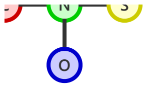
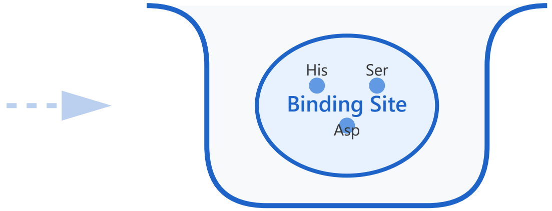
Drug-Target Affinity



MW: 350.4

Drug-Target Binding Prediction

Target Protein



Kinase domain

AI Prediction

Binding Affinity (Kd):	2.3 nM
IC50:	15.7 nM
Selectivity Score:	0.92

Advanced Predictions

- Allosteric sites
- Cryptic pockets
- Residence time
- Off-targets

Model Confidence: 84%

Binding prediction
Kd, Ki, IC50 values

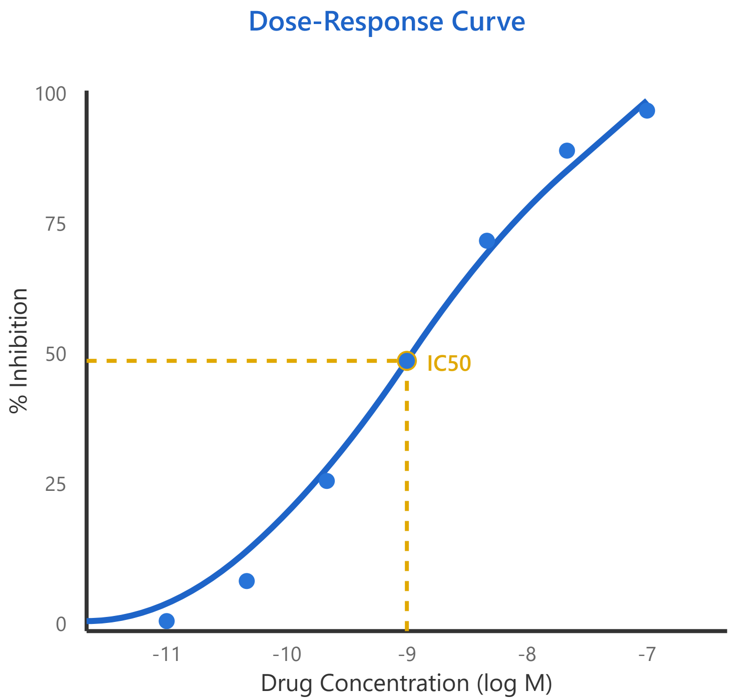
Kinase selectivity
Off-target profiling

Allosteric sites
Non-competitive binding

Cryptic pockets
Hidden binding sites

Residence time
Drug-target kinetics

1. Binding Prediction (Kd, Ki, IC50)



Binding affinity quantifies the strength of interaction between a drug molecule and its target protein. Three key metrics are commonly used:

Key Parameters:

Kd (Dissociation Constant): The equilibrium constant for the dissociation of a drug-target complex. Lower Kd values indicate stronger binding.

```
Kd = [Drug][Target] / [Drug-Target Complex]
```

Ki (Inhibition Constant): Measures the affinity of an inhibitor for its target enzyme. Represents the concentration needed to produce half-maximum inhibition.

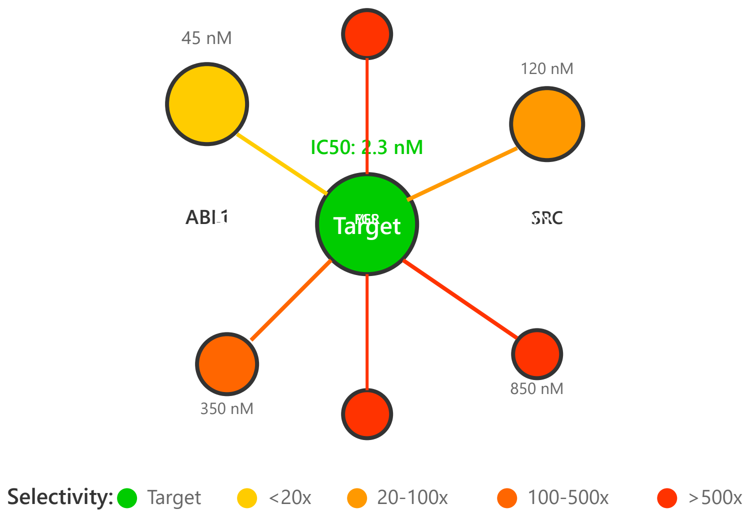
IC50: The concentration of drug required to inhibit 50% of the target activity. Most commonly used in drug screening.

