

## **Exploring the bromodomain of SMARCA4 (BRG1) by Weak Affinity Chromatography (WAC™)**

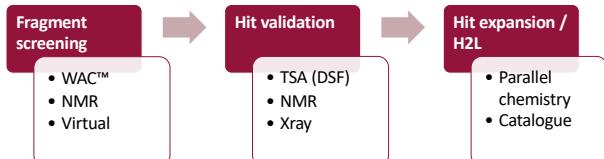


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<sup>2</sup>SARomics Biostructures, Lund, Sweden

## **Our FBLD platform and workflow**

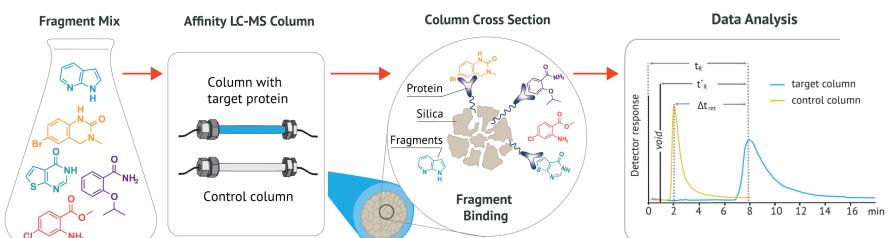


## Completed targets



- > 50 FBLD projects over 5 years
  - 20 distinct target classes
  - Hit rates from 1% to 20%, avg 6%

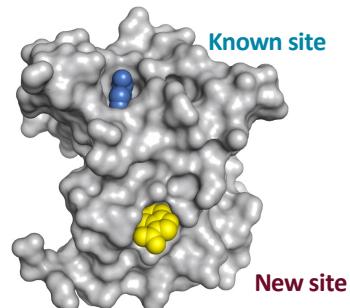
## **WAC™ screening**



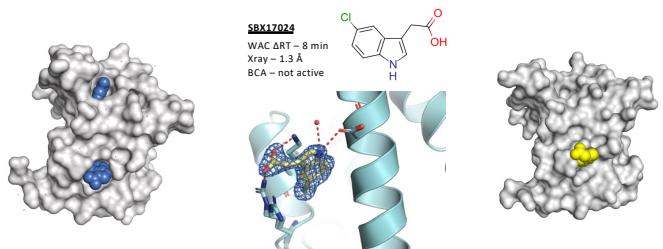
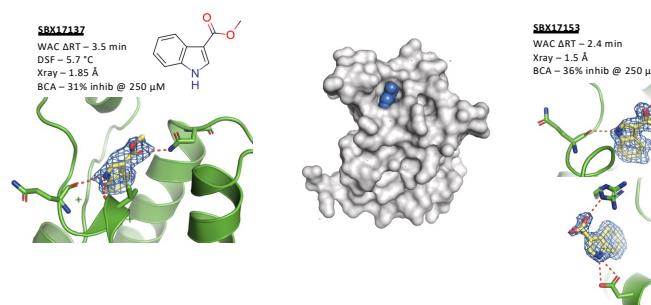
- Protein load – 2-5mg
  - High throughput ( $> 5000$ cpds / week)
  - Affinity range high nM to mM
  - MS-detection, built-in QC
  - $K_D = B_{tot}/(\Delta t_{ret} \times \text{flow rate})$
  - Used along TSA, NMR, X-ray

SMARCA4 FBLD Case Study

Fragment screen by WAC™	Hit validation	Xray crystallography	Hit expansion
<ul style="list-style-type: none"> <li>Ligandability set 250 cpds</li> <li>20 hits (8% hr)</li> <li>Top hit WAC ΔRT = 11min</li> <li>Hit threshold = 0.5min</li> </ul>	<ul style="list-style-type: none"> <li>TSA (DSF)</li> <li>6 hits confirmed</li> </ul>	<ul style="list-style-type: none"> <li>5 structures</li> <li><b>New pocket identified</b></li> </ul>	<ul style="list-style-type: none"> <li>Parallel chemistry</li> <li>Computational</li> <li>Catalogue</li> </ul>



X-ray crystallography: binders to known site identified, new site discovered



**Hit expansion:** analogue screening by WAC™, CC parallel chemistry reveals SAR trends and site-selectivity patterns

ID										
WAC ΔRT (min)	2.4	3.5	6.1	2.1	5.6	?asap	8.2	10.7	3.6	4.2
Xray	Yes, P1&P2	Yes, P1	Yes, P2		Yes, P2		Yes, P2			
BCA %inhib	36% @ 250 μM	31% @ 250 μM							65% @ 250 μM	85% @ 250 μM