

Advanced Quantum Methods for Next-Gen Drug Design

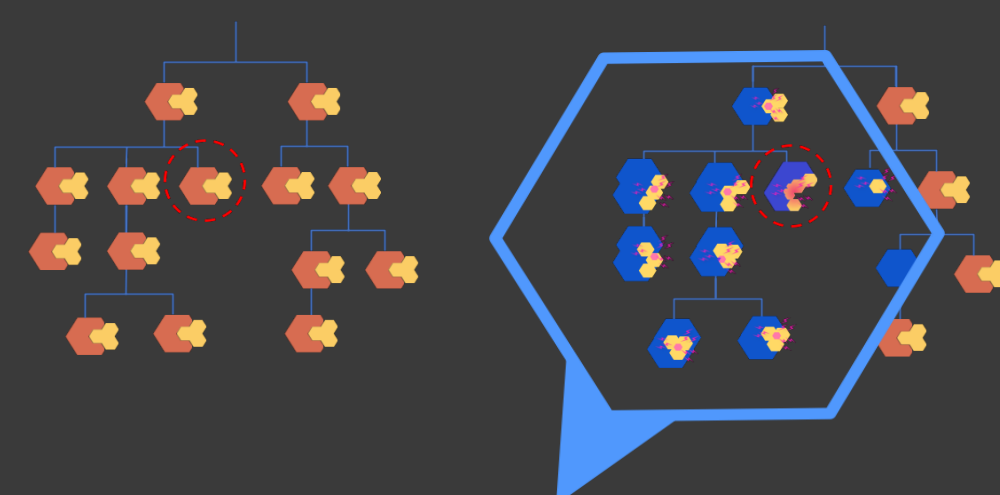
Unlocking Challenging Enzymes and Covalent Reactivity

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Abstract: Kuano's advanced quantum methods produce sophisticated, high-resolution predictions of complex systems, including transition states and transition metals. A Quantum Pharmacophore coupled with AI, rapidly explores untapped chemical space and offers unique insights for design of potent, selective small-molecule inhibitors.

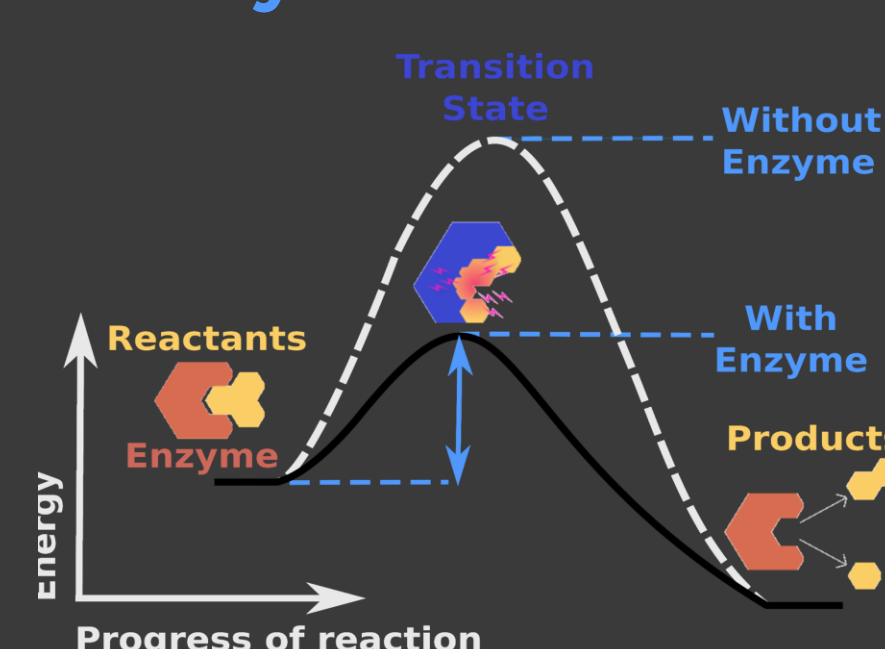
This technology addresses some of drug design's hardest problems: Quantum Fingerprints explain selective binding, unveiling druglike molecules that specifically inhibit highly-charged targets like phosphatases, and reveal possibilities for targeting amino acids beyond cysteine with covalent ligands.

