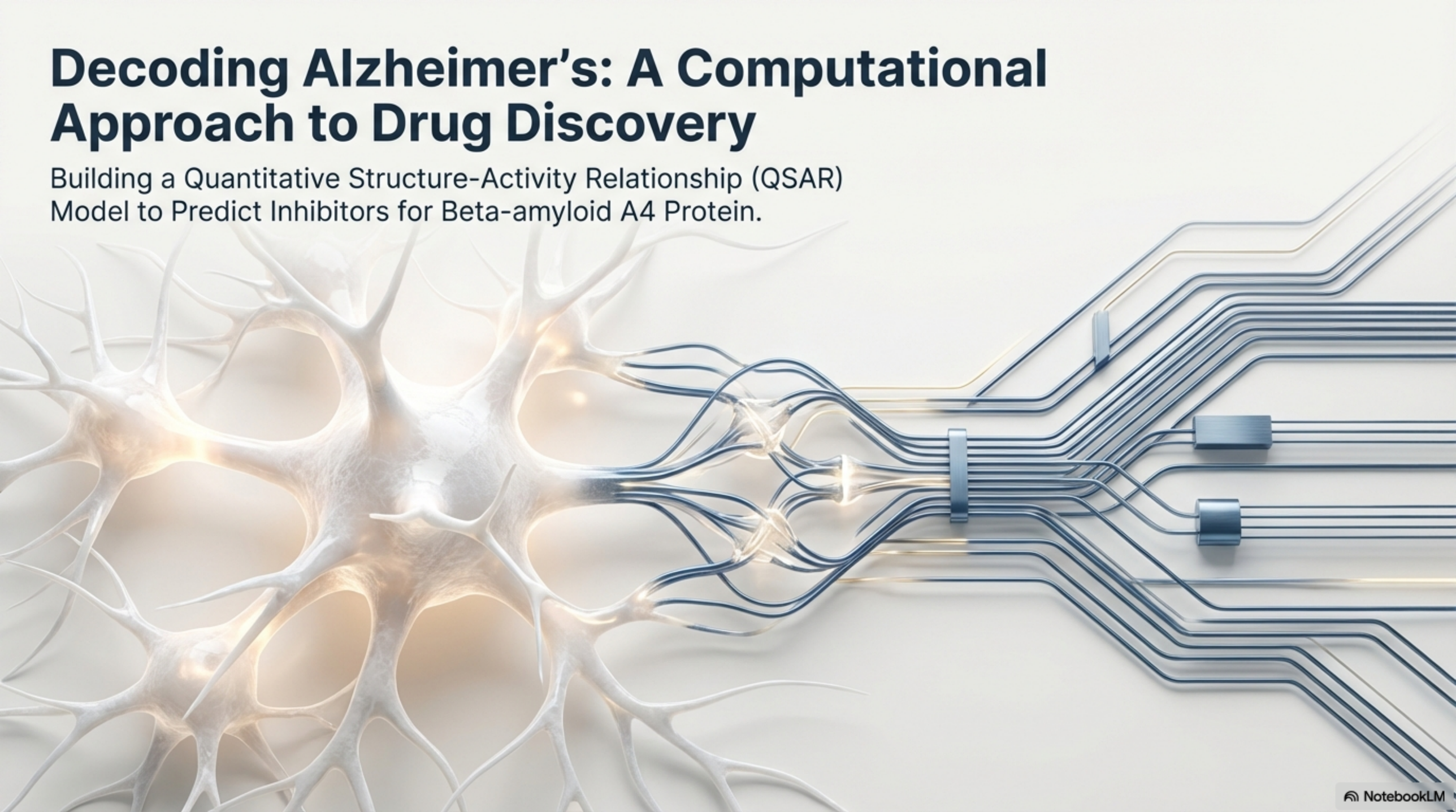
Decoding Alzheimer's: A Computational Approach to Drug Discovery

Building a Quantitative Structure-Activity Relationship (QSAR) Model to Predict Inhibitors for Beta-amyloid A4 Protein.



The Alzheimer’s Challenge: A Global Health Crisis

Affects ~50 million people globally.

Causes 60-70% of all dementia cases.

The 6th leading cause of death in the US.

Currently, no cure exists.

