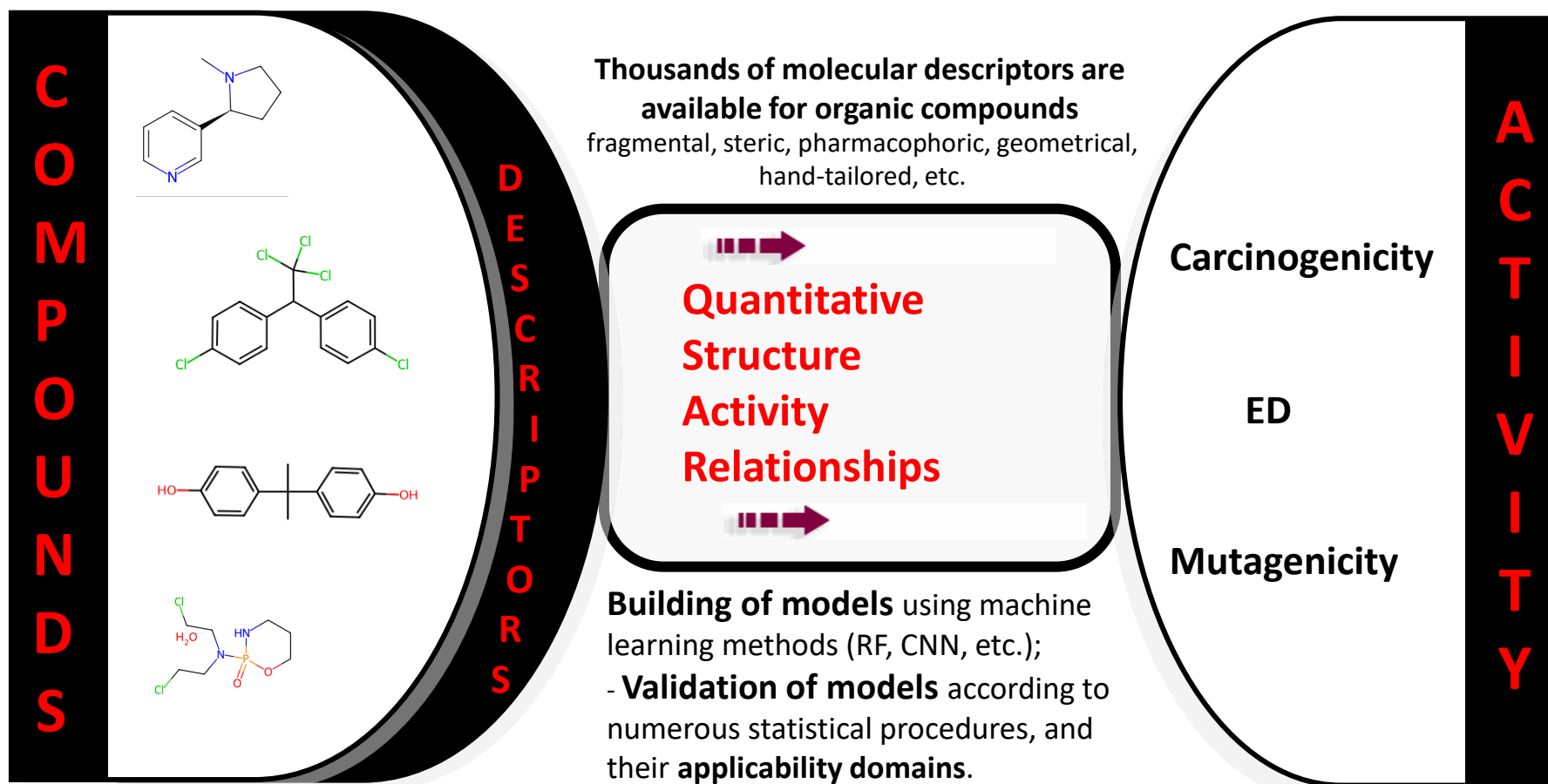
Early Safety Screening: High-Throughput Cheminformatics & Docking



The Value Hook:

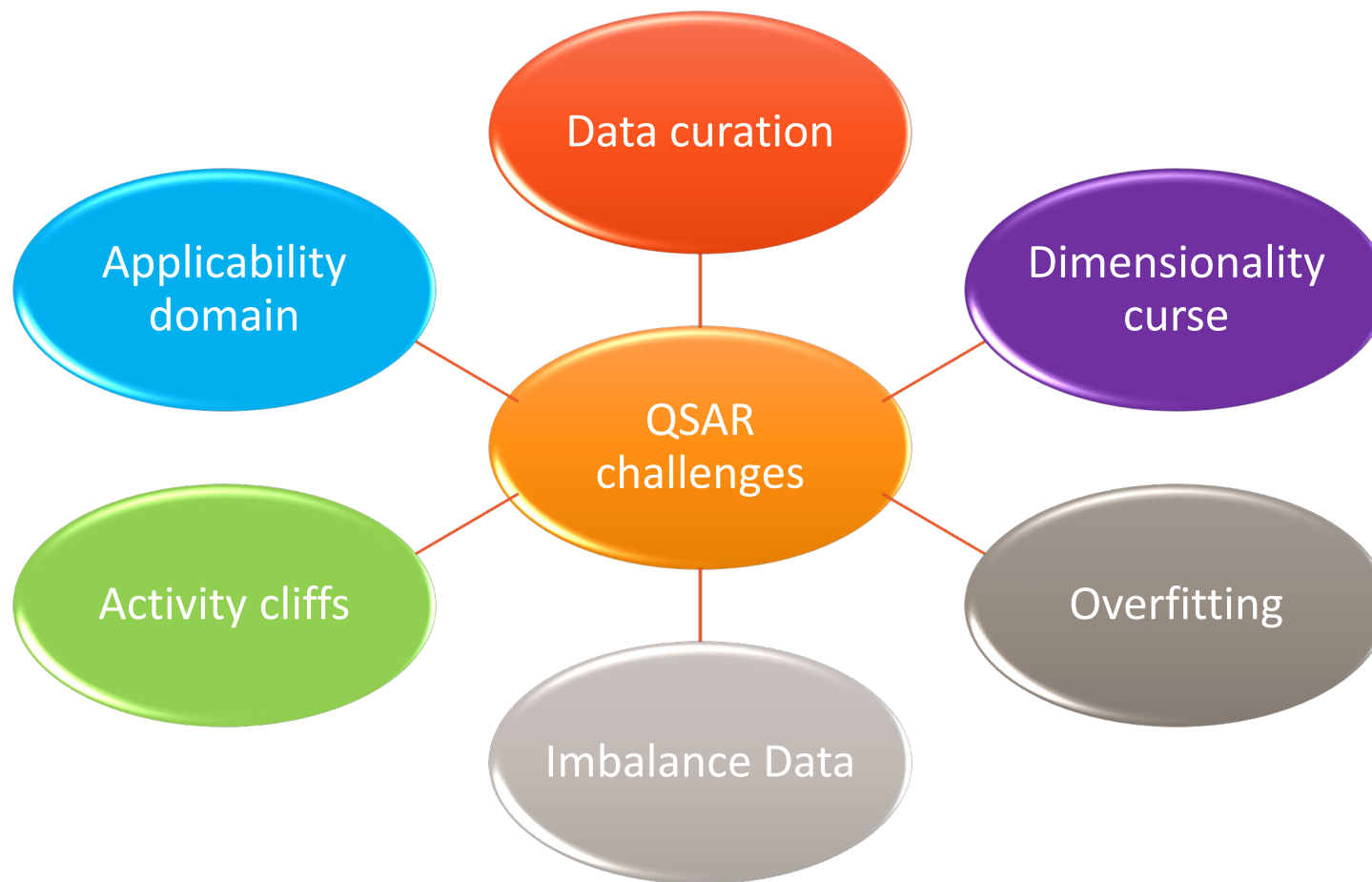
- ❑ Screen thousands of compounds in days vs. months, rapidly prioritize winners.
- ❑ QSAR & read-across leverage regulatory-accepted databases (OECD QSAR Toolbox, ToxCast).
- ❑ Molecular docking identifies off-target binding risks before synthesis costs escalate.
- *"We help you triage your chemical library before you spend a dime on wet lab work. Think of it as intelligent compound portfolio management."*

