



# Targeting Transcription Factor – BAF Interactions in Cancer

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04/13/23

# Drugging Transcription Factors

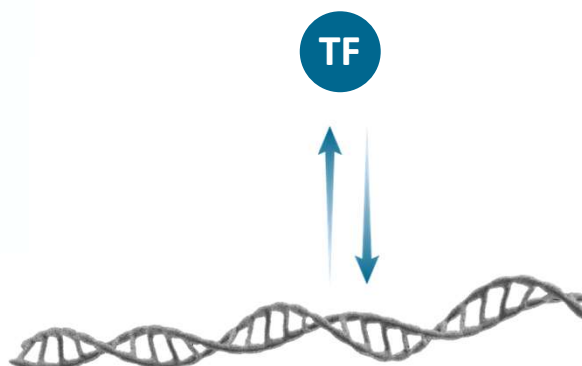


## TFs are compelling drug targets...

- Highly involved in gene expression
- Implicated in range of cancers and other diseases

## ...but historically difficult to target

- Featureless surface:  
no druggable binding pocket
- Challenges with drugging charged  
DNA-protein interactions



# BAF controls chromatin accessibility



# Drugging Transcription Factors

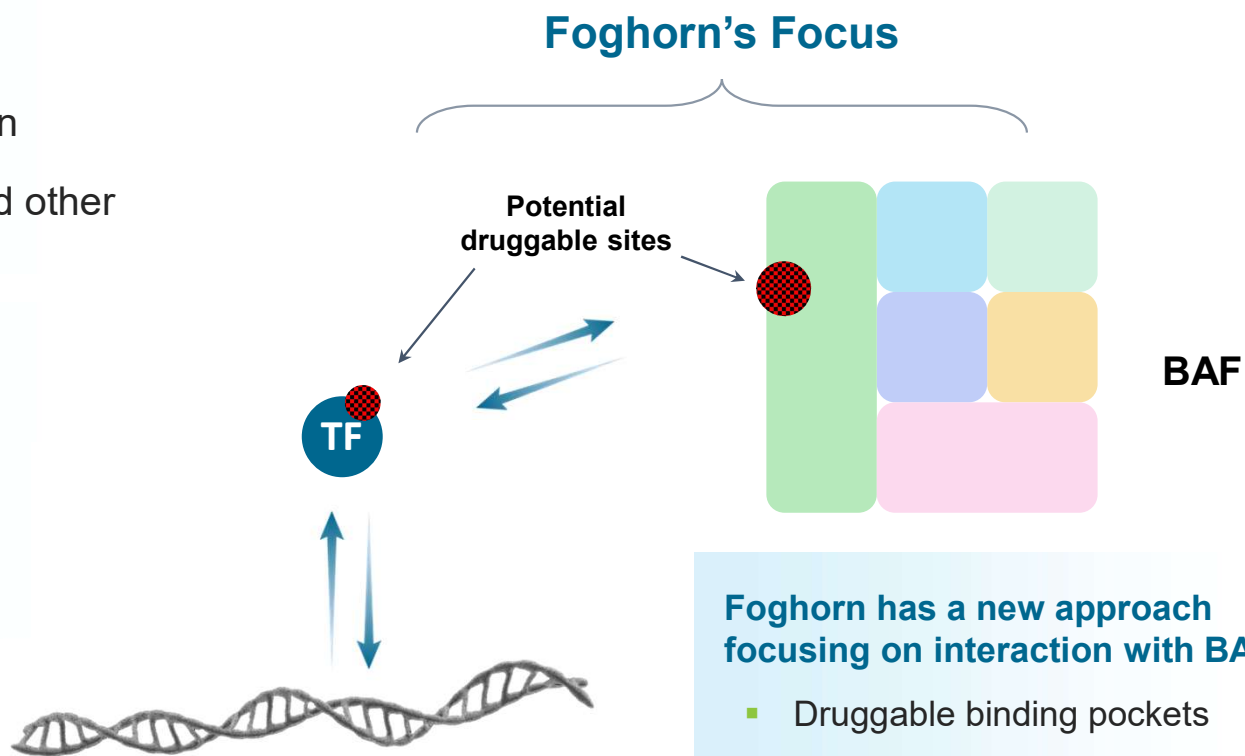