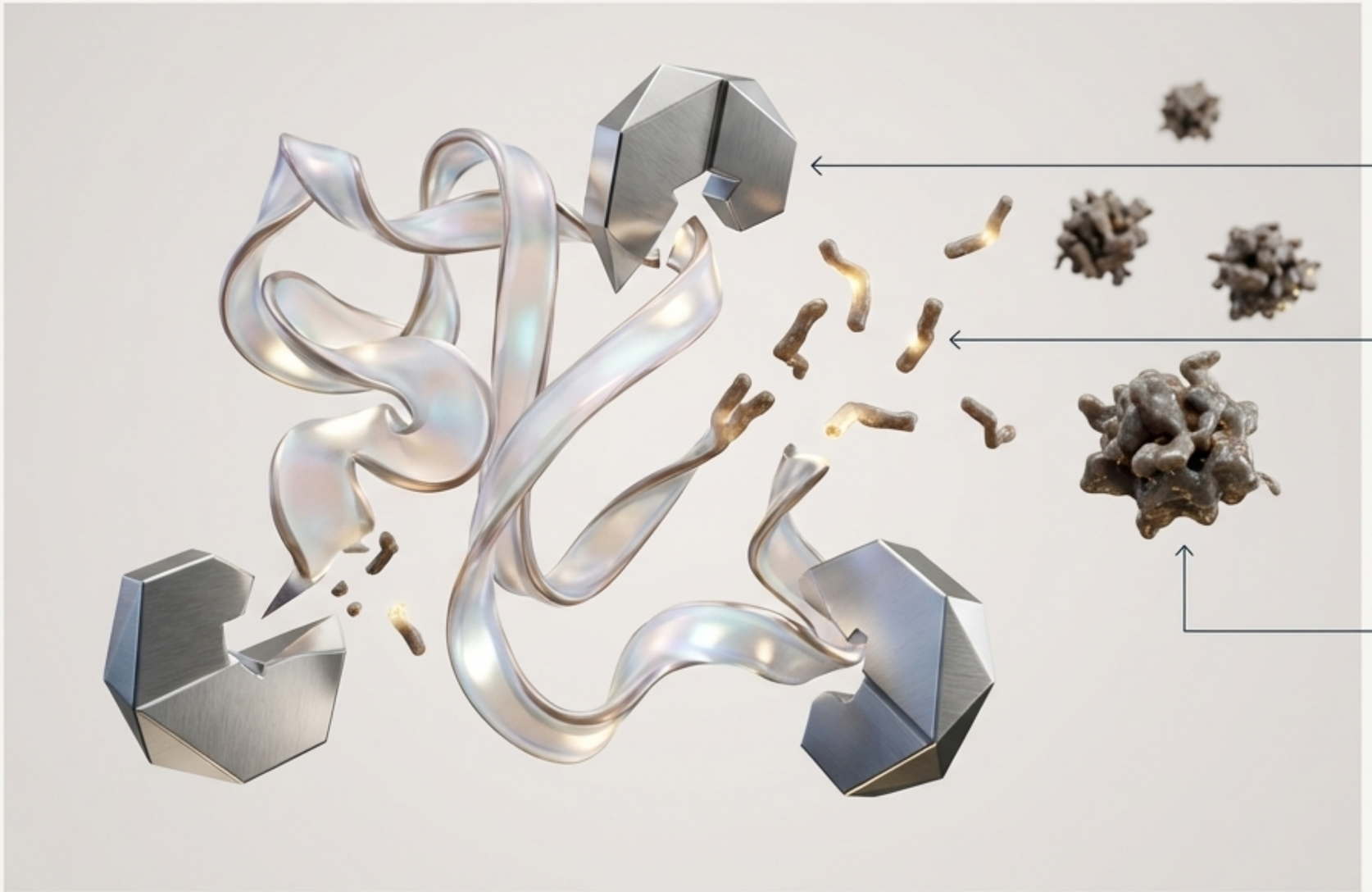
The Economic Barrier to a Cure

Traditional drug discovery is a slow, expensive, and inefficient process.

$2.6 billion

The average cost to bring a new drug to market, a process that can take over a decade with a high failure rate in lab testing.

