Targeting Receptor Dimerization:

Unlocking First-In-Class Drug Discovery Targeting Novel Functional Interfaces

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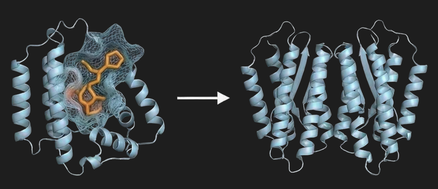
From Orthosteric Inhibitors to Dimerization Disruption
SandboxAQ Oncology Research Partnership

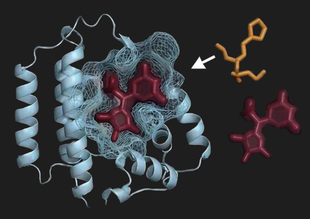
1. Natural Process

Protein binds natural ligand → dimerization → function → proliferation



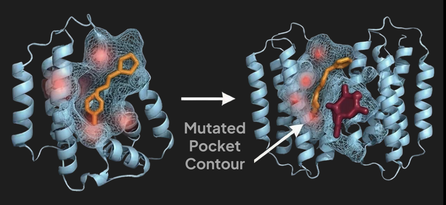
2. Classic Inhibition Approach

Inhibitor blocks natural ligand → prevent dimerization → no function → no proliferation



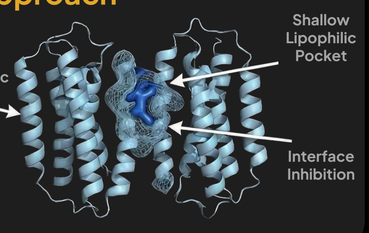
3. Resistance Development

Binding pocket mutates → binds natural ligand & turns inhibitors into activators → dimerization → function → proliferation



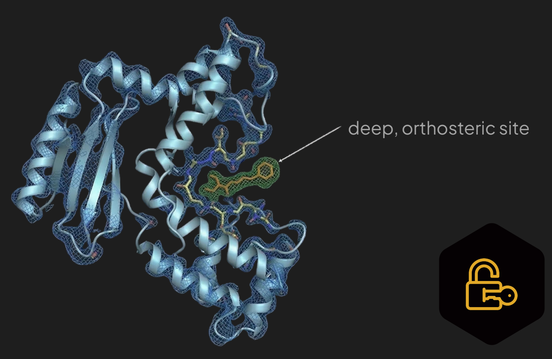
4. SandboxAQ Approach

Targeting dimerization interface → prevents dimerization → overcomes resistance → no function → no proliferation



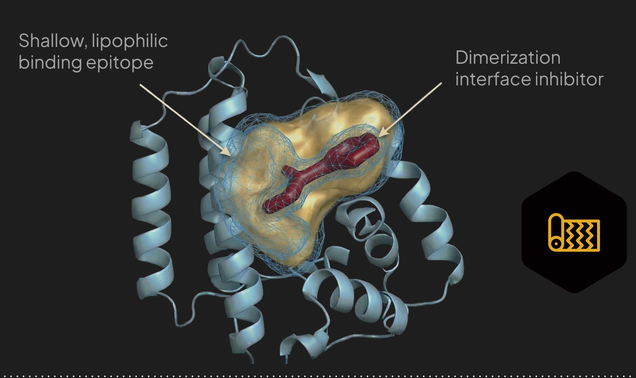
Why is this Hard?
Moving from Lock-and-Key to Velcro

Classic Inhibition Approach



- Deep binding pocket with various types of protein-ligand interactions
- Addressable via classical MedChem approaches

Allosteric Inhibition (SandboxAQ Approach)



- Shallow, lipophilic binding epitope
- Requires exploration of non-classical chemistry
- Relies on SandboxAQ approach for computational chemical space exploration and Multiparameter-Optimization (MPO)

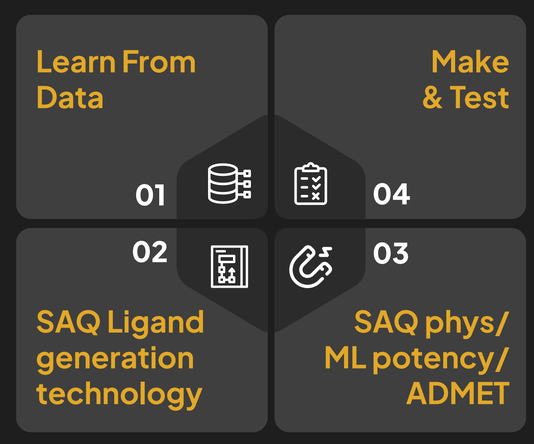
From Orthosteric Inhibitors to Dimerization Disruption
SandboxAQ Partnership

Challenge	Addressing the Hallmarks	SandboxAQ Solution
Clinical Failure Incomplete understanding of novel target biology	**Unlocking Phenotypic Plasticity** Targeting evading splicing variants	**Derisking** Identifying protein targets with proven clinical benefit or strong causative evidence
Cross-Resistance Orthosteric targets confer cross-resistance	**Non-mutational Epigenetic Reprogramming** Preventing recruitment of epigenetic modifiers	**Exploring The Unexplored** Targeting new functional regions of derisked targets
Lack of Speed Drug development too slow	**Sustaining Proliferative Signaling** Disrupting dynamic assembly	**Acceleration** Generative AI and computational modeling
	Genomic Instability Rendering mutations to orthosteric site irrelevant	

Efficient Discovery:
Sub-µM Inhibition and Favorable PK from <1000 Compounds

Partner/SandboxAQ screening cascade integrates:

- State of the art in silico models
- Comprehensive experimental assays
- In vivo PK/PD data for more efficient ligand optimization and increased likelihood of success



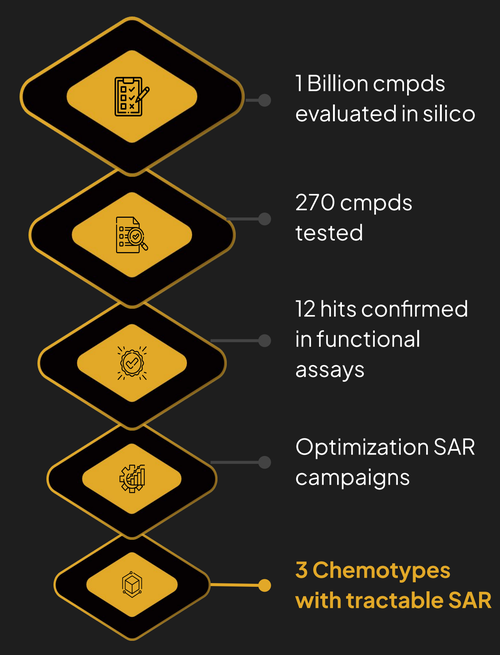
SandboxAQ In Silico Screening

In Vitro Pharmacology

Selectivity ADME/PK (Mic. and Hep. Stability, Solubility, Caco-2 Permeability)

In Vitro Safety and Tox, In Vivo PK, Cytotoxicity, CYP induction, hERG, mouse PK

In Vivo PD, Genotoxicity, Mouse Xenograft Proof of Concept Study, AMES, Micronucleus



Continuous Model Improvement
Data enhanced AI/ML+Physics based models optimize full TPP

Experimental data
Time stamped experimental MPO shows improvement in global desired TPP