## TFs are compelling drug targets...

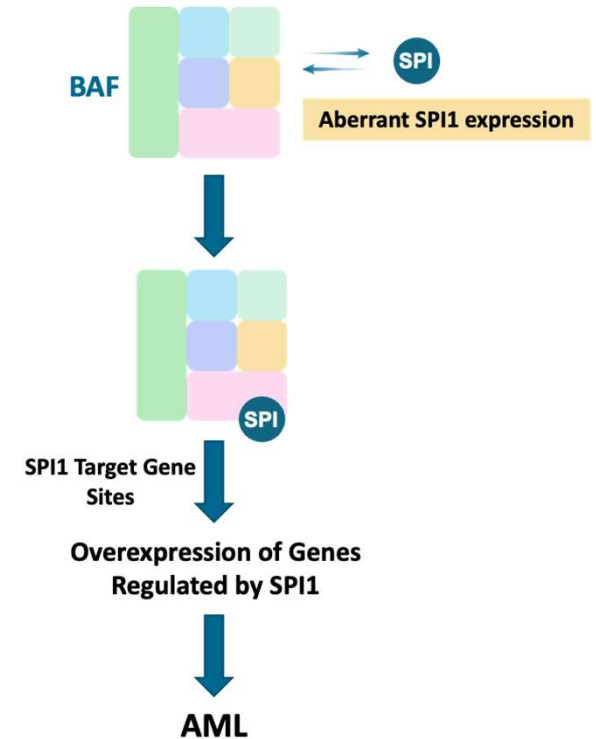
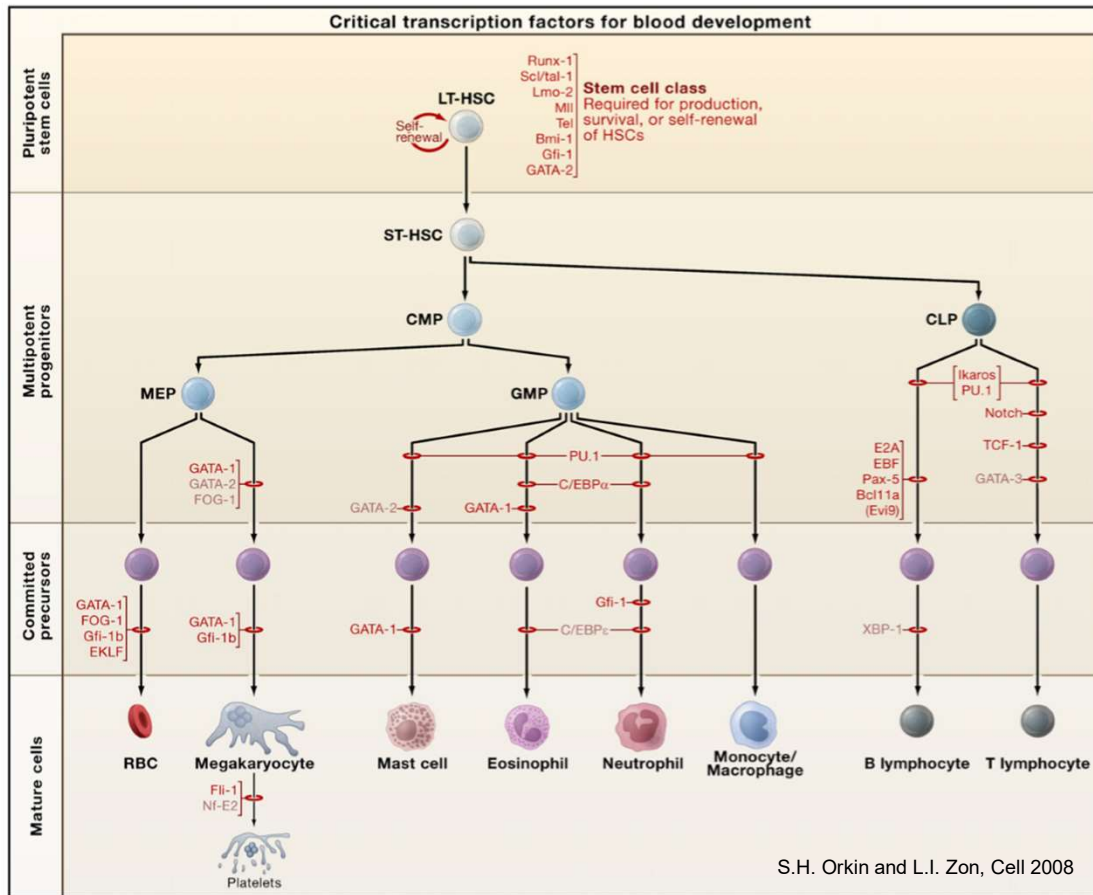
- Highly involved in gene expression
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## ...but historically difficult to target

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# SPI1 (PU.1) transcription factor known to control Hematopoiesis



Dependency on the TF and BAF activity

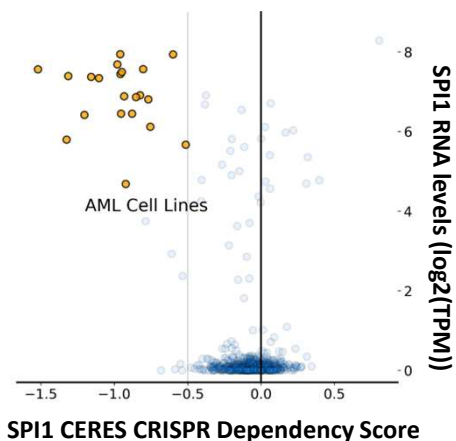
NGS based approaches

Co-IPs

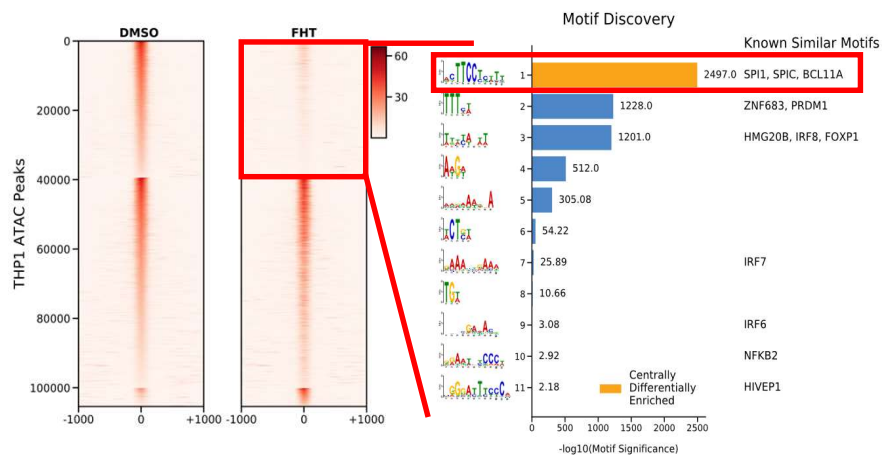
# Validating the SPI-BAF collaboration in AML



