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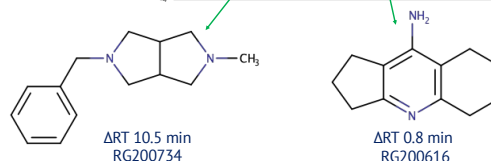
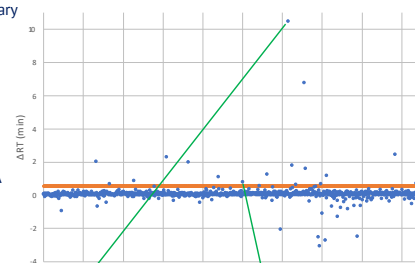
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Targeting IL-23

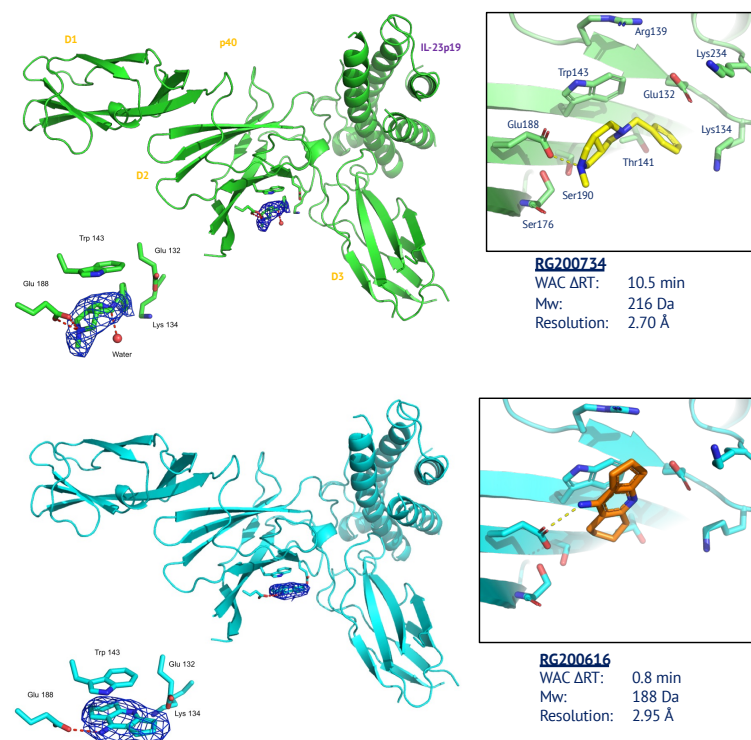
- Interleukin 23 (IL-23) is a heterodimeric inflammatory cytokine composed of an IL-12B (p40) and an IL-23A (p19) subunit
- IL-23 signals through a receptor complex formed by IL-12Rβ1 and IL-23R
- Key cytokine for T helper type 17 cell (Th17 cell) maintenance and expansion
- Aberrant Th17 activity is associated with multiple autoimmune conditions
- Clinically, antagonist antibodies targeting IL-23 (ustekinumab) have been approved for the treatment of autoimmune diseases
- An orally administered small-molecule inhibitor of the IL-23 pathway has the potential to provide significant benefits for patients suffering from autoimmune inflammatory disorders
- Identifying small molecule inhibitors of the IL-23 pathway has proven to be a challenging process
- Fragment screening by WAC is well suited to generate hits for PPIs

WAC™ screening

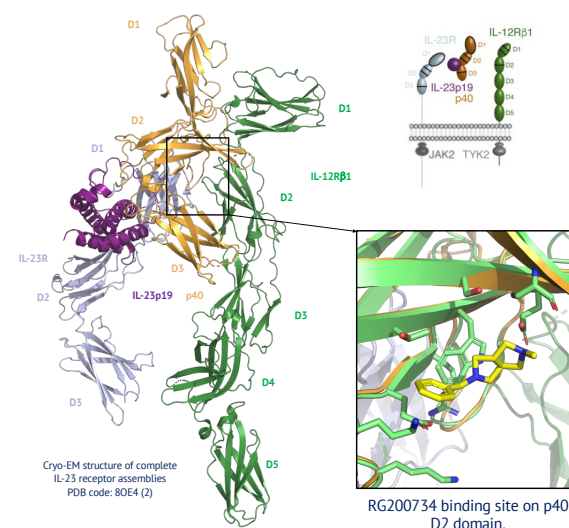
- WAC screen with fragment library
 - 1013 cmpds
 - Diverse set
 - Screened at 1 μM
- **19 hits (2% hit rate)**
- Top WAC hit ΔRT = 10.5 min
- Hit threshold = 0.5 min
- Hits validated by NMR and TSA
- 6 hits nominated for X-ray
- 2 hits successfully crystallized



Hit-validation by X-ray crystallography



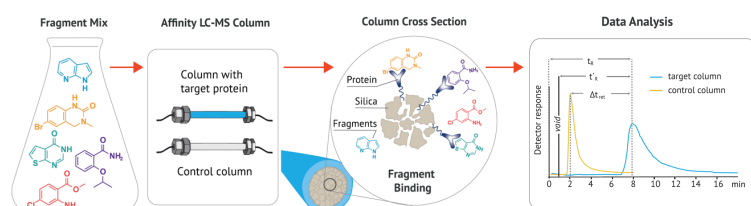
Binding site validation



Conclusions

- WAC screening successfully generated fragment hits towards this challenging PPI
- Two fragment hits successfully crystallized
- Unfortunately, compounds do not block receptor interaction

Principles of WAC™



Key WAC™ features

- Affinity chromatography with immobilized target
- MS-detection enables screening at low μM, built-in QC
- Affinity range low μM to mM, direct detection with immediate K_D ranking
- High throughput (>5000 cmpds/week; cocktails of 25-100)
- Used along with TSA, NMR, X-ray for integrated hit finding, validation and progression workflow

References

1. Lupardus et al., "The structure of interleukin-23 reveals the molecular basis of p40 subunit sharing with interleukin-12", *J Mol Biol*, 382 (2008):931-941.
2. Bloch et al., "Structures of complete extracellular receptor assemblies mediated by IL-12 and IL-23", *Nat Struct Mol Biol*, January 29 (2024).

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