The Target: Beta-amyloid A4 Protein



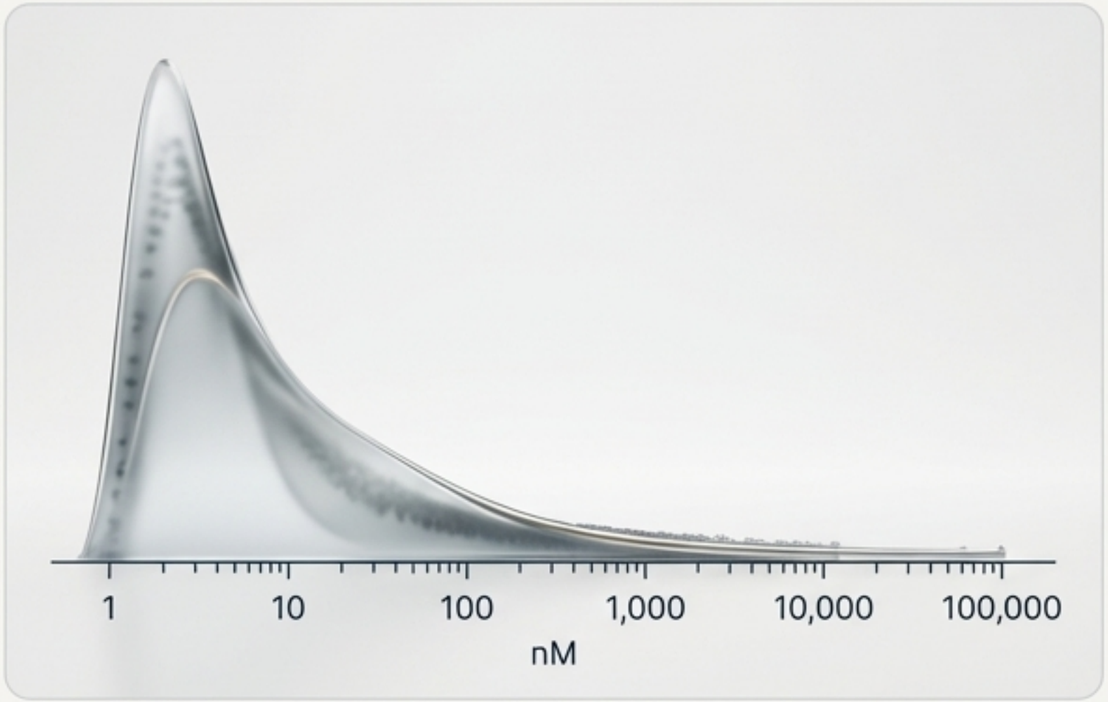
The Amyloid Hypothesis

1. A **larger protein (APP)** is cut by **enzymes**.
2. This produces small protein fragments called **Beta-amyloid (Aβ)**.
3. In Alzheimer's, these fragments accumulate, forming **toxic clumps** (plaques) that **disrupt synapses and lead to neuron death**.

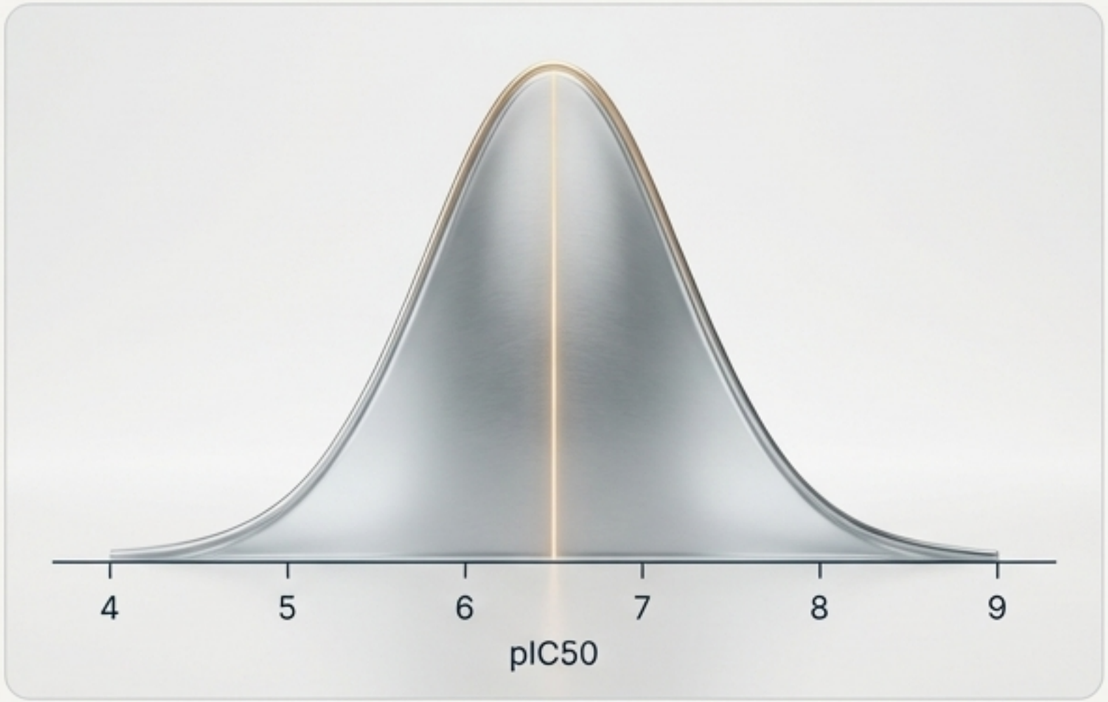
ChEMBL Target ID: CHEMBL2487

Quantifying Potency: From IC50 to pIC50

IC50 (Lower is Better)



pIC50 (Higher is Better)