## SPI1 Expression vs. Dependency



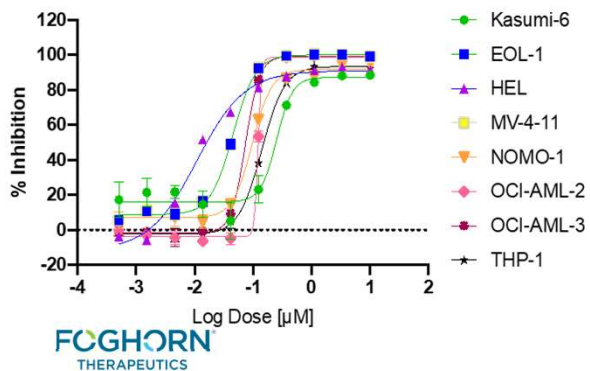
## ATAC-seq +/- BAF Dual Inhibitor



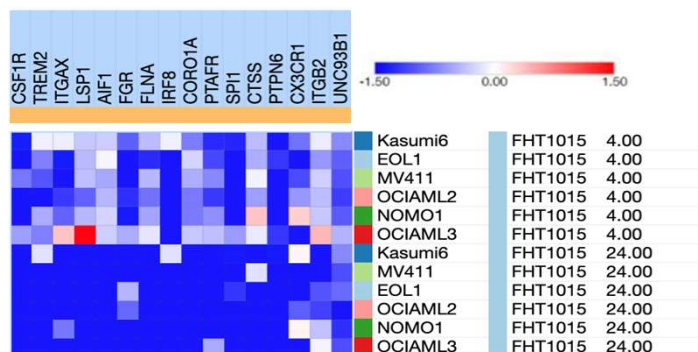
## Co-IP: SPI1 and BAF



## BAF Dual Inhibitor Treatment



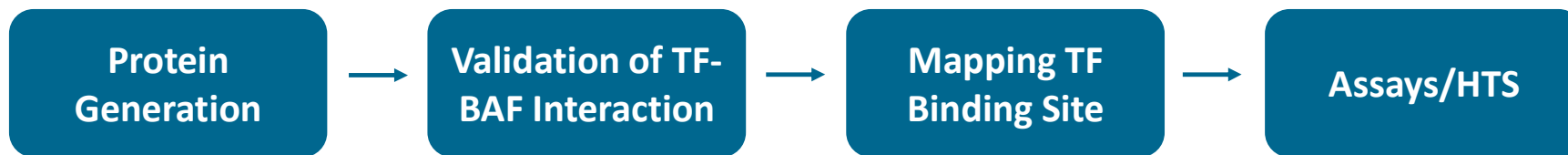
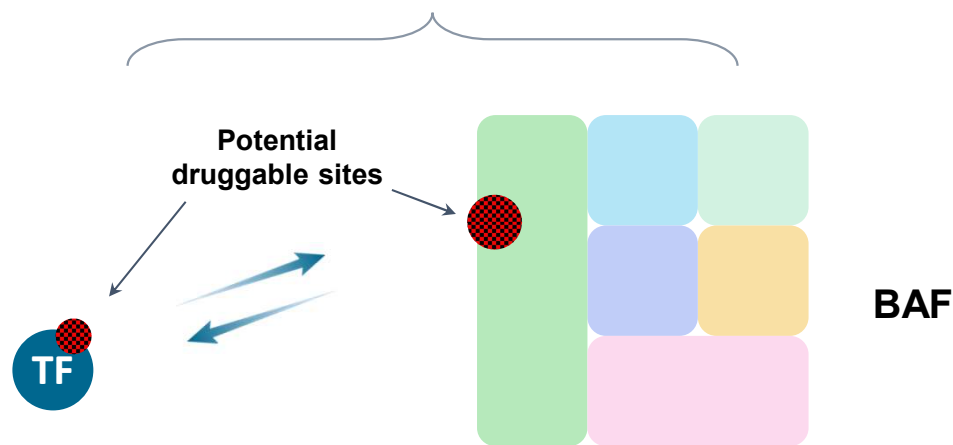
## RNA-seq: SPI1 Target Genes



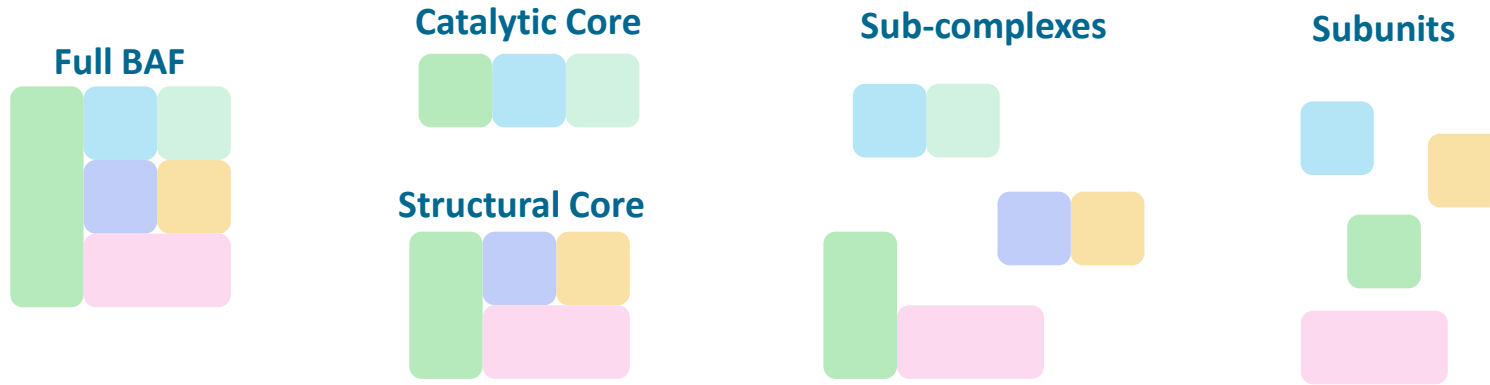
# Foghorn's approach to targeting TF-BAF interactions



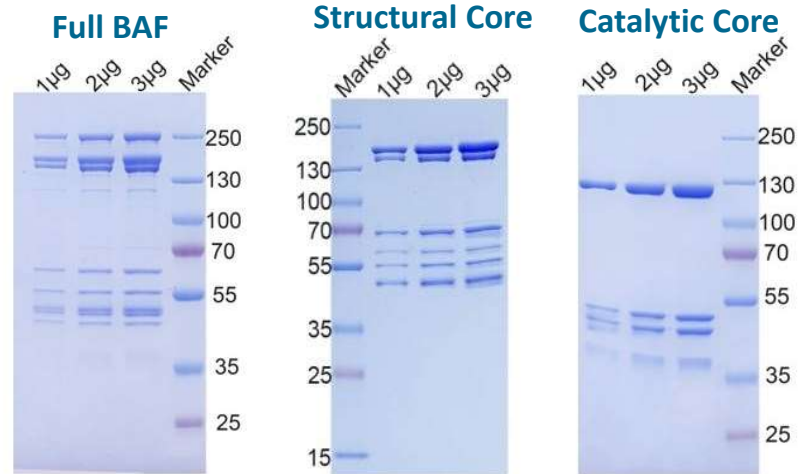
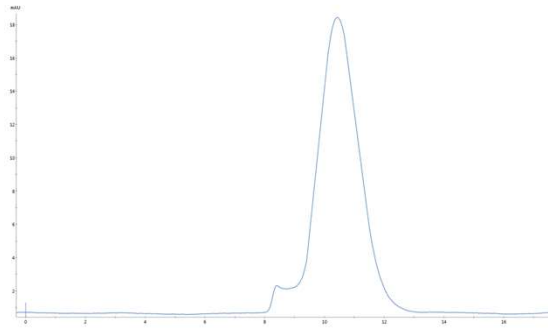
## Foghorn's Focus



