Astex Pharmaceuticals

Fragment-based drug discovery to identify small molecule allosteric inhibitors of SHP2

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TAIHO

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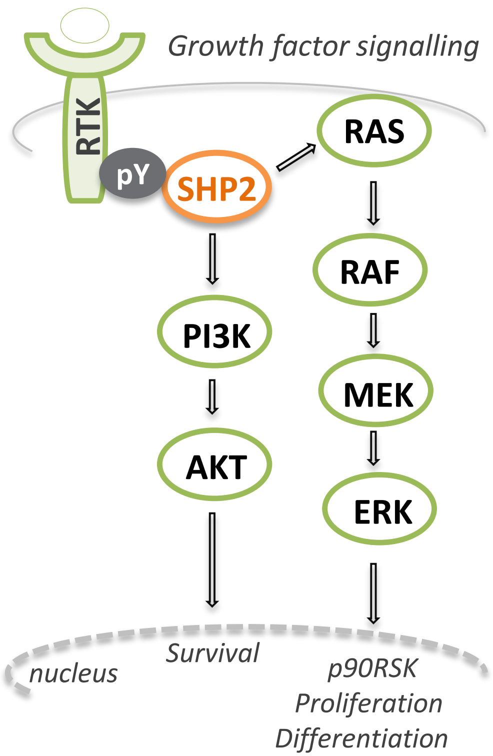
Disclosure

- **The presenter and co-authors are employees of Astex Pharmaceuticals or Taiho Pharmaceutical Co. Ltd.**

Src Homology Phosphatase 2 (SHP2)

- **Protein tyrosine phosphatase family member**
  - Downstream of multiple RTKs
  - Regulator of RAS/MAPK signalling
  - Clinically validated pathway
  - Many opportunities in KRAS & RTK driven cancers for SHP2 inhibitor as single agent or in combination
  - Astex has a fragment-derived ERK1/2 kinase inhibitor in Phase 1

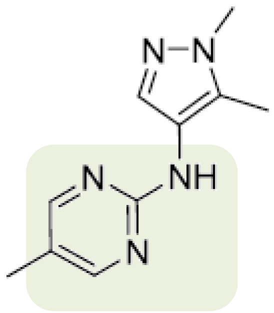
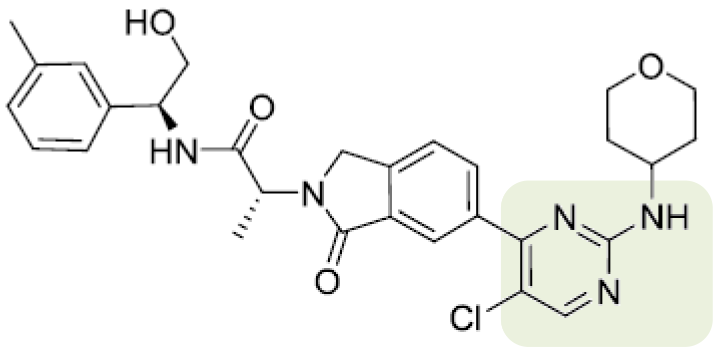
- **Talk describes the SHP2 fragment screen and early hit-to-lead program**



Why Use a Fragment-Based Approach?

- **Proven approach: many fragment-derived compounds currently in clinical development, with three approved drugs**
  - Vemurafenib (BRAF-V600E), venetoclax (BCL-2), erdafitinib (FGFR)

- **Astex has successfully targeted another node downstream of SHP2 in the RAS/MAPK pathway using fragment-based drug design: ERK1/2**

	
MW 203; ClogP 1.4	MW 550; ClogP 2.9

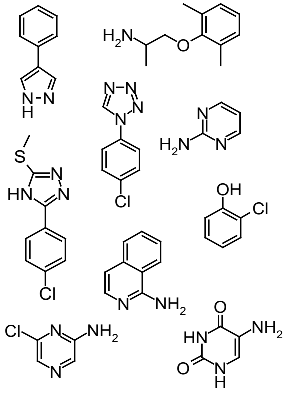
Fragment IC_{50} 76 µM **Lead IC_{50} 0.0030 µM**

Heightman et al., J. Med. Chem. 2018, 61, 4978–4992

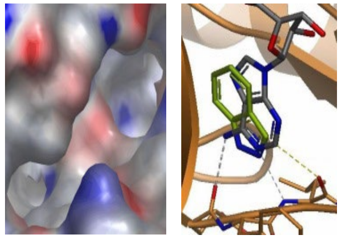
Fragment-Based Drug Discovery at Astex - Pyramid™