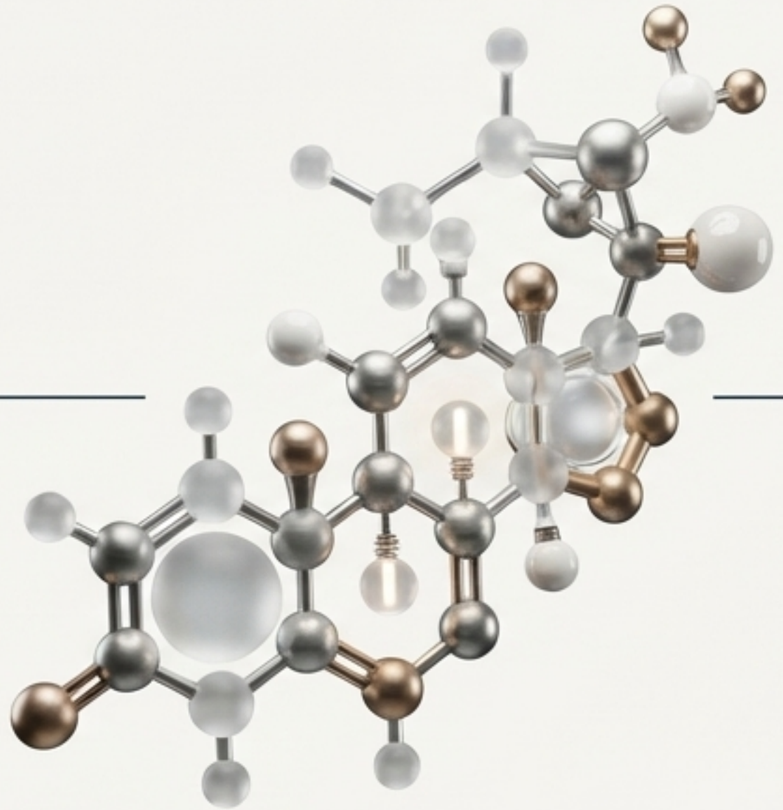
IC50 (Half Maximal Inhibitory Concentration)
Definition: The amount of a drug needed to inhibit a biological process by 50%.
Scale: **Lower is Better** (e.g., 5nM is more potent than 50,000 nM).

The pIC50 Transformation
Formula: `pIC50 = -log10(IC50)`
Why? It converts the skewed, exponential IC50 scale into a linear one suitable for regression models and makes the scale more intuitive: **Higher is Better.**

Translating Molecules into Machine-Readable Language

The Language (SMILES)

- **SMILES**: Simplified Molecular Input Line Entry System.
- **Function:** Represents a 3D chemical structure as a simple text string. (e.g., CCO for Ethanol).



The Features (Molecular Fingerprints)

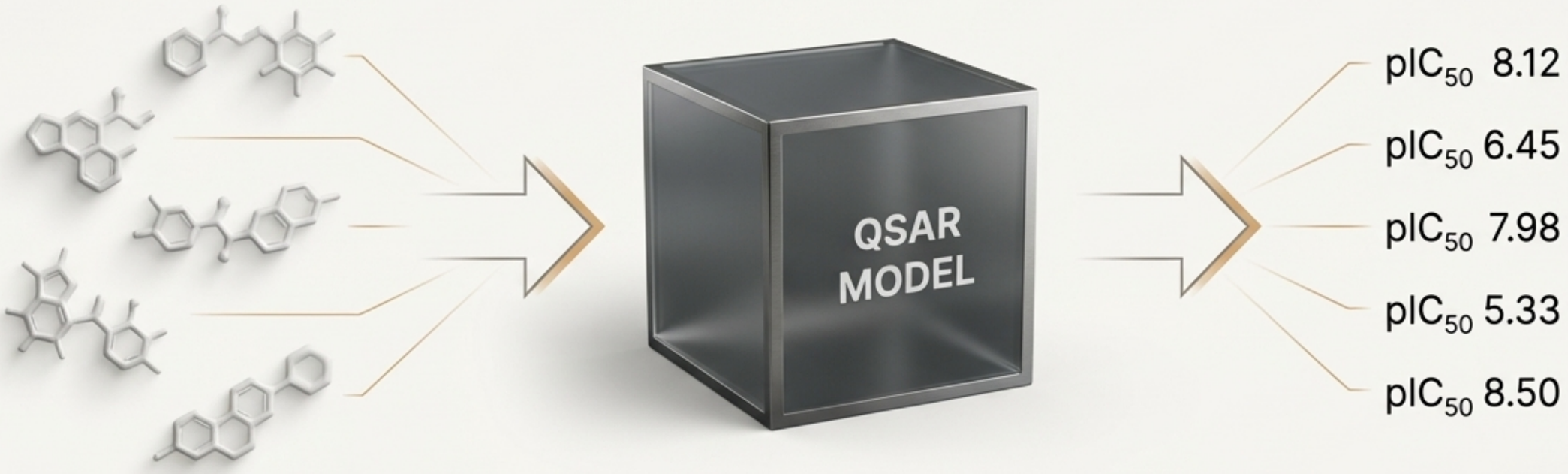
- **Analogy:** A ‘molecular barcode.’
- **Method:** We use PubChem Fingerprints, which generate an 881-bit binary vector (an array of 0s and 1s) representing the presence or absence of 881 specific chemical substructures.

The Guiding Principle: Quantitative Structure-Activity Relationship (QSAR)

Core Hypothesis: Biological Activity can be predicted as a function of Chemical Structure.