Quantitative Structure Activity Relationship (QSAR)



Adapted from Denis Fourches, PhD, UNC 2010

QSAR Modelling Challenges



Key Advantages



COST-EFFECTIVENESS: QSAR IS SIGNIFICANTLY CHEAPER AND FASTER THAN TRADITIONAL EXPERIMENTAL TESTING.



ETHICAL CONSIDERATIONS: IT REDUCES THE USE OF ANIMALS IN TESTING.

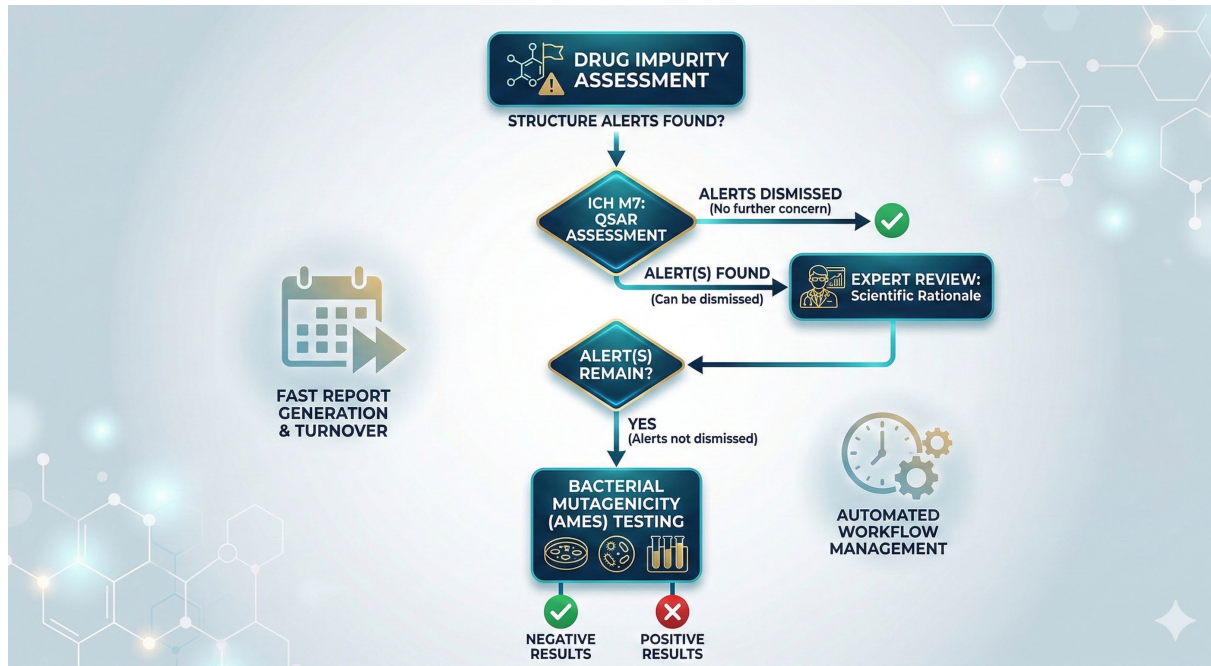


EFFICIENCY: IT ALLOWS FOR THE RAPID SCREENING OF LARGE NUMBERS OF CHEMICALS.