Typical ranges:
- Strong binders: Kd/Ki < 1 nM
- Moderate binders: 1-100 nM
- Weak binders: > 100 nM

AI Prediction Advantages: Machine learning models can predict binding affinity from molecular structure, reducing the need for extensive experimental screening and accelerating drug discovery.

2. Kinase Selectivity & Off-Target Profiling

Kinase Selectivity Heatmap



Kinase selectivity is critical for developing safe and effective kinase inhibitors. The human kinome contains over 500 protein kinases with similar ATP-binding sites, making selectivity a major challenge.

Why Selectivity Matters:

Poor selectivity can lead to:

- Off-target toxicity and adverse effects
- Reduced therapeutic window
- Unpredictable drug interactions
- Clinical trial failures

Selectivity Metrics:

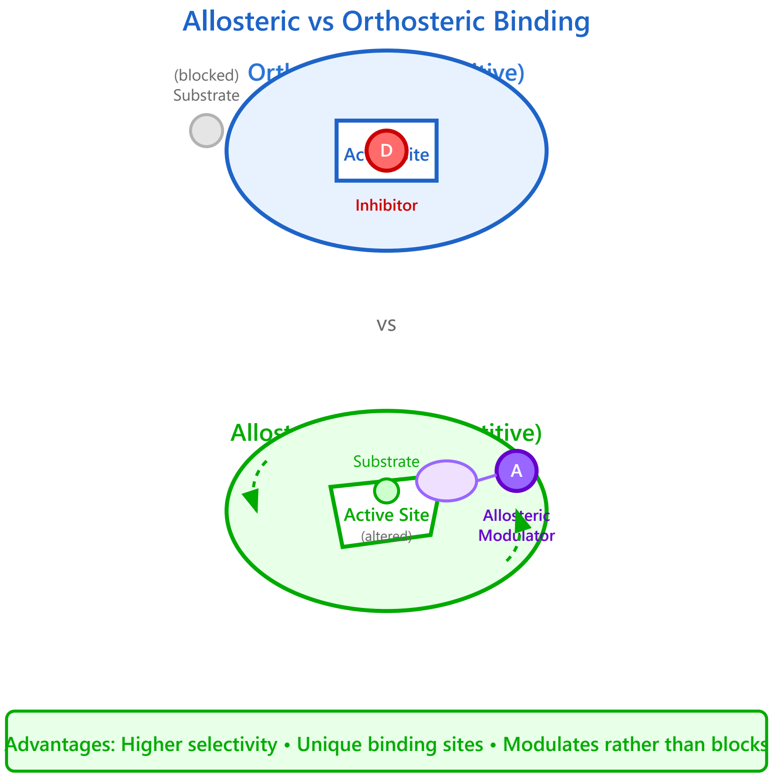
```
Selectivity Score = IC50(off-target) /
IC50(target)
```

Selectivity Index: A score typically ranging from 0 to 1, where values closer to 1 indicate higher selectivity for the intended target.

Example: A drug with IC50 = 2.3 nM for target kinase and IC50 = 120 nM for SRC kinase has a selectivity ratio of ~52-fold, indicating good selectivity.

AI-Powered Profiling: Machine learning models can predict binding to hundreds of kinases simultaneously, identifying potential off-targets early in development and enabling structure-based optimization for improved selectivity.

3. Allosteric Sites & Non-Competitive Binding



Allosteric sites are binding pockets located away from the active site that regulate protein function through conformational changes. Unlike orthosteric inhibitors that compete with natural substrates, allosteric modulators offer unique therapeutic advantages.

Key Characteristics:

- **Non-competitive binding:** Does not compete with natural substrate/ligand
- **Conformational regulation:** Induces structural changes that affect activity
- **Can be activators or inhibitors:** Positive or negative allosteric modulators (PAMs/NAMs)

Therapeutic Advantages:

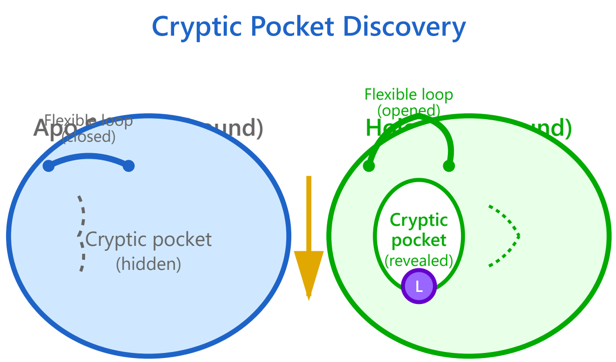
1. Enhanced Selectivity: Allosteric sites are often less conserved than active sites across protein families, enabling development of highly selective drugs.