Formal Expression:

`Biological Activity = f(Chemical Structure)`



Our Goal: Use machine learning to learn this function, allowing us to predict the pIC50 of any new molecule from its structure alone.

The Computational Workflow: An End-to-End Pipeline

Data Mining

Query the ChEMBL database for the Beta-amyloid A4 target (CHEMBL2487).

Data Curation

Filter for IC50 values in standard units (nM). Remove entries with missing data.

Labeling & Transformation

Classify compounds as Active, Intermediate, or Inactive. Convert IC50 to pIC50.

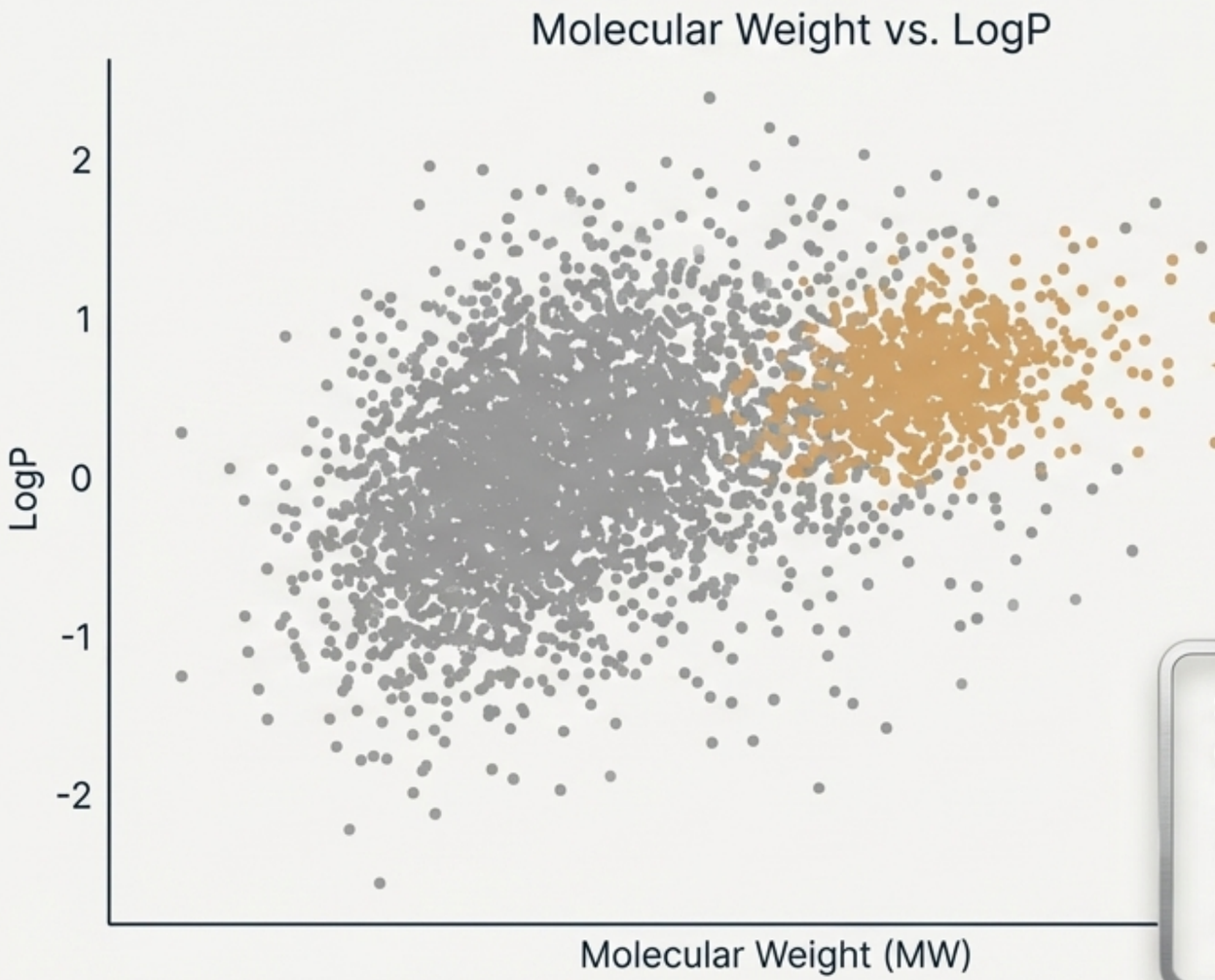
Feature Engineering

Convert SMILES strings into 881-bit PubChem fingerprints using the PaDEL-Descriptor software.

Model Building

Split data 80/20 (Train/Test) and train regression models.

Exploring the Chemical Space: Finding the Signal in the Noise



Insight: **Active** compounds tend to cluster in a specific, 'drug-like' region, consistent with Lipinski's Rule of 5.

Statistical Proof: A **Mann-Whitney U Test** was performed, confirming that the difference in descriptor distributions between Active and Inactive groups is statistically significant ($p < 0.05$), not due to random chance.