# Foghorn can generate BAF/BAF components with high purity and at scale



**SEC: Full BAF**



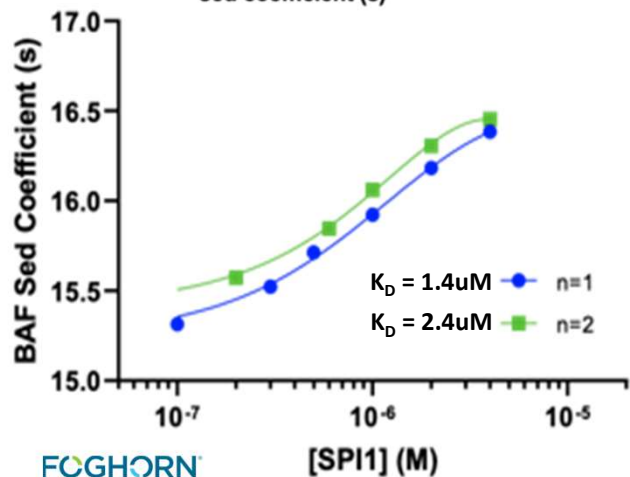
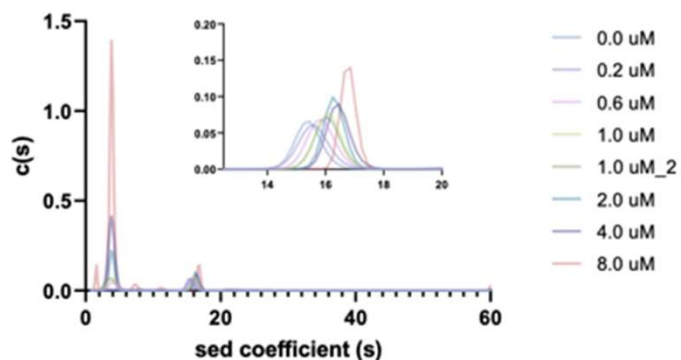