FRAGMENT SELECTION

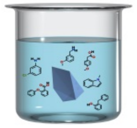
Astex Proprietary Fragment Library

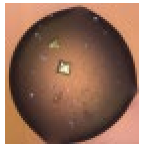


Targeted & Virtual Screening Sets

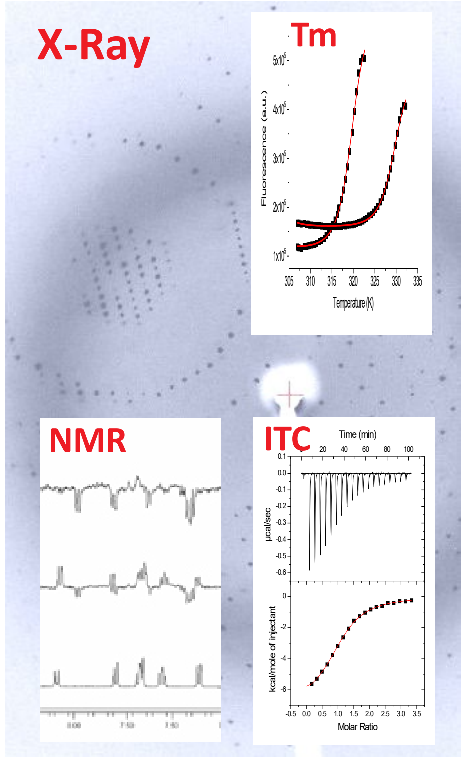


<HAC> 12 <MW> 176

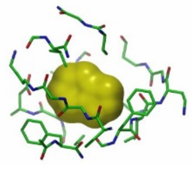




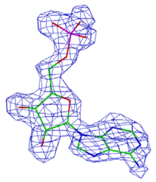
INTEGRATED BIOPHYSICAL SCREENING



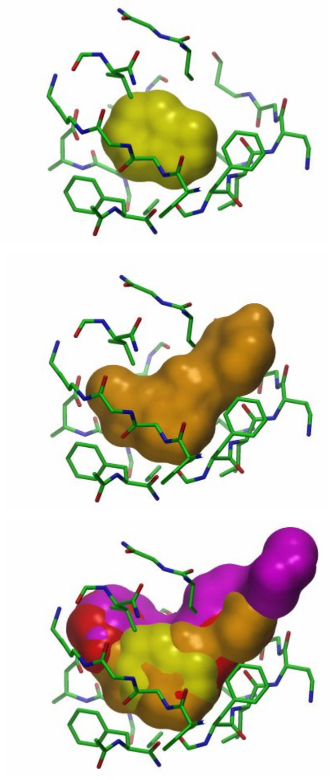
Astex PYRAMID™ Screening



AutoSolve®



STRUCTURE-LED OPTIMIZATION

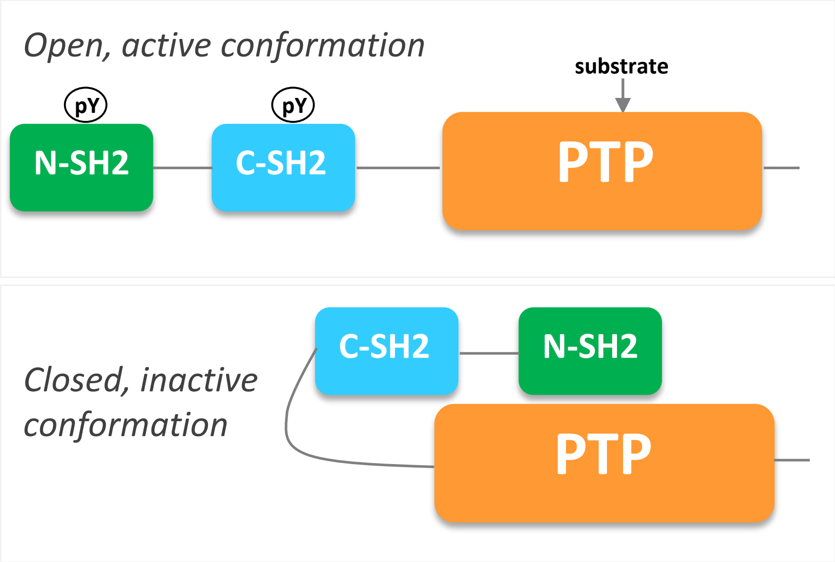


Fragment-to-Candidate Chemistry

Jhoti, et al. *Nature Reviews Drug Discovery*, 12, 644 (2013)

The Challenge for Drugging SHP2

- **Historically phosphatase enzymes were deemed undruggable**
  - Targeting direct inhibition of catalytic site has proven very difficult
  - Opportunity to use fragment screening to identify allosteric sites

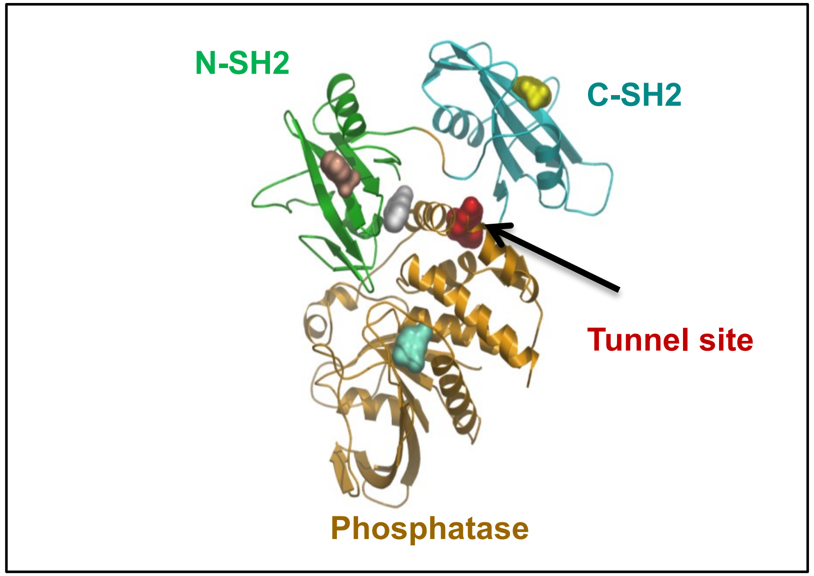


PTP = protein tyrosine phosphatase (catalytic) domain

- **Objective: to discover an allosteric inhibitor stabilizing the closed, catalytically-inactive, form of the protein**