VERSATILITY: MULTIPLE FUNCTIONALITIES AND APPLICATIONS

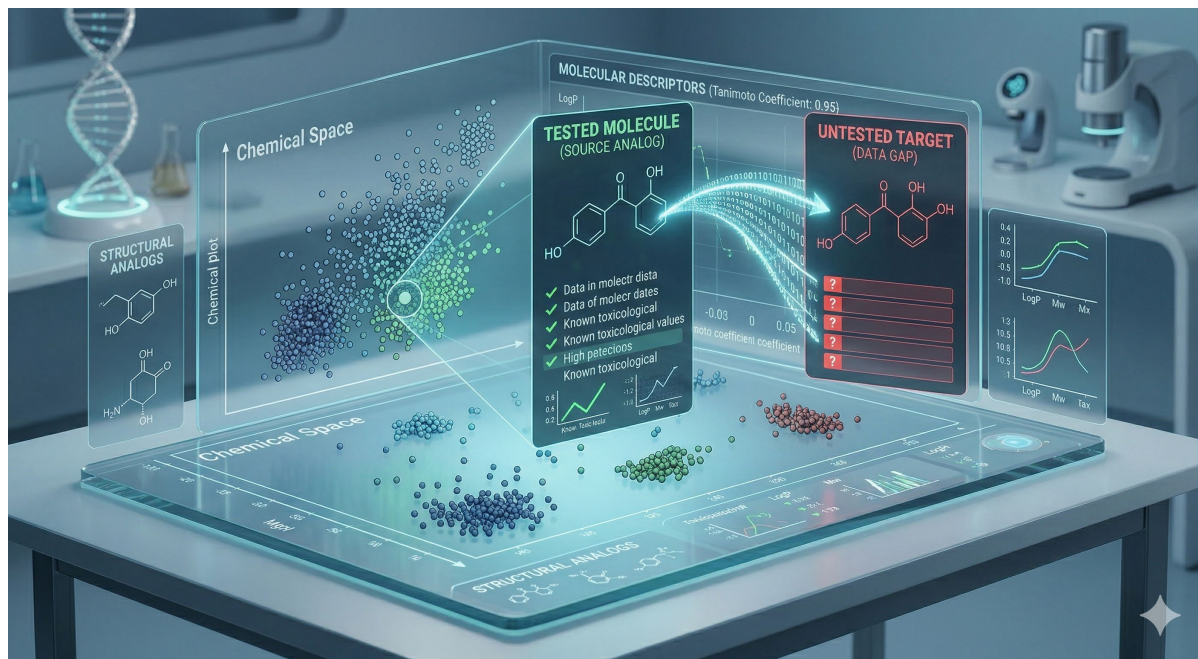
Regulatory Safety: Addressing Drug Impurities (ICH M7) & Mutagenicity



The Value Hook:

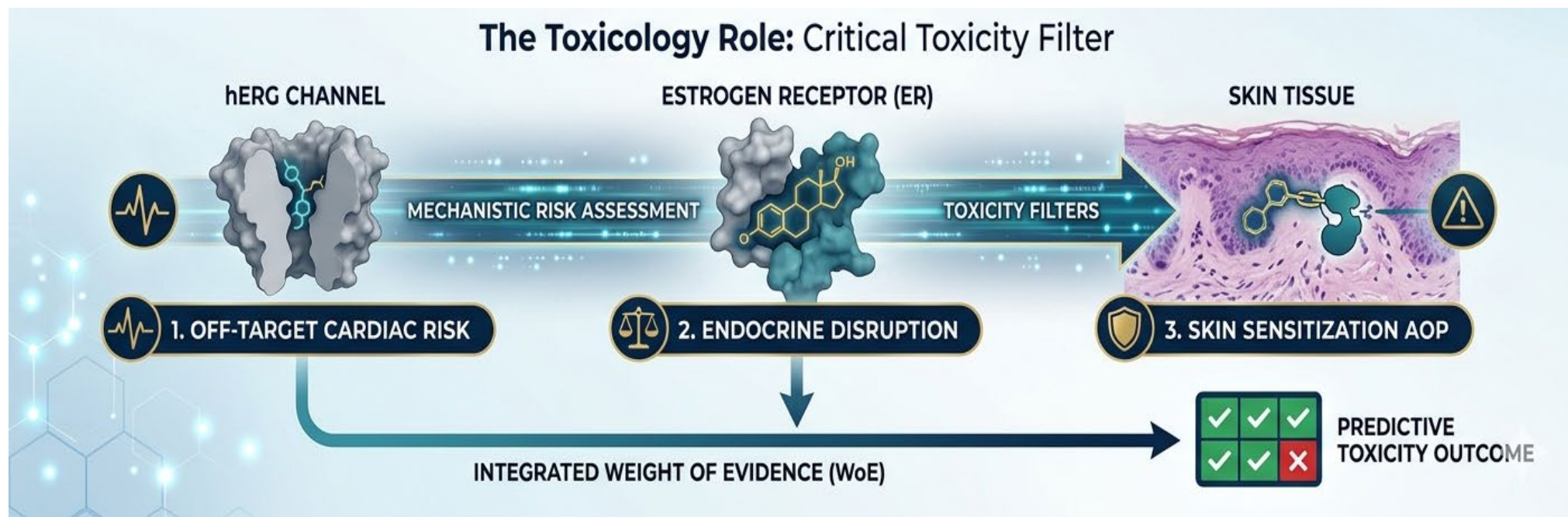
- ❑ ICH M7 compliance is mandatory for impurities, we provide defensible, auditable reports.
- ❑ Bacterial mutagenicity testing (Ames) integrated with computational predictions = faster clearance.
- ❑ Reduce regulatory hold risk: catch genotoxic impurities before they reach the FDA.
- *"Impurity qualification is a regulatory landmine. We turn it into a controlled, predictable process that keeps your IND on track."*