# Validating the SPI1-BAF interaction *in vitro*



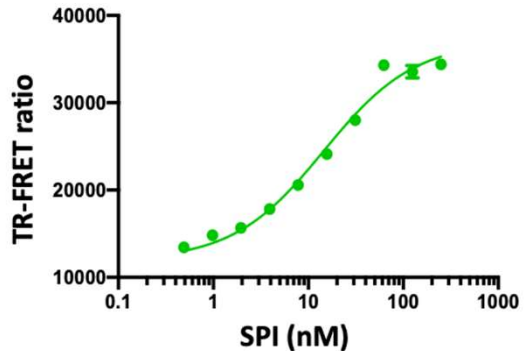
## Full BAF-SPI AUC

### SPI1 Titration



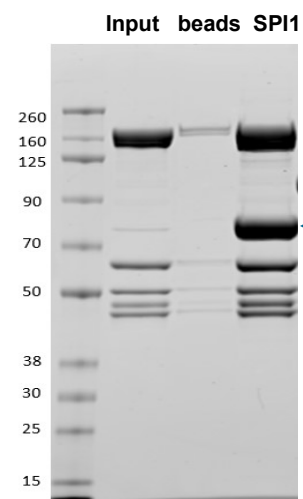
FOGHORN  
THERAPEUTICS

## Full BAF-SPI TR-FRET

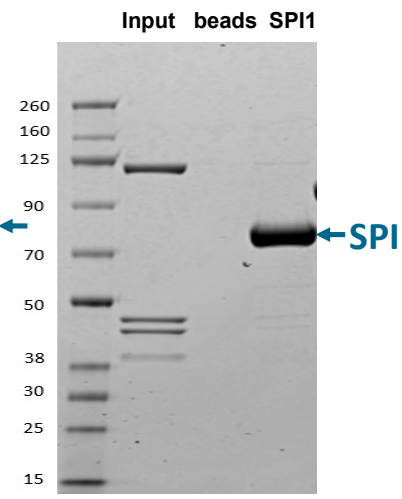


## Pull-down Assay

### Structural Core



### Catalytic Core

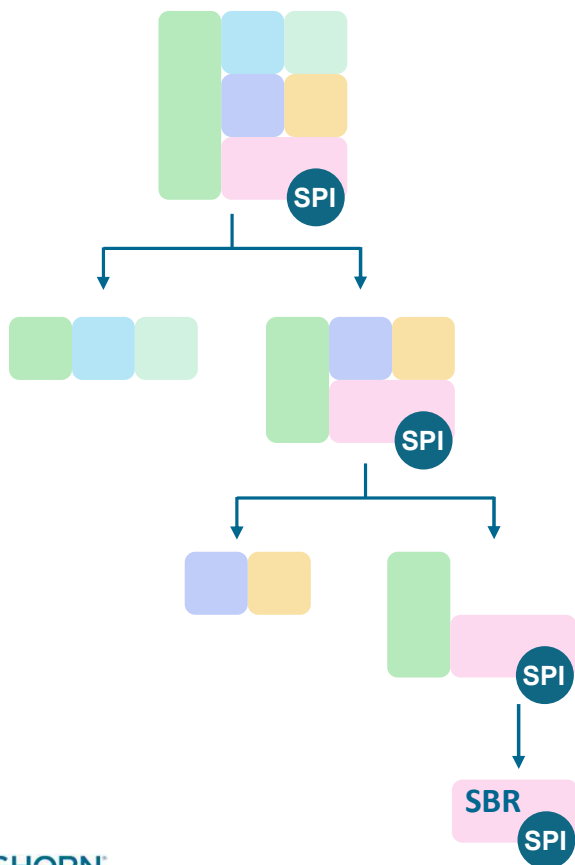


# The reductionist approach: determining where SPI1 binds on BAF

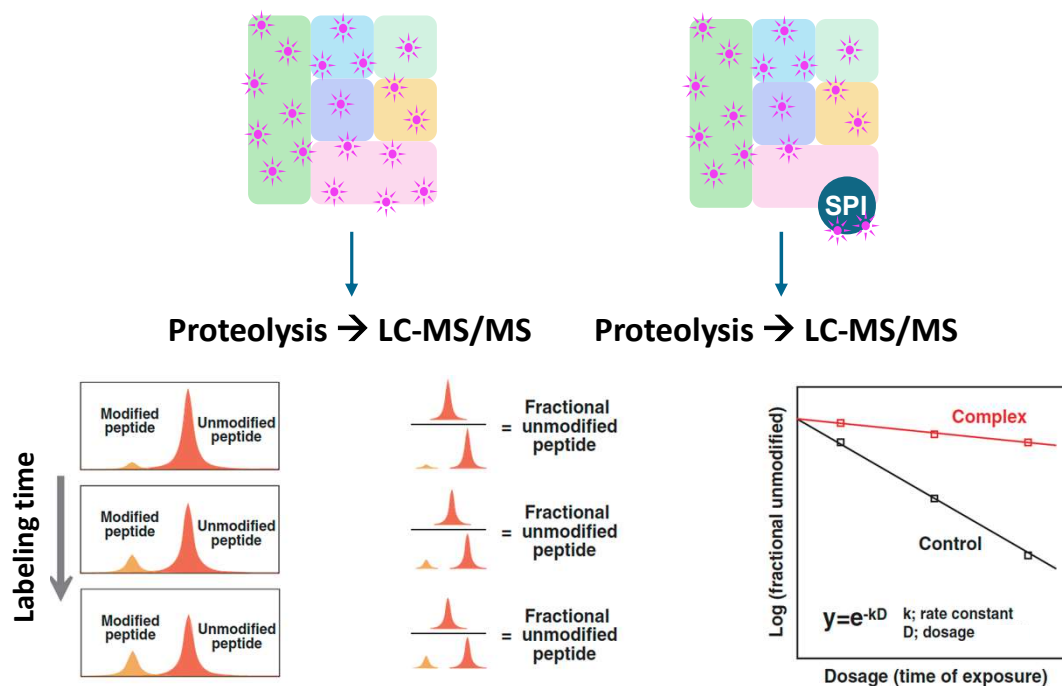
SBR = SPI Binding Region