Quantum Drug Design



Subtle quantum details separate similar enzymes. Kuano's simulation approaches allow us to "see" subtle differences to design inhibitors that bind their targets **effectively & selectively**.

Enzymes catalyse reactions by lowering the activation energy: they contort themselves and the reactants into incredibly tightly bound conformations called **Transition States**, which are unique to the specific environment of each enzyme. Accurately modelling this holistic view of the transition state is key to unlocking 'undruggable' enzymes.



However, even recent in silico physics-based methods do not have sufficient resolution to truly understand the nuances of binding, inhibition, and reactivity. Only advanced quantum physics can do this; only Kuano's platform has been able to apply this at scale on conventional digital computers.

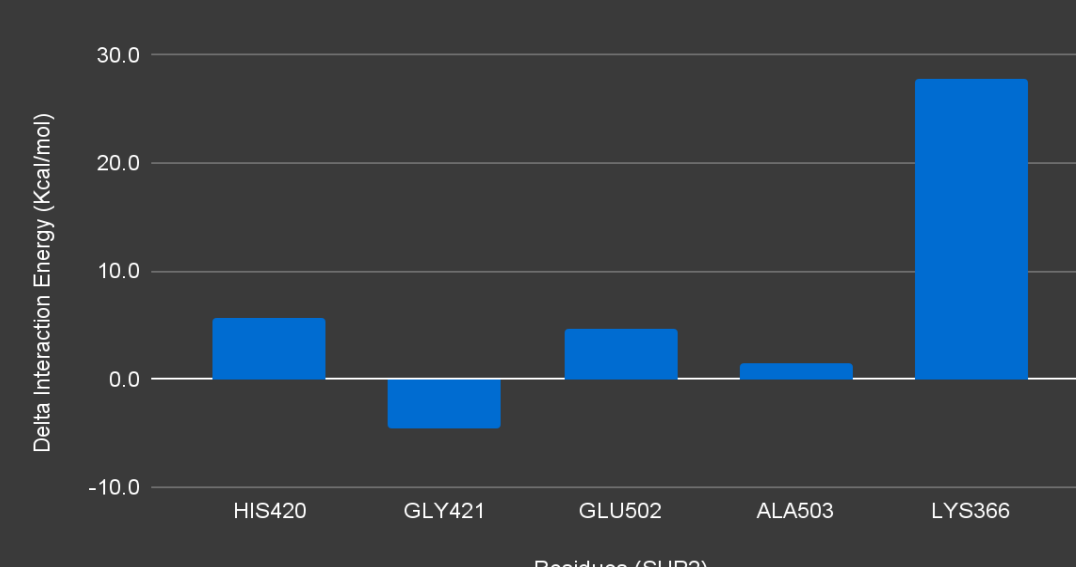
Kuano's unique platform enables **rapid and accurate quantum simulation of reactions** and the interactions that shape them.

Converting simulation results into physics-informed scoring function allows generative AI to **explore novel chemical space** to design transition state based inhibitors and covalent binders.