Read-Across

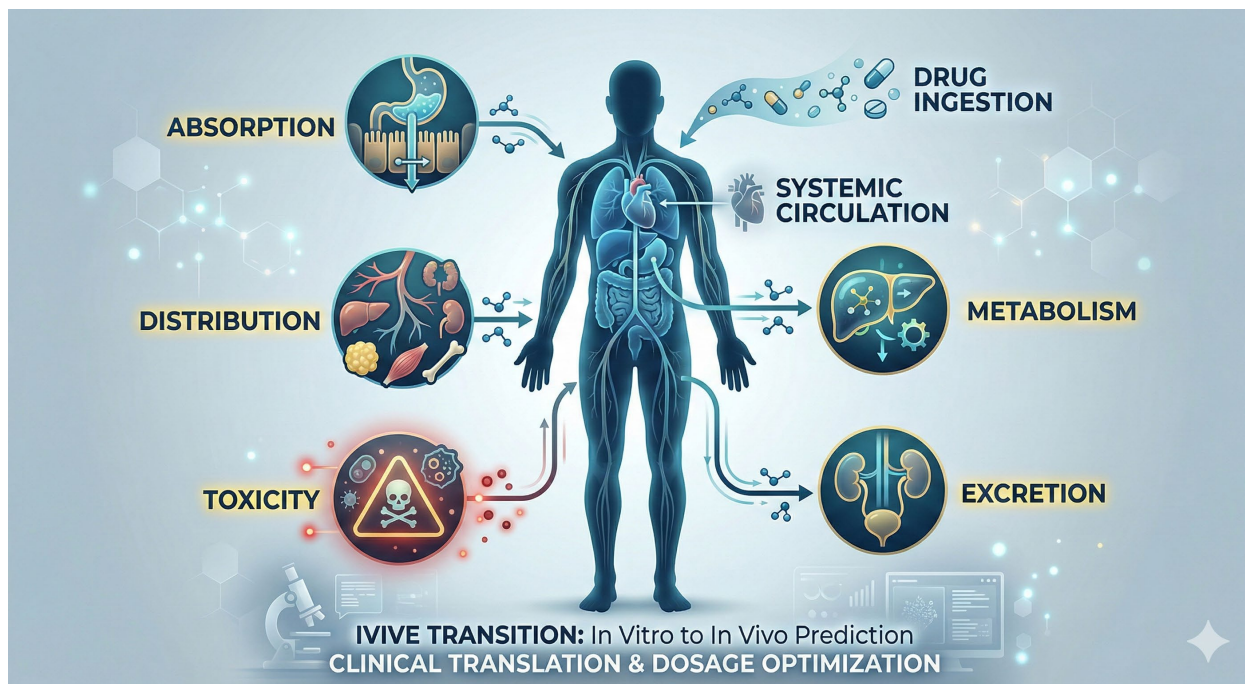


- **The Core Logic:** If two or more chemicals are structurally similar and share a common metabolic pathway or mechanism of action, they are likely to have similar toxicological profiles.
- **The Process:** Instead of conducting new in-vivo tests, you "read" the data from a well-studied analog "across" to your untested substance.

Molecular Docking

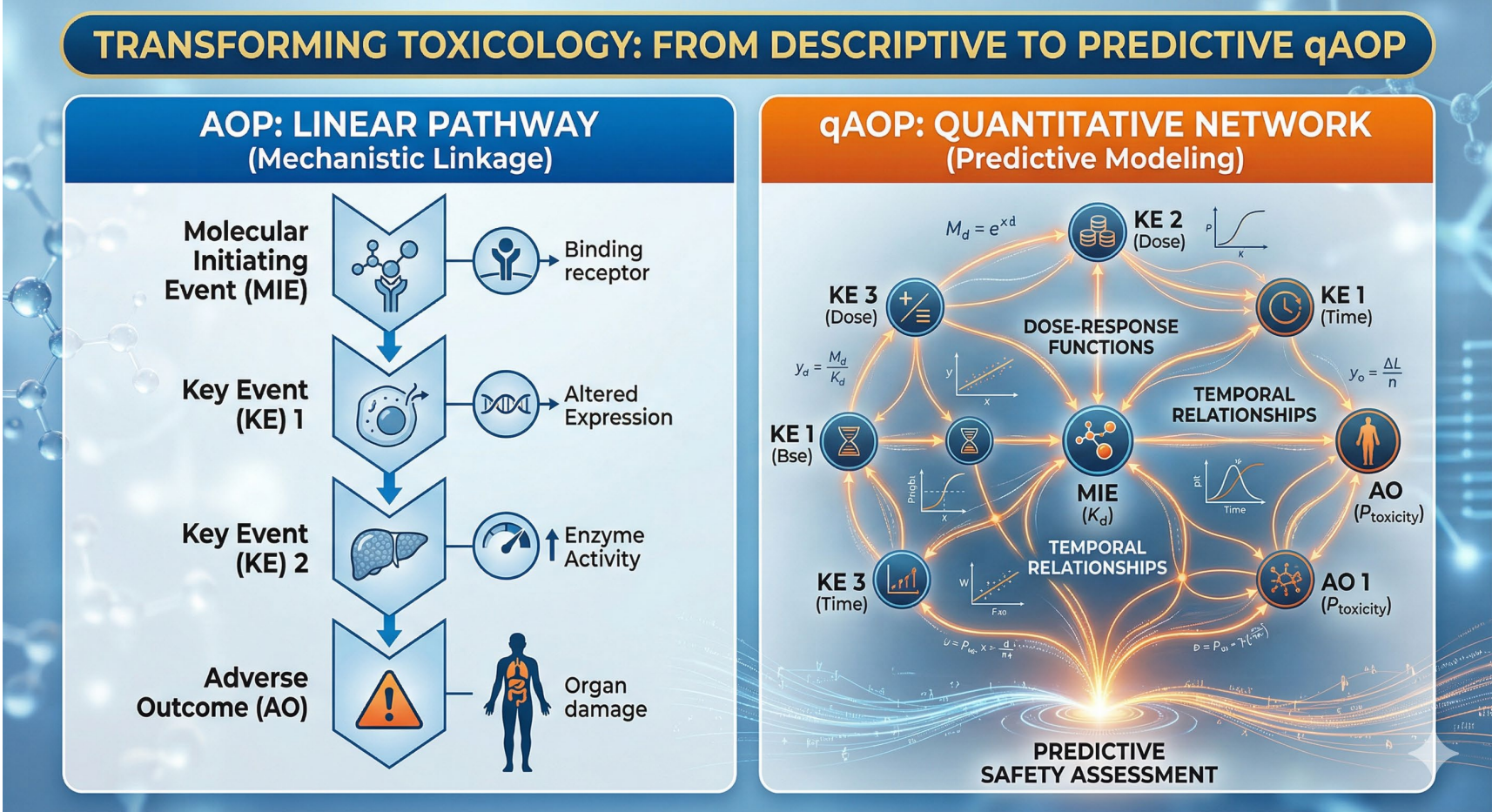


ADMET & Predictive ADME: Understanding Compound Behavior Early



The Value Hook:

- ❑ Predict pharmacokinetic properties, e.g. bioavailability, clearance, half-life—before compound synthesis.
- ❑ Flag toxicity liabilities, e.g. hERG interactions, reactive metabolites, CYP interaction, that cause late-stage failures.
- ❑ Integrate with medicinal chemistry feedback loops to guide iterative design.
- *"ADMET prediction is your early warning system. We help you avoid investing in compounds that will never make it to humans."*