## Pull-Down Assay



## Mass Spec. Footprinting



$$\text{Protection Ratio} = \frac{k_{\text{labeling}}(\text{BAF})}{k_{\text{labeling}}(\text{BAF:TF})}$$

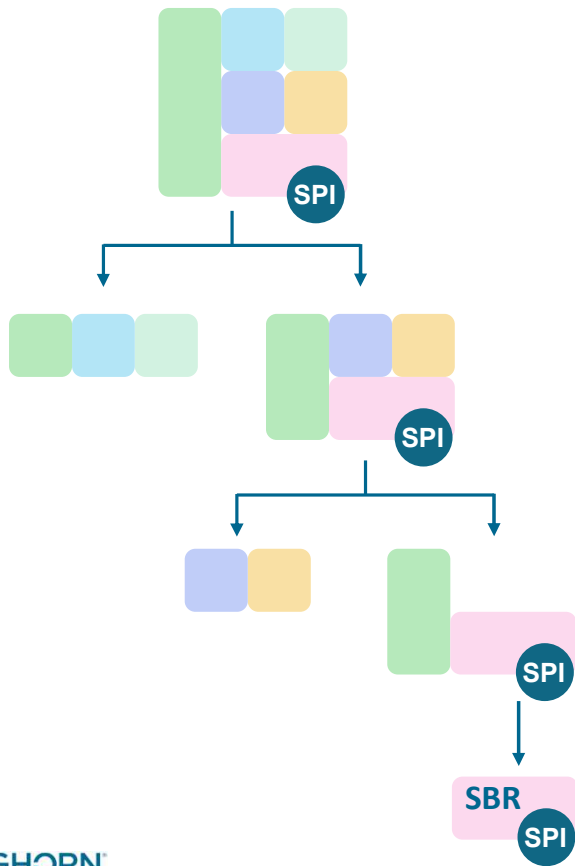
PR > 1 = protected, PR < 1 = deprotected, PR = 1 = no effect

# The reductionist approach: determining where SPI1 binds on BAF

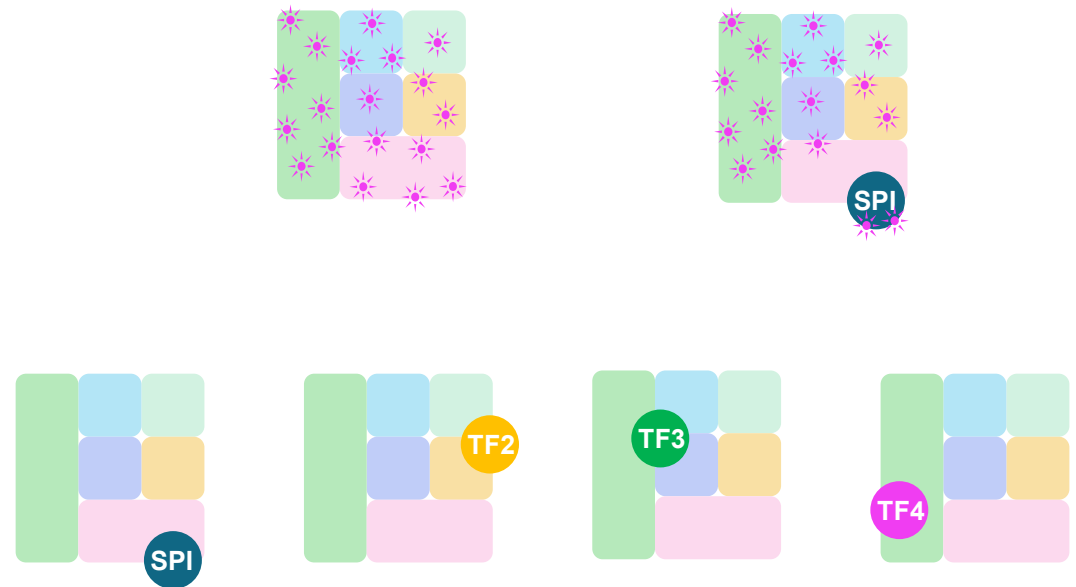
SBR = SPI Binding Region



## Pull-Down Assay



## Mass Spec. Footprinting

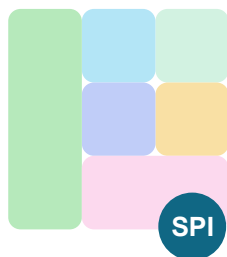


Various TFs map to different surfaces on BAF

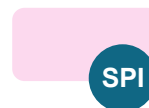
# The reductionist system recapitulates the affinity of SPI1 for Full BAF