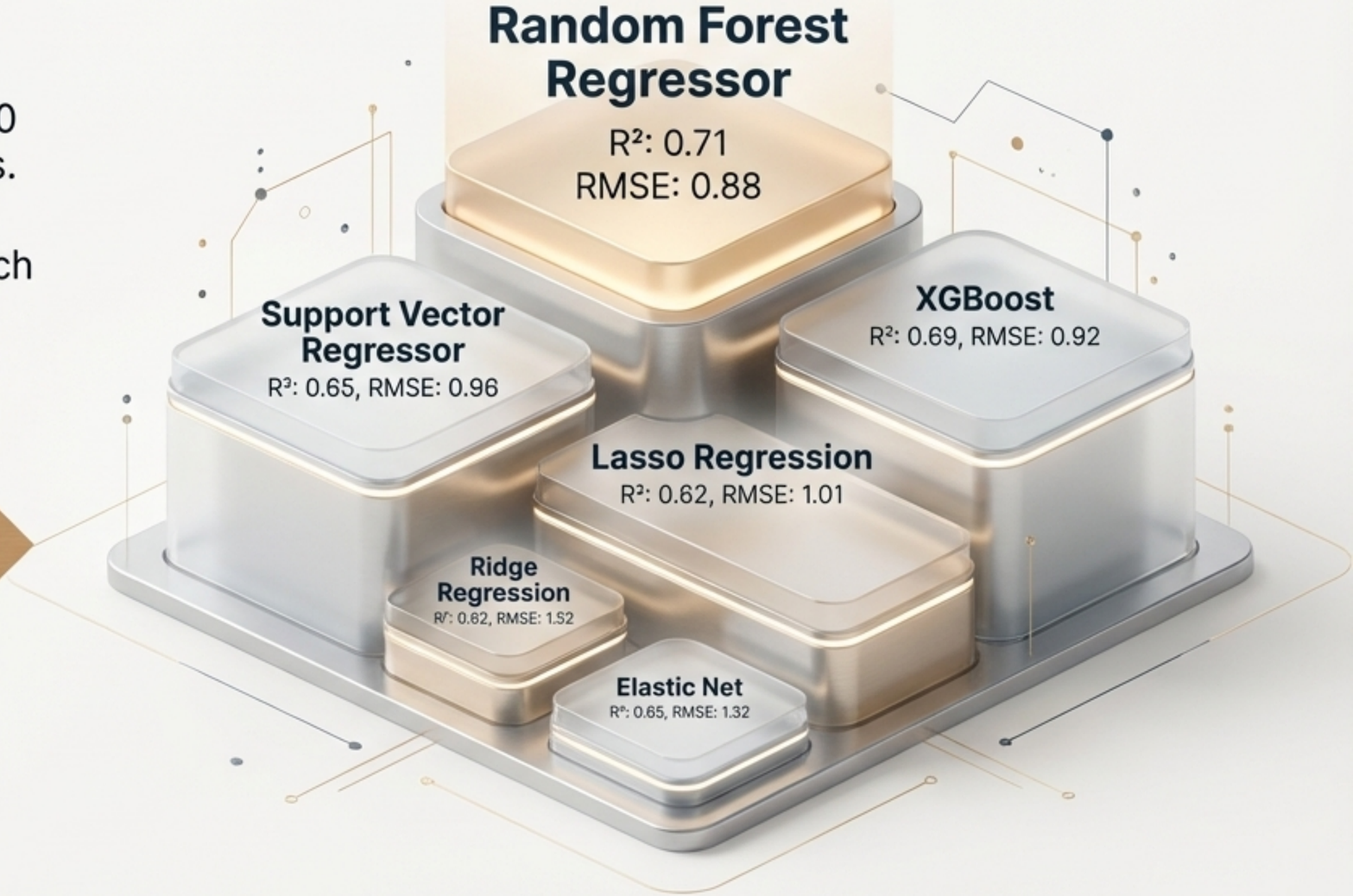
Mann-Whitney U Test: $p < 0.05$

An Algorithm Tournament to Identify the Top Performer

Methodology: We used the **LazyPredict** library to rapidly build and evaluate over 30 regression models with default parameters.

Purpose: Instead of guessing, this approach provides an empirical baseline, ranking algorithms based on their performance on our specific chemical dataset.

Result: The **Random Forest Regressor** consistently emerged as a top-performing model.