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Bioinformatics in predictive toxicology

- Uses computational tools, AI, and big data to analyze high throughput –omics data to predict toxic effects before chemicals or drugs reach humans or the environment:
 - > Identify toxic mechanisms, pathways, and targets linking to adverse outcomes or specific biological processes
 - > Biomarker discovery for molecular initiating events (MIE)
 - > Predict compound safety earlier in pipelines without relying solely on animal models
 - > Rapid, cost-effective screening of toxic hazards and enhances mechanistic understanding
 - > Reducing animal testing saving time and money through early in silico screens

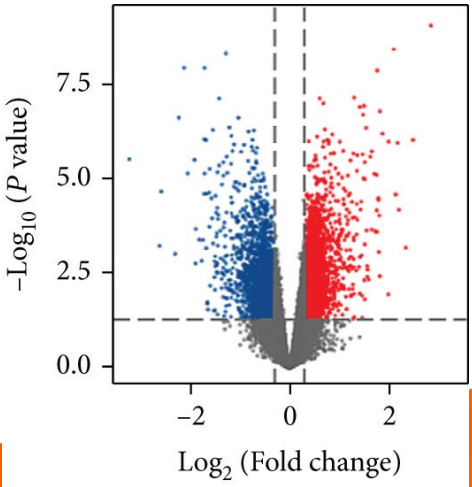
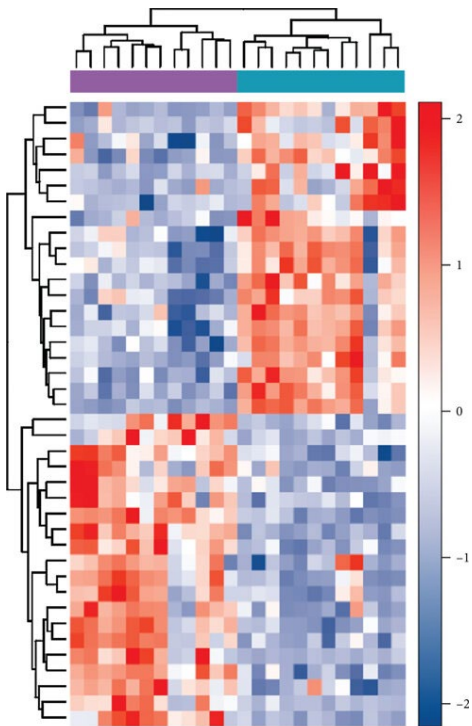
Tools and services offered in Computational Toxicology at Inotiv	
Transcriptomics	Spatial Transcriptomics
Proteomics	Network and Pathway Analyses
Additional services	
PBPK	IVIVE

Transcriptomics

- Transcriptomics is the study of all RNA transcripts (the transcriptome) in a cell or tissue. It provides a snapshot of gene expression at a given moment in time.

Importance	Usage
Early Target Identification/Toxicity Screening	Gene expression differences in healthy vs sick cells
Dose-Dependent Changes	Gene expression differences due to changes in dose leading to adverse effects
Mechanism of Action	Identify genes, MIE, and signaling events that respond to drug/chemical
Biomarker Discovery	Identify gene expression signatures that respond to drugs, chemicals, toxic agents Detecting early stress and signaling responses.

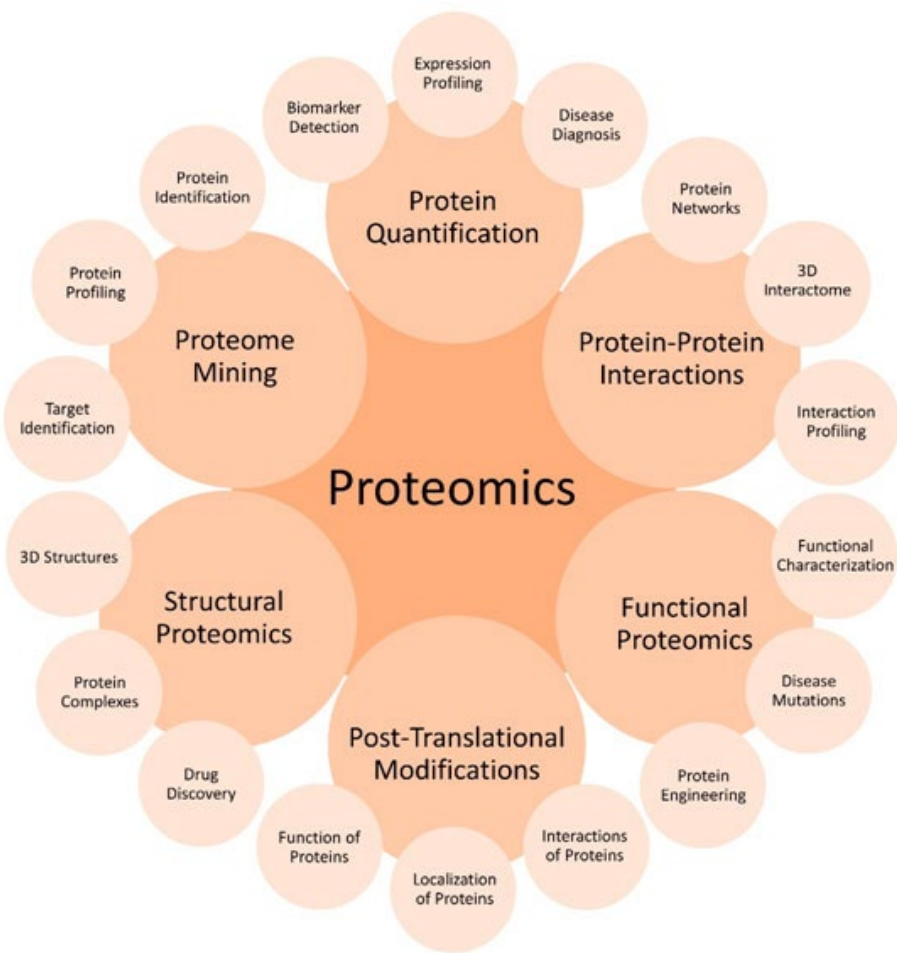
- Apply RNA-Seq analyses
 - > Bulk tissue vs Single cell RNA-seq



Proteomics

- Proteomics is the large-scale study of proteins, including their structure, function, and interactions.