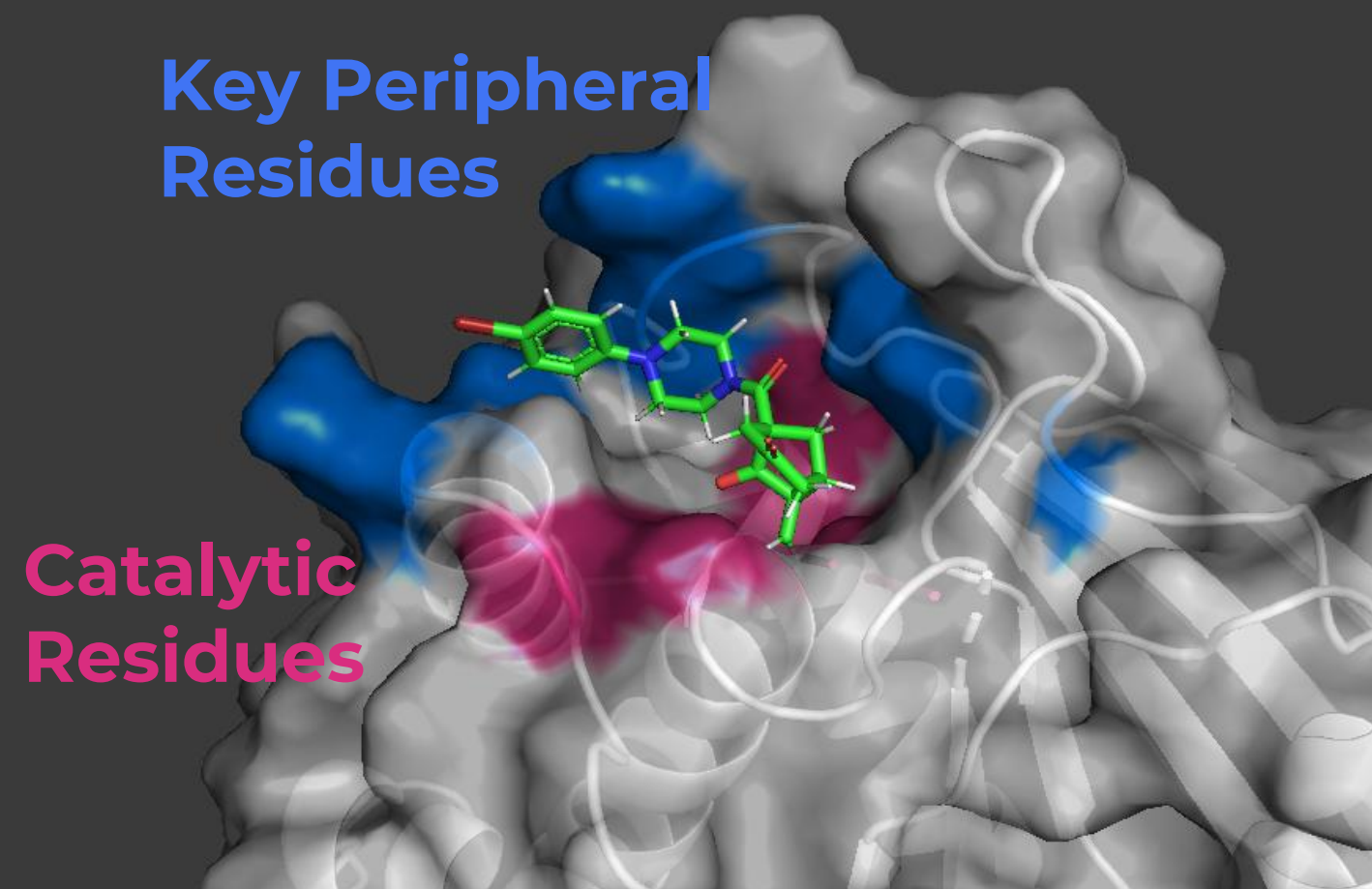
Phosphatases

Phosphatases have highly-conserved active sites, which hampers the design of selective, orthosteric inhibitors.

Kuano's **Quantum Lens** (Fragment Molecular Orbital) **explains 10 fold selectivity between SHP1 and SHP2**^[2]



Site	SHP1 (%)	SHP2 (%)
Catalytic	28.2	21.0
Peripheral	54.7	50.2



[2] compound 37 in W. Liang, et al., Tetrahedron (2024) 28;156: DOI:10.1016/j.tet.2024.133918

- Small differentiation at the active site / catalytic residues
- Peripheral pockets dominate distinction: Key interactions with LYS366 not detected by previous methods

Kuano's advantages

- ✓ Decompose **both attractive & negative components**
- ✓ Capture charge transfer
- ✓ Look **beyond active site**

Pipeline

Kuano's platform has designed successful compounds addressing complex targets, with minimal number of compounds made.