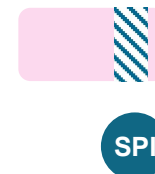
Full BAF



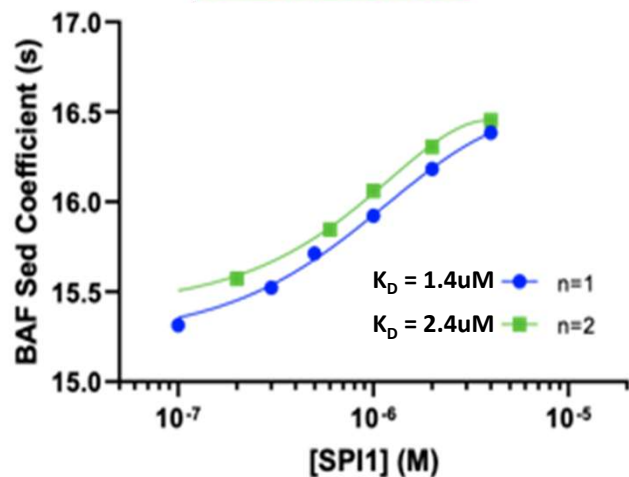
SBR



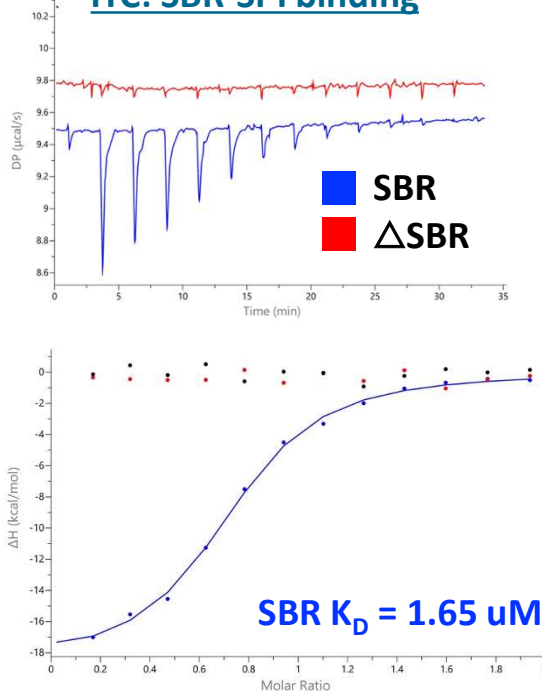
$\Delta$ SBR



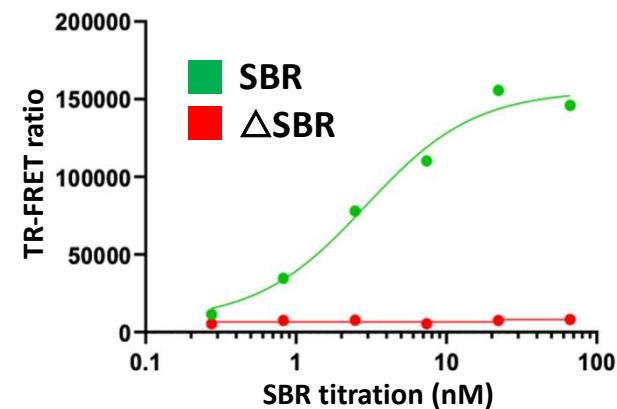
Full BAF-SPI AUC



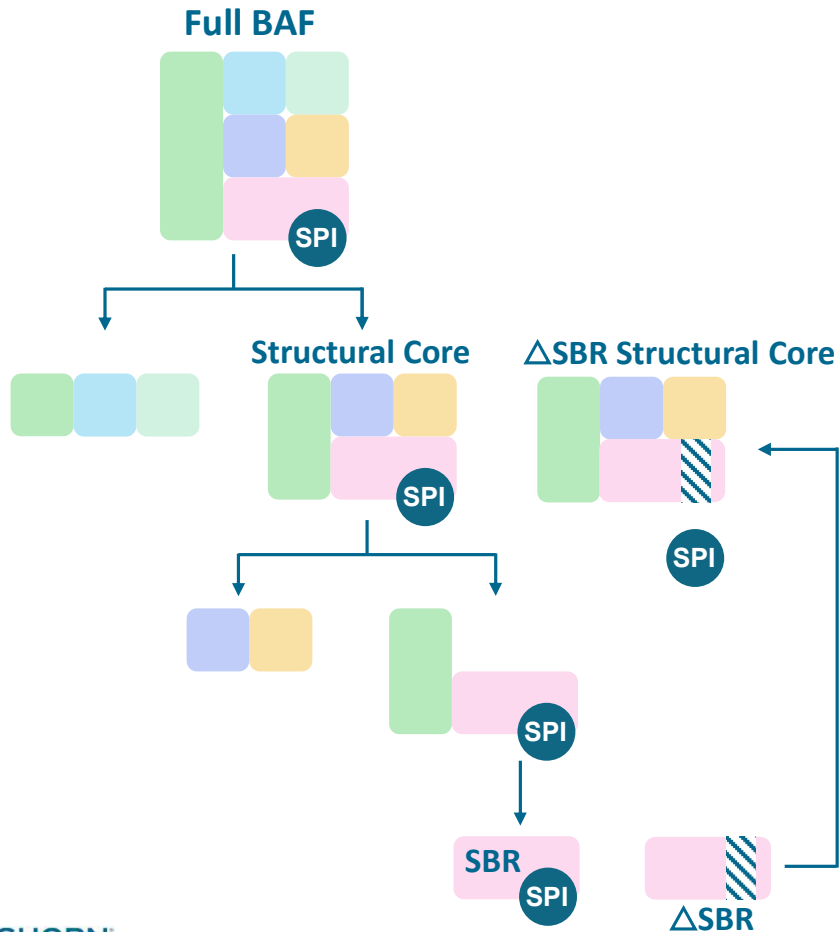
ITC: SBR-SPI binding



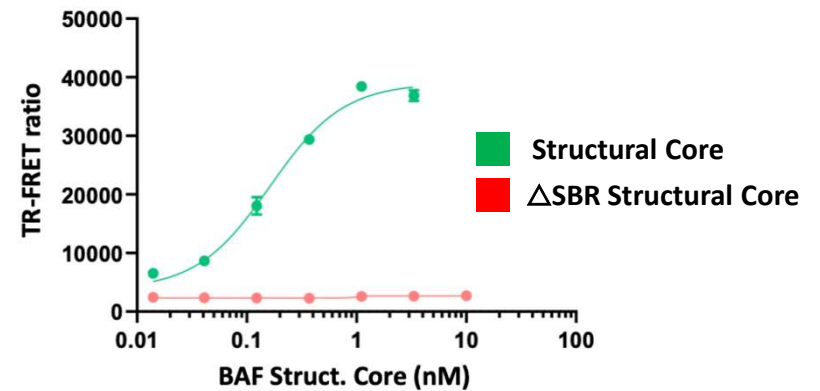
SBR-SPI TR-FRET



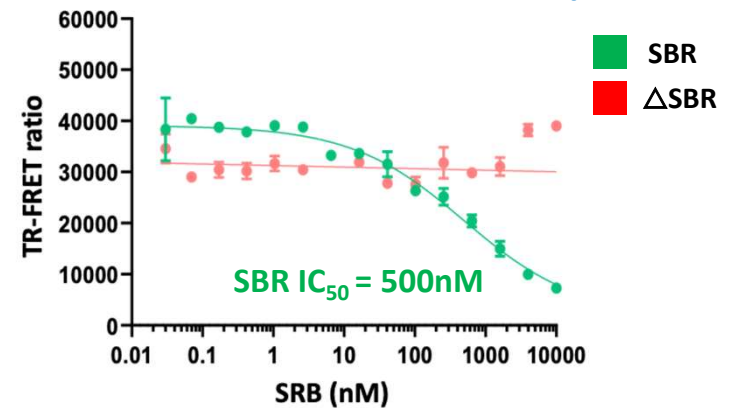
# Validating the reductionist system in context of the BAF Structural Core