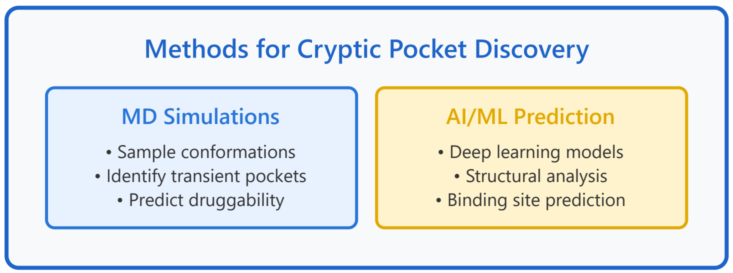
2. Tunable Efficacy: Can fine-tune protein function rather than completely blocking it, potentially reducing side effects.

3. Overcome Resistance: Mutations in active sites that confer drug resistance may not affect allosteric sites.

Clinical Examples: MEK inhibitors (trametinib), BCR-ABL allosteric inhibitors (asciminib), and EGFR allosteric modulators represent successful allosteric drug strategies.

4. Cryptic Pockets & Hidden Binding Sites





Cryptic pockets are binding sites that are not visible in the native protein structure but can be revealed through conformational changes induced by ligand binding or protein dynamics. These hidden pockets represent untapped opportunities for drug discovery.

Characteristics of Cryptic Pockets:

- **Transient nature:** Form through protein breathing motions and conformational fluctuations
- **Induced fit:** Ligand binding stabilizes the open pocket conformation
- **Often druggable:** Can provide binding sites in "undruggable" targets

Discovery Approaches:

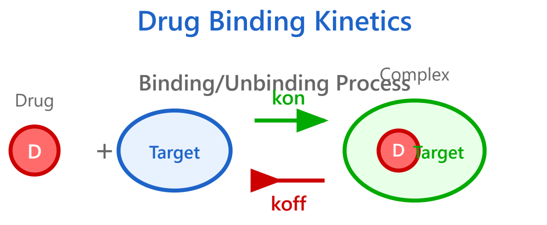
Molecular Dynamics (MD) Simulations: Computational simulations that sample protein conformational space to identify transient pockets that appear during protein motion.

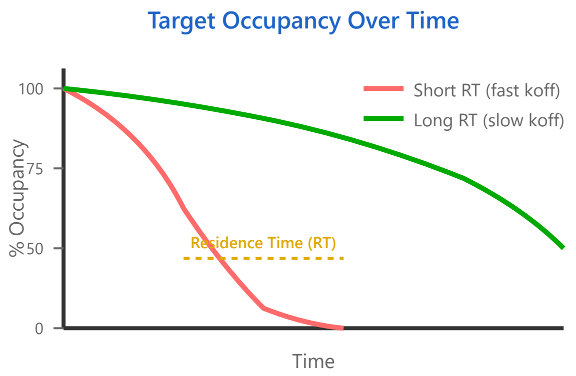
AI-Based Prediction: Machine learning models trained on protein structures and dynamics can predict the location and druggability of cryptic pockets without extensive MD simulations.

Success Story: Cryptic pockets have been successfully targeted in proteins previously considered "undruggable," including K-Ras (AMG 510/sotorasib) and BCR-ABL (asciminib).

Impact on Drug Discovery: Cryptic pocket identification expands the druggable genome by 30-40%, opening new therapeutic opportunities for difficult targets such as transcription factors and scaffold proteins.

5. Residence Time & Drug-Target Kinetics





Residence time (RT) is the average duration a drug molecule remains bound to its target. It has emerged as a critical parameter in drug design, often correlating better with in vivo efficacy than binding affinity alone.

Key Concepts:

```
Residence Time (RT) = 1 / koff
```

Where **koff** is the dissociation rate constant. A smaller koff means slower unbinding and longer residence time.

```
Kd = koff / kon
```

Two drugs can have identical Kd but very different residence times depending on their kon and koff values.

Clinical Importance:

Extended Efficacy: Long residence time can provide sustained target engagement even when plasma drug concentrations drop, allowing for less frequent dosing.

Selectivity Enhancement: Longer residence time on target vs. off-targets can improve the therapeutic window.

Example: Alectinib (ALK inhibitor) has a residence time of ~200 minutes compared to crizotinib's ~30 minutes, contributing to superior efficacy and ability to overcome resistance.

Prediction Challenges:

Residence time is influenced by multiple factors including binding pathway, conformational changes, and rebinding events, making it computationally challenging to predict. Advanced AI models now incorporate molecular dynamics and transition state modeling to estimate RT.