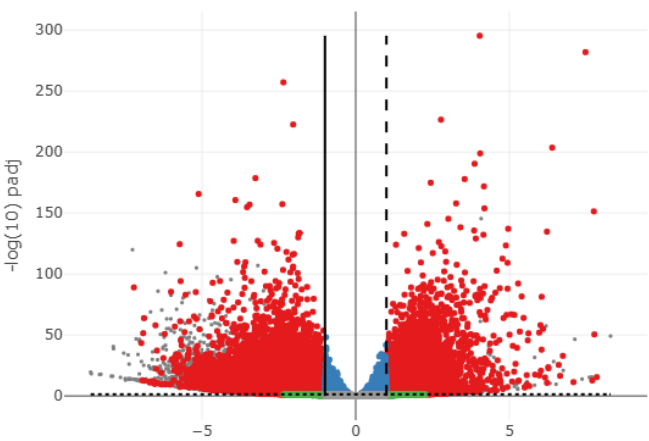
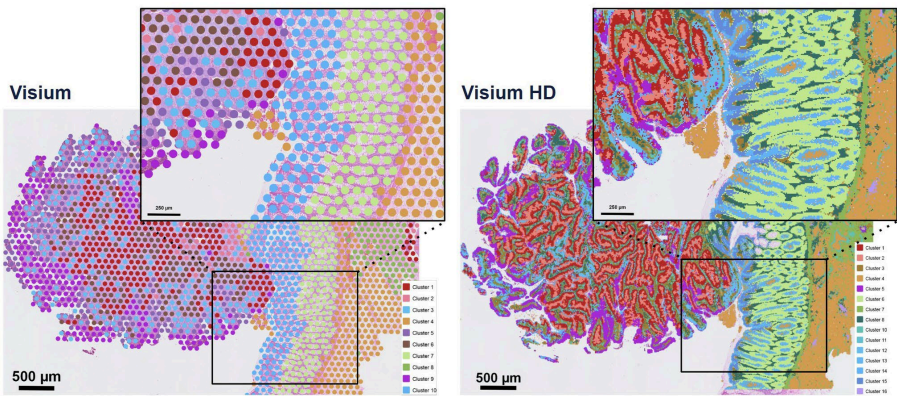
Importance	Usage
Functional Insights	Explores protein pathways and networks for mechanism of action (MoA) studies
Drug Target Validation	Confirmation of protein translation
Off-Target Effects	Identify unintended protein interactions to understand drug adverse effects
Dose-Response	Identifies protein level thresholds to differentiate adaptive vs adverse drug responses Improve dose estimation
Risk Prediction	Link protein level changes to function and phenotypic effects



Spatial Transcriptomics

- Spatial transcriptomics allows for the measurement of gene expression while retaining information about the location of RNA transcripts within a tissue section.

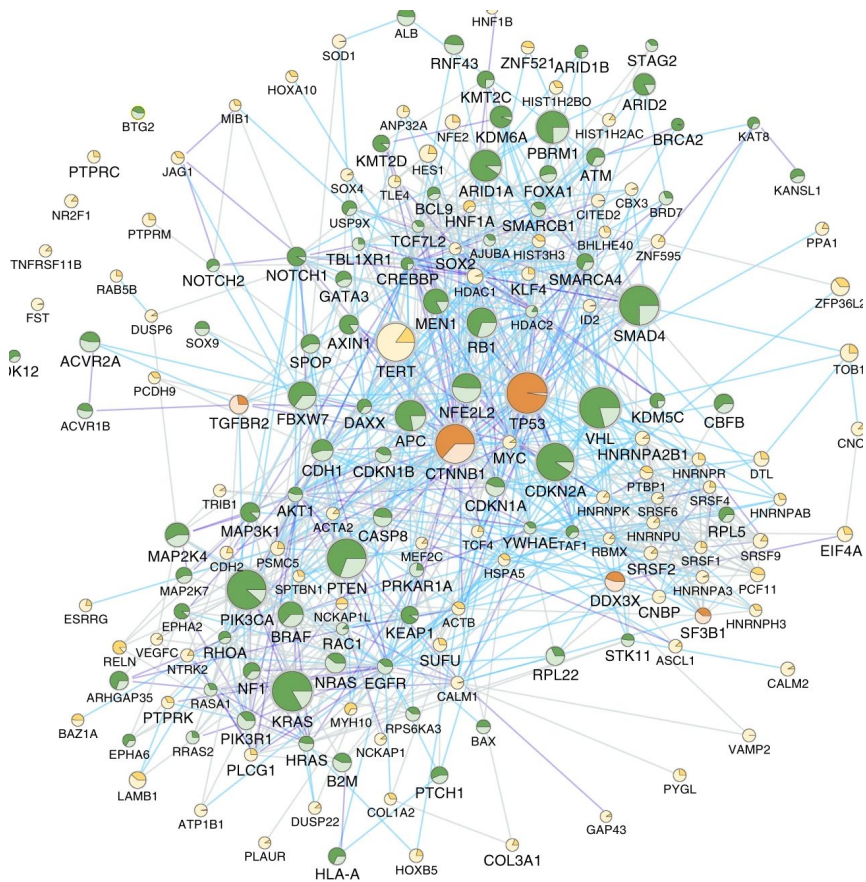
Importance	Usage
Preserving Context	Keeps location of gene expression inside the cells for all cells in the sample
Cell-cell Communication	Understand cell interaction and signaling
Disease Heterogeneity	Differentiate healthy vs diseased/damage states
If disease or damage is detected	Identifies region-specific susceptibility and dose-dependent damages. Identifies localized MIEs to then map progression of AOPs within tissues



Network and Pathway Analysis

- Diseases are often the result of disruptions in complex biological networks (like signaling pathways).
- Bioinformatics tools can map these networks and pinpoint key nodes or "hubs" that, if modulated, would have a significant therapeutic effect.
- Network pathways strongly relate to adverse outcome pathways (AOPs)
 - > Relies on -omics data and bioinformatic tools
 - > Link exposure -> molecular initiator events (MIE) -> key events -> adverse outcomes

Importance	Usage
Mechanistic Insights over Observations	Defines the chain of MIE to toxicity to have a better understanding of how a chemical is toxic
Adverse Outcome Pathways	Network and signaling pathways help create AOPs Provide additional gene context to chemical exposure
Improve Toxicity Predictions	Understand mechanism level perturbations from conserved pathways or changes in dose and identify key network modules
Risk Assessment	Faster screening for chemical safety by predicting potential adverse effects through simulations



The Importance of Multi-Omics Integration

- **What is it?**

Multi-omics integration involves combining data from multiple 'omics' platforms (e.g., transcriptomics, genomics, proteomics) to create a comprehensive, holistic view of a biological system.