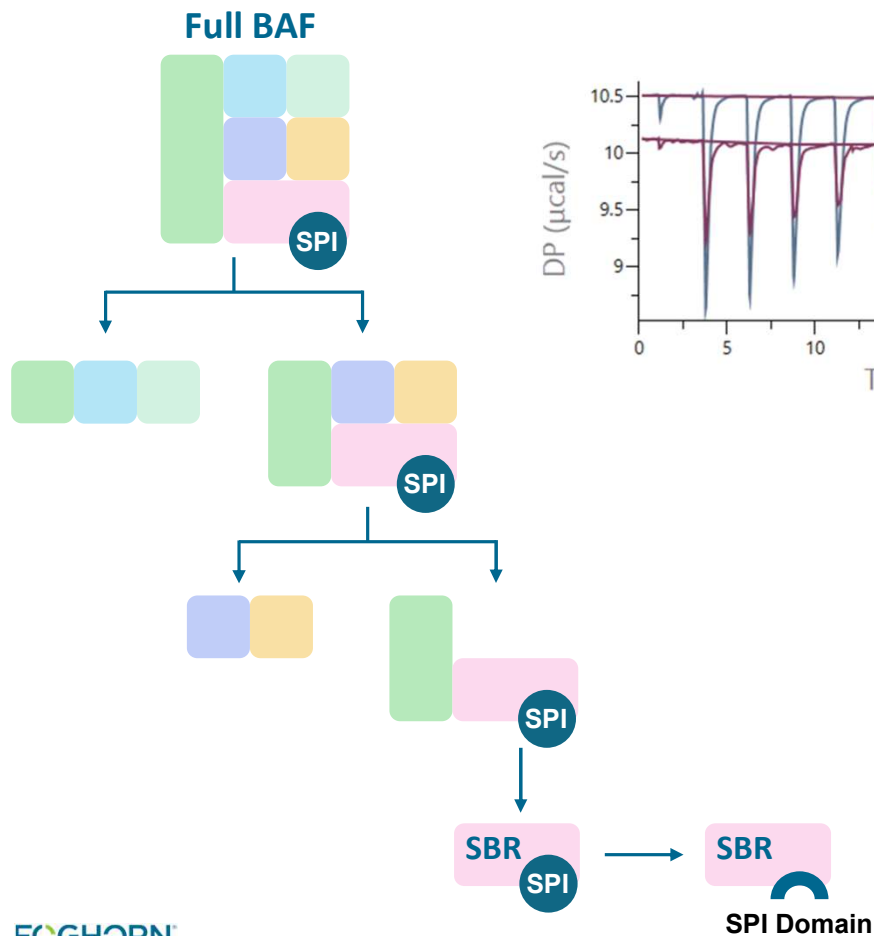
## SPI-Structural Core Binding



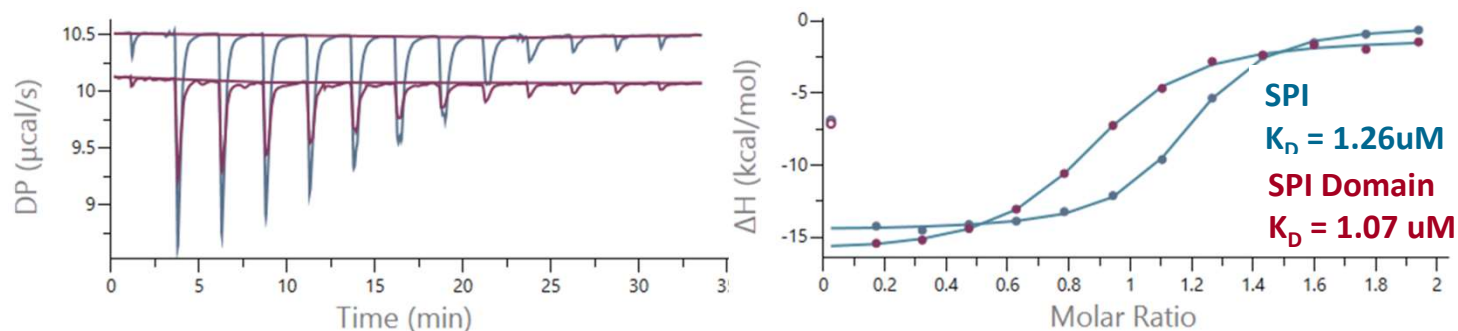
## Structural Core - SBR competition



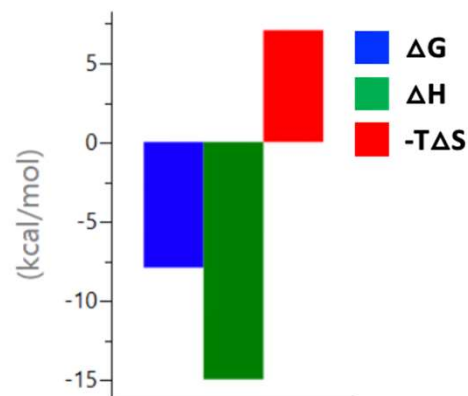
# A specific domain within SPI is responsible for binding to BAF



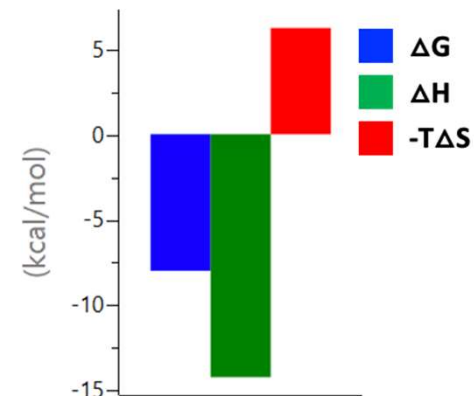
**ITC: SBR-SPI vs. SBR-SPI Domain**



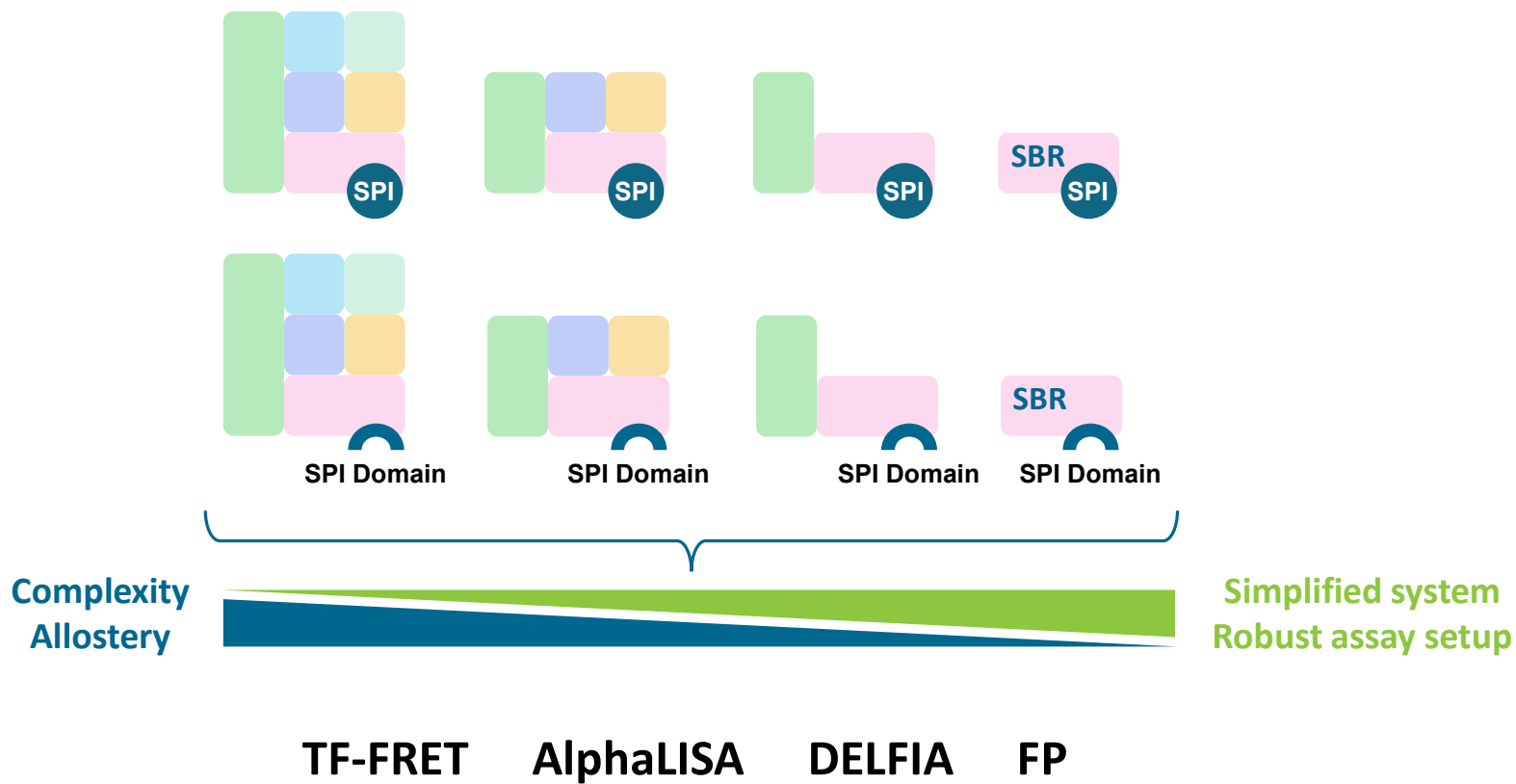
**SBR-SPI**



**SBR-SPI Domain**



# Variety of screening options for finding inhibitors of SPI-BAF



# Acknowledgements: Foghorn Team

