

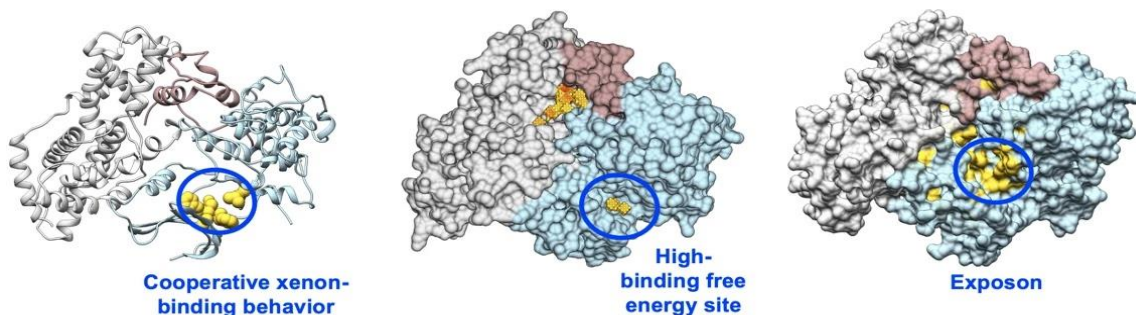


Enhanced Sampling of Protein Conformations for Cryptic Pocket Detection

To identify these cryptic pockets, we have implemented enhanced sampling molecular dynamics (ESMD) using the WESTPA package and a suite of analysis tools on our cloud-native platform, Orion. ESMD generates equilibrium ensembles of protein conformations in a variety of environments, including a mixed solvent with xenon atoms as probes for both hydrophobic and hydrophilic binding sites. Subsequently, these ensembles undergo diverse analysis methods to identify protein motions that may reveal a cryptic pocket.

Candidate pockets are analyzed using three complementary methods:

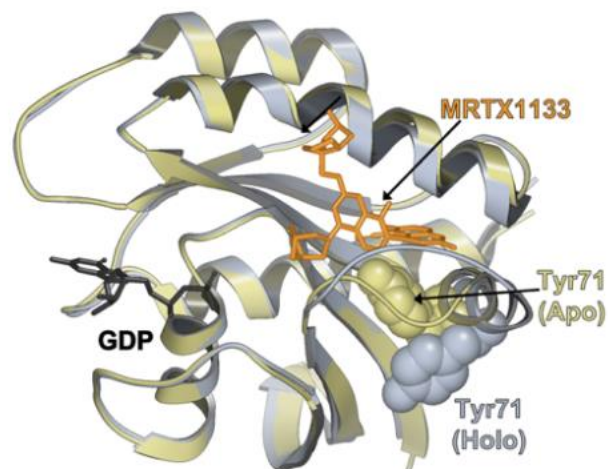
1. exposon formation, correlated changes in residue solvent exposure that may indicate pocket opening and closing;
2. dynamic probe binding, correlated changes in residue-co-solvent interaction;
3. probe occupancy mapping, stable binding locations for xenon atoms.



Validation Study on K-RAS

Discovery of MRTX1133

In a cooperative project with Mirati Therapeutics the cryptic pocket tool was applied to K-RAS, a protein that has been very difficult to target (requiring over 30 years from discovery to first marketed drug). The project successfully identifying two adjacent cryptic pockets that are targeted by a new class of K-RAS inhibitors.



Cryptic Pocket identified in K-RAS led to Mirati's discovery of MRTX1133

Summary:

- Enhanced sampling molecular dynamics to explore protein conformational space for a variety of tasks including cryptic pocket detection
- Physics-based methods to detect pocket formation
- Successful identification of cryptic pockets in multiple targets, including the difficult to drug K-RAS protein

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