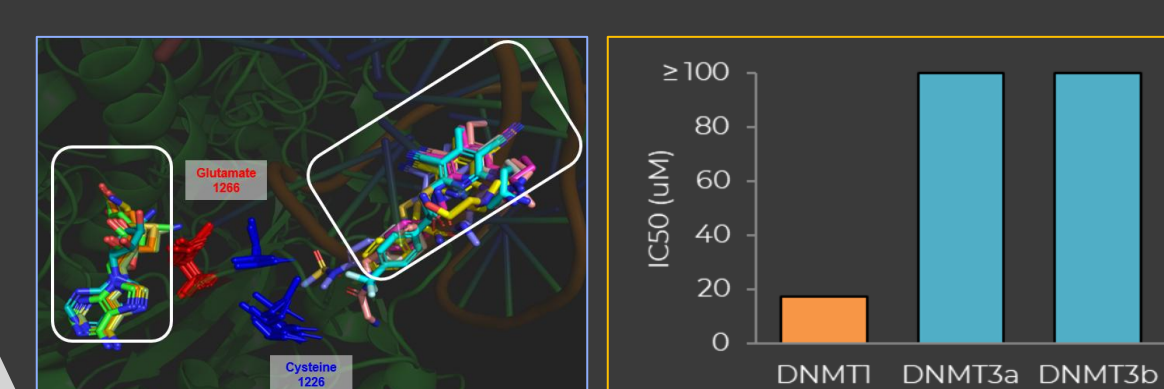
Therapeutic Area	Target	Discovery	Optimisation
Oncology; CRC	NOTUM	████████████████████	████████████████████
Oncology; AML	DNMT1	████████████████████	████████████████████
Diabetes & Solid Tumours	PTP1B	████████████████████	████████████████████

Scalable franchises where models and knowledge are reused across related targets.

Addressing long-standing problems not solvable by other methods:

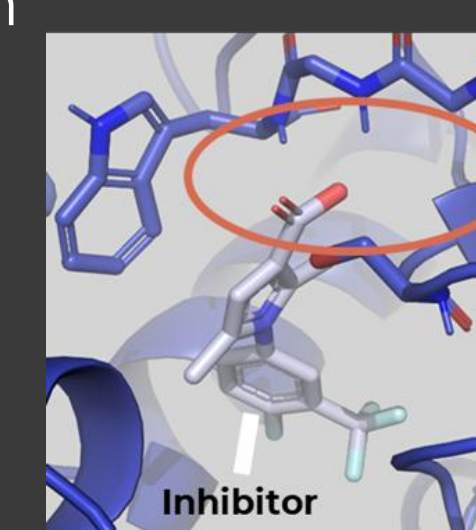
Case Study - DNMT1

Unique pharmacophore points leads to distinct chemotypes, solving selectivity issue in <50 compounds made



Case Study - NOTUM

Quantum Simulation reveals oxyanion hole, enabling generation of novel, superior compounds to First-in-Class target, with *in vivo* activity