- **Holistic Understanding:**

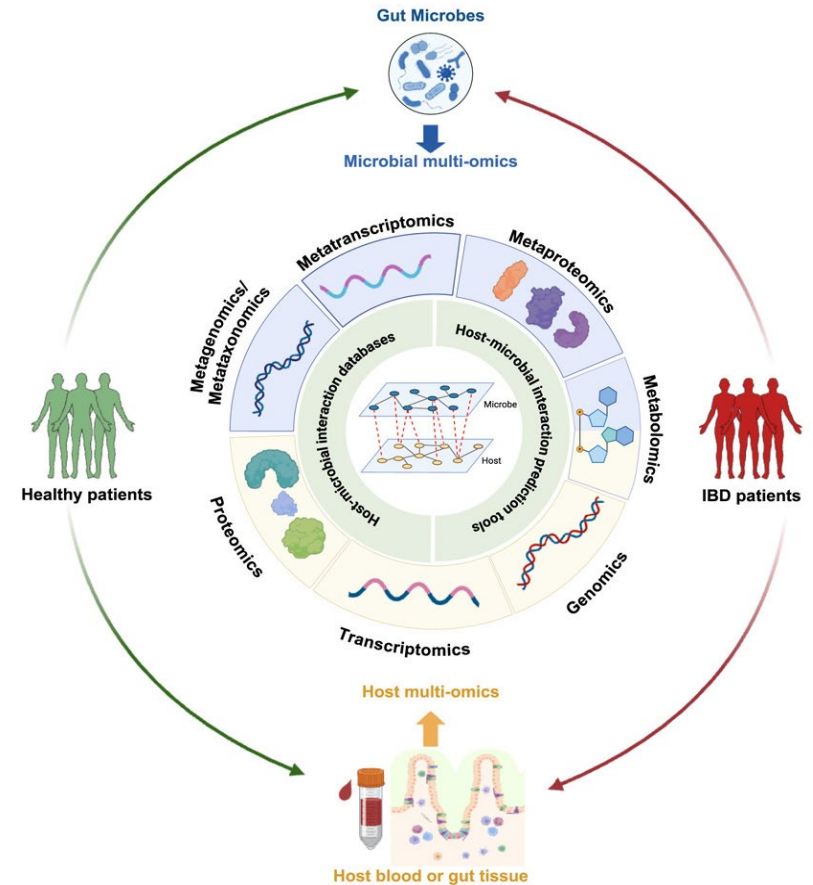
- > Integrating multi-omics allows us to see how gene expression relates to protein abundance and how they affect cellular function and disease.

- **Revealing Hidden Patterns:**

- > Integration can uncover novel insights and complex relationships that would be missed by analyzing each dataset in isolation.

- **Enhanced Predictive Power:**

- > A multi-omics approach leads to more robust biomarkers and more accurate predictions of drug response and toxicity.



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Pharmacokinetics (PK)

Physiology Based PK (PBPK)

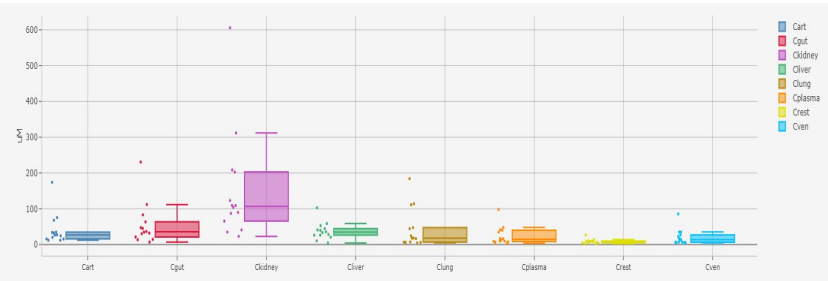
- Predicts tissue-specific chemical concentrations
- Computational modeling method that breaks body into tissue compartments to show concentration of chemical over time in plasma and each tissue compartment

Importance and Application in Predictive Toxicology

- Predict drug/chemical build up in tissues from max concentration (toxic or safe accumulation)

Importance	Usage
Early Screening	Predict PK properties to estimate safer dose levels
Mechanistic Insights	Relate external exposure to internal concentrations
Reduce Animal Use	Simulate and predict internal organ concentrations for different species using physiological parameters

Predict Tissue Accumulation

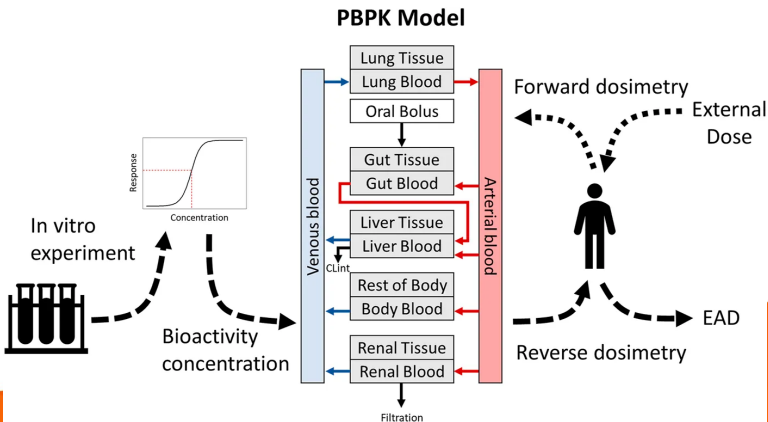


In Vitro to In Vivo Extrapolation (IVIVE)