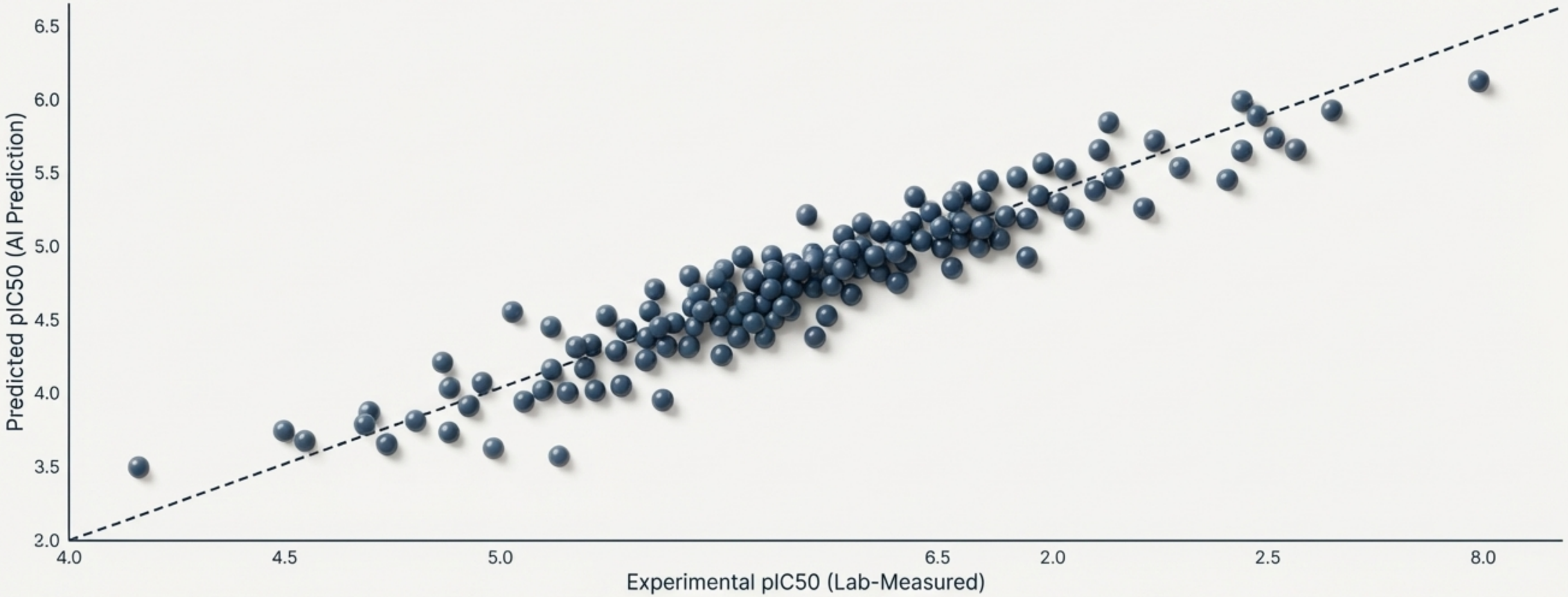


The Verdict: Predicting Biological Activity with High Accuracy

Model: Random Forest Regressor

$R^2 = 0.71$

(Note: An R^2 value > 0.6 is generally considered a strong result for QSAR models).



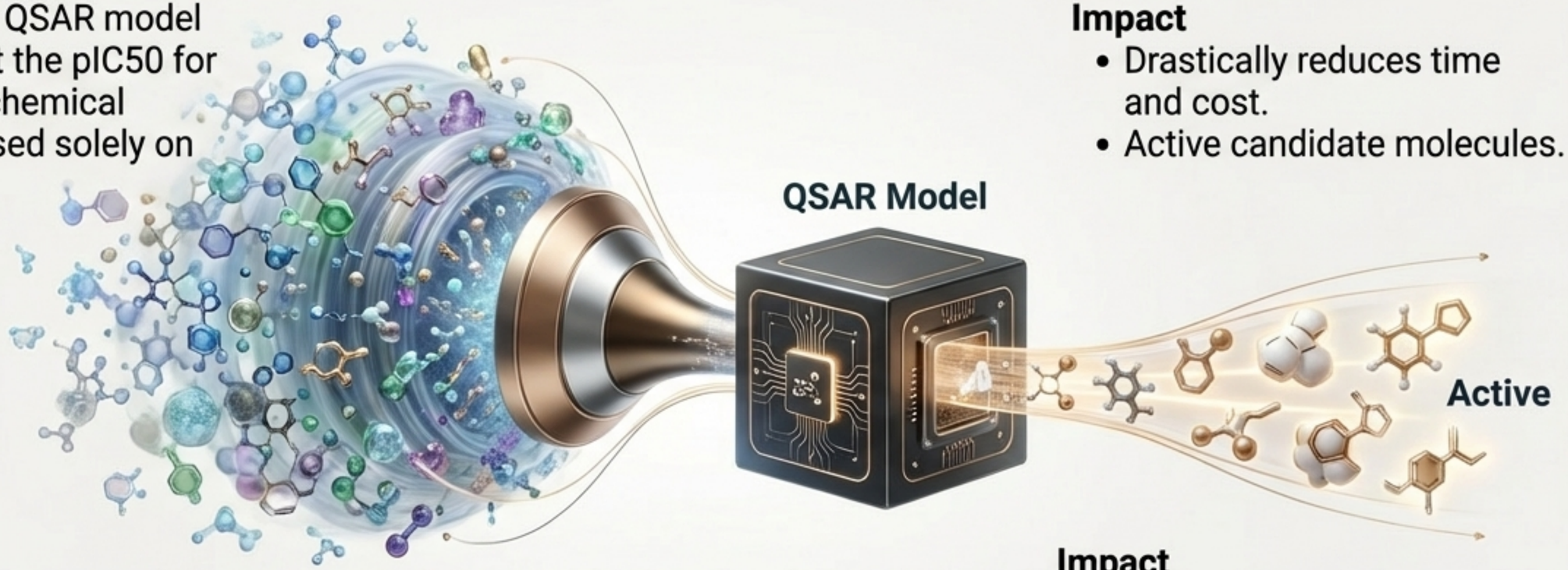
The data points cluster tightly along the diagonal line, indicating a strong correlation between the lab-measured values and the AI's predictions.