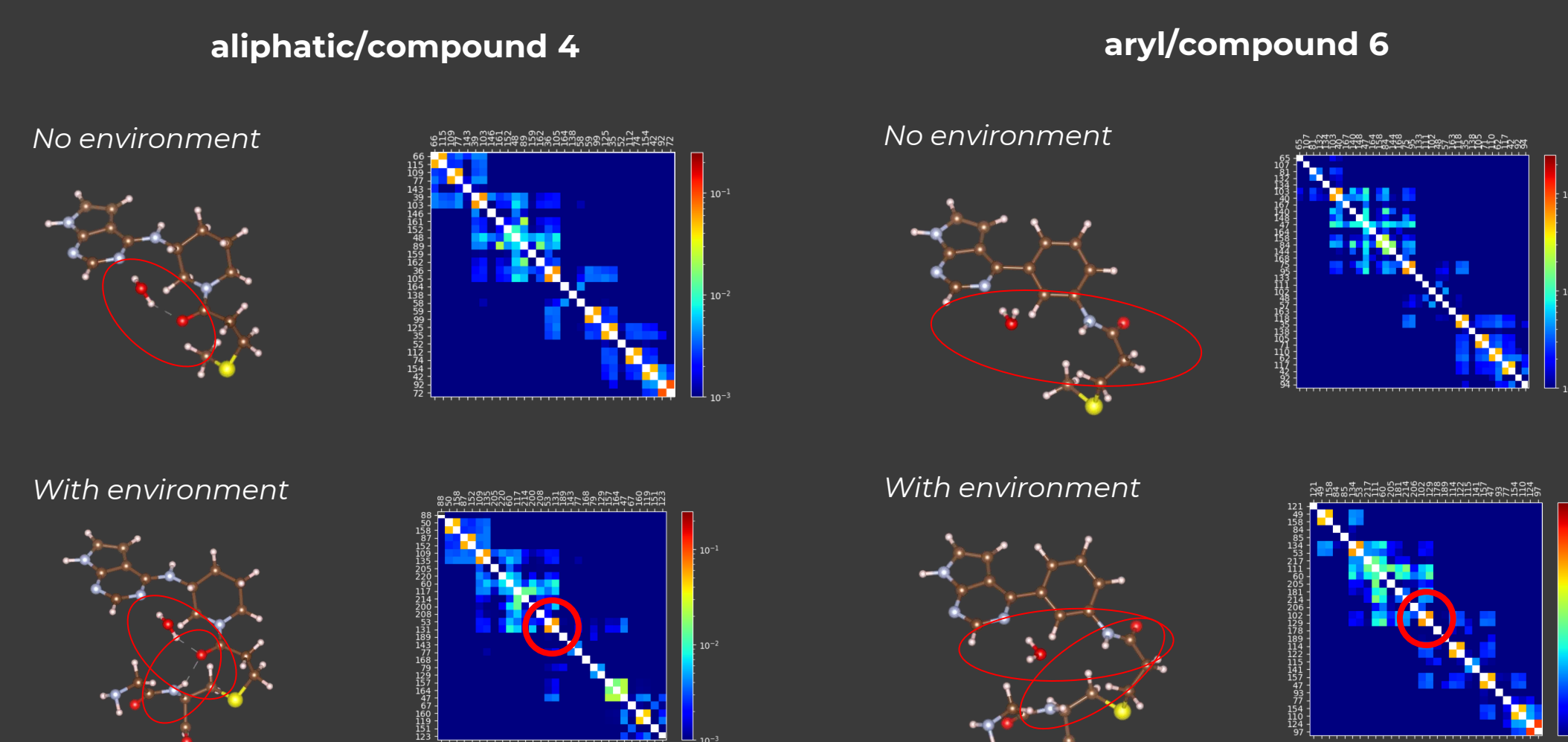


"Kuano's novel approach exploiting quantum mechanics has unlocked a unique target that permits an exciting biologically effective novel therapy for a much larger proportion of cancer sufferers."

Prof. John Bridgewater, Clinical Professor, UCL

Covalent Inhibitors

Quantum information fingerprints reveal subtle differences between warheads that lead to selectivity