- Predict equivalent administered dose (EAD) from in vitro or in silico data
- Estimates the EAD from plasma (in vivo) concentration of a chemical equal to the active concentration to an in vitro assay

Importance and Application in Predictive Toxicology

- Is the chemical concentration safe in vitro?
- Is the chemical dose safe in vivo?
- Explains exposure-risk relationship
- Predict human or species relevant doses and quantifies risk assessment from in vitro/in silico data



Biopesticide & Specialty Risk Assessment (dsRNA)



The Value Hook:

- ❑ dsRNA (double-stranded RNA) biopesticides are emerging—regulatory frameworks are evolving.
- ❑ We provide off-target risk assessment for non-target organisms (pollinators, aquatic species).
- ❑ EPA and EFSA require mechanistic data; we deliver bioinformatics-driven safety profiles.
- *"Biopesticides are the future of agriculture, but regulators are cautious. We provide the science to prove safety and accelerate approval."*

Evidence Synthesis: Lit Reviews & Regulatory-Ready Manuscripts



The Value Hook:

- ❑ Systematic literature reviews for weight-of-evidence (WoE) submissions.
- ❑ Regulatory-style manuscripts for ICH, FDA, EMA dossiers, written by toxicologists.
- ❑ Fast turnaround: automated workflows mine PubMed, ToxBank, and proprietary databases.
- *"Regulators demand thorough literature support. We turn messy science into clean, defensible narratives that satisfy auditors."*

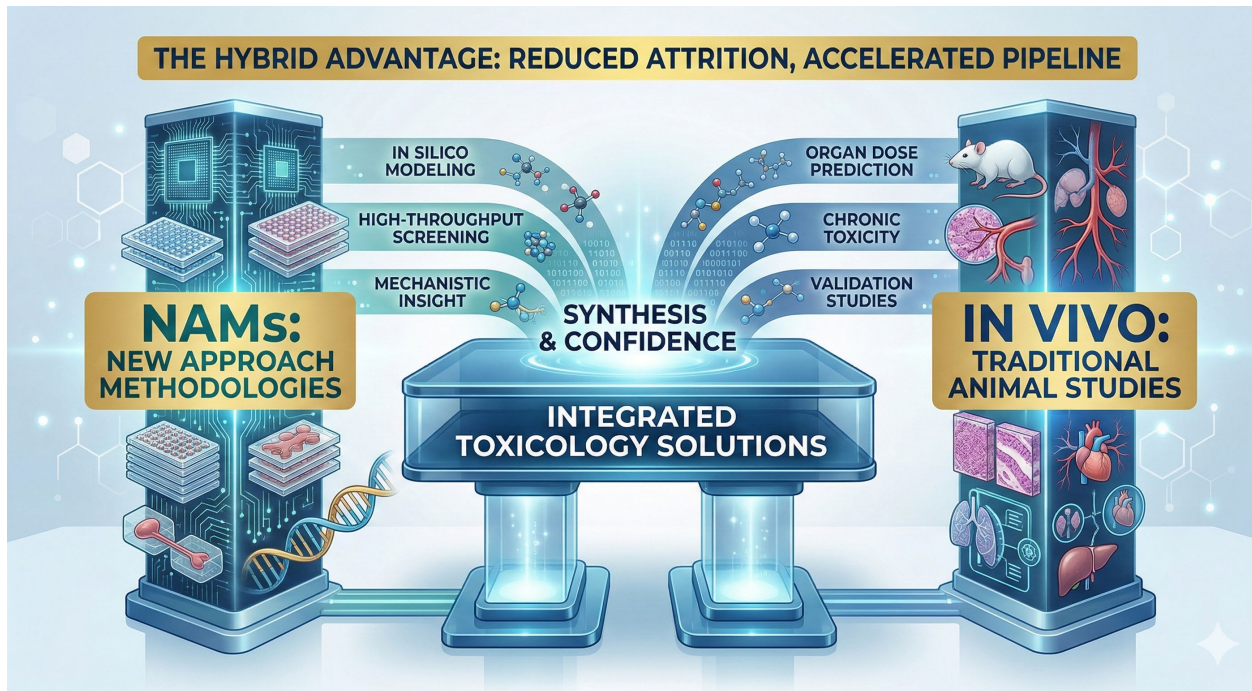
Operational Speed: Automated Workflows & Fast Turnaround



The Value Hook:

- ❑ Automated pipelines for QSAR, ADMET, and bioinformatics = 10x faster than manual analysis.
- ❑ Priority queues for urgent IND-enabling studies or competitive intelligence.
- *"Speed is competitive advantage in pharma. We deliver NAMs insights in weeks, not quarters, so you can make faster Go/No-Go decisions."*

Why Clients Choose Us: The Hybrid Advantage (NAMs + In Vivo)



The Value Hook:

- ❑ **Credibility:** Our animal model legacy makes computational predictions trustworthy.
- ❑ **Integration:** Seamless workflows from in silico → in vitro → in vivo, no vendor juggling.
- ❑ **Regulatory fluency:** We speak FDA/EMA language and design studies they accept.
- *"Other vendors offer pieces; we offer the whole puzzle. NAMs for speed, in vivo for validation, and regulatory expertise to tie it together."*

Our Services Catalog: Comprehensive Solutions for Every Stage

Cheminformatics & Early Safety

- QSAR (Quantitative Structure-Activity Relationships)
- Read-Across Analysis
- Molecular Docking
- Ultra-Virtual Screening (100K+ compounds)
- Chemical Alert Flagging

Pharmacokinetics & ADME

- ADMET Analysis (Absorption, Distribution, Metabolism, Excretion, Toxicity)
- PBPK (Physiologically Based Pharmacokinetics)
- IVIVE (In Vitro to In Vivo Extrapolation)
- PK/PD Modeling

Specialized Services

- Biopesticide Risk Assessment (dsRNA Off-Target)
- Systematic Literature Reviews
- Regulatory Manuscript Writing
- Automated Computational Workflows

Bioinformatics & Omics

- NGS (Next-Generation Sequencing): RNAseq, Bulk & Single-cell
- Spatial Transcriptomics
- Proteomics
- Multi-Omics Integration

Regulatory & Impurities

- Drug Impurities Assessment (ICH M7)
- Bacterial Mutagenicity Testing (Ames)

Questions?