The Outcome: A Validated Tool for Virtual Screening

Capability: Our QSAR model can now predict the pIC50 for *new, untested* chemical compounds based solely on their structure.

Impact

- Drastically reduces time and cost.
- Active candidate molecules.



Capability: Our QSAR model can now predict the pIC50 for *new, untested* chemical compounds based solely on their structure.

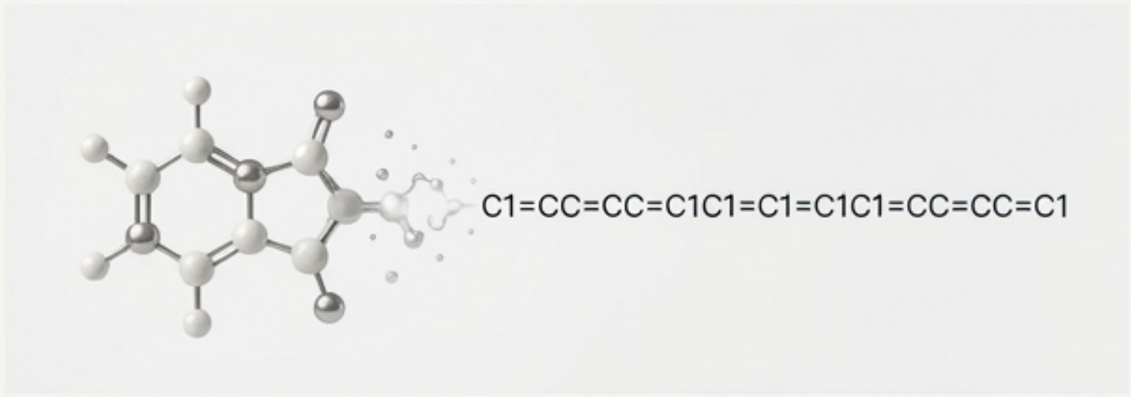
Application (High-Throughput Virtual Screening): We can computationally screen vast digital libraries of millions of molecules to identify the most promising candidates for synthesis and lab testing.

Impact

- Drastically reduces time and cost.
- Focuses lab resources on high-potential compounds.
- Accelerates the entire drug discovery pipeline.

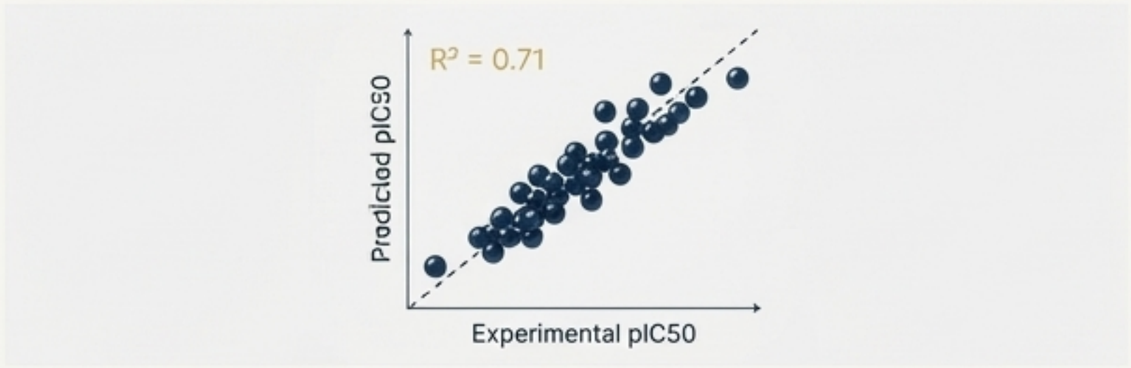
The Journey: From Biological Chaos to Computational Clarity

We started with the complex problem of Alzheimer's and identified the **Beta-amyloid protein**.



We translated molecules into a machine-readable language using **SMILES**.

We converted chemical structures into numerical **fingerprints** to serve as features.



We built a predictive **QSAR model** that learned the rules connecting structure to activity.

Accelerating the Path to a Treatment