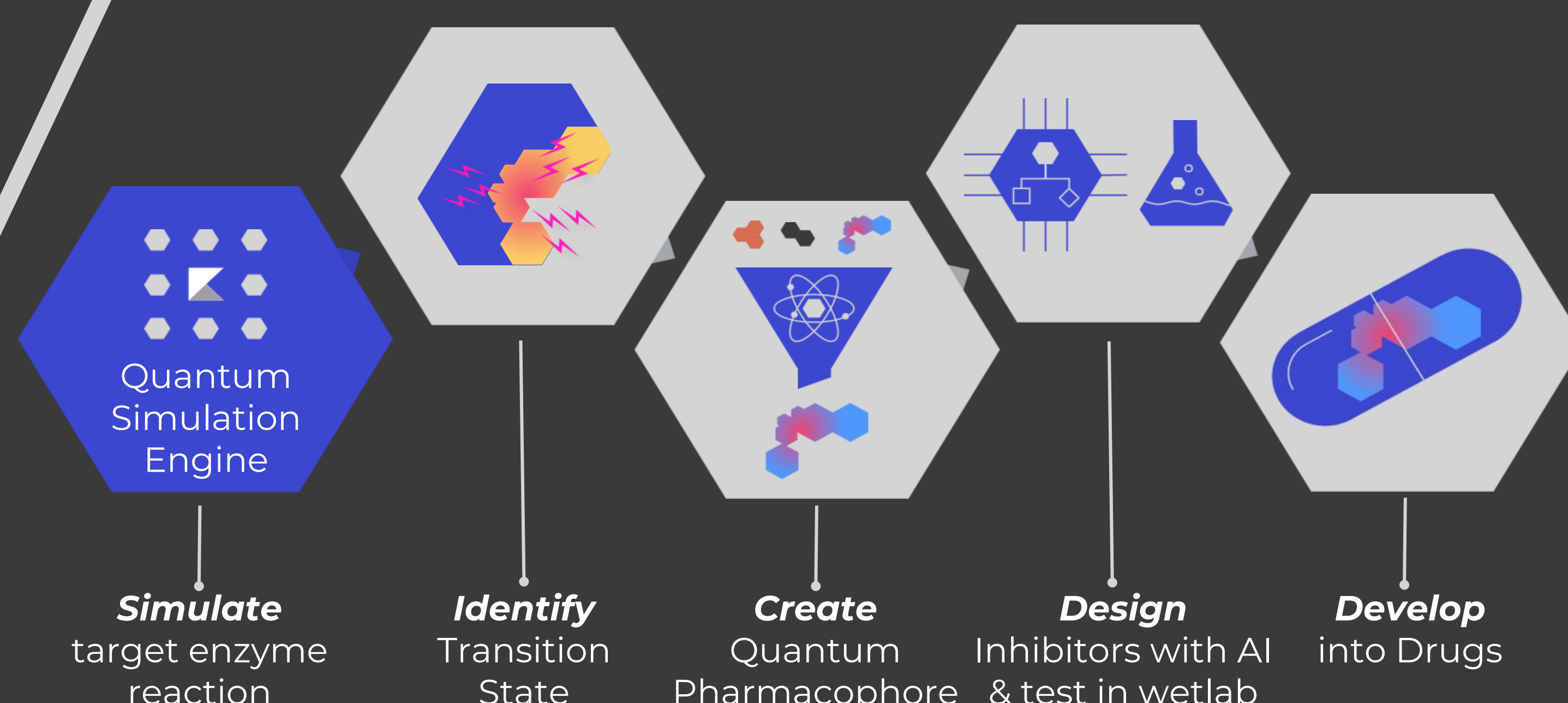


Analysed post-rationalised design of JAK3 covalent inhibitors by Pfizer^[1]. Our fingerprint shows:

- ✓ Greater experimental reactivity of Aryl warhead containing ligands reflected in 12% stronger entanglement compared to Aliphatic warheads
- ✓ Increased selectivity of Aliphatic compounds correlates to difference in correlation energy ΔE_{corr} with and without enzyme environment (-3.1% change for Aliphatic, 0.7% for Aryl)
- Able to discern (and therefore predict) **different reactivity** of different chemical species

Now piloting this approach in expert-driven and AI assisted design – seeking partnered projects.

[1] A. Thorarensen, et al., J Med Chem, (2017), 9;60(5), DOI: 10.1021/acs.jmedchem.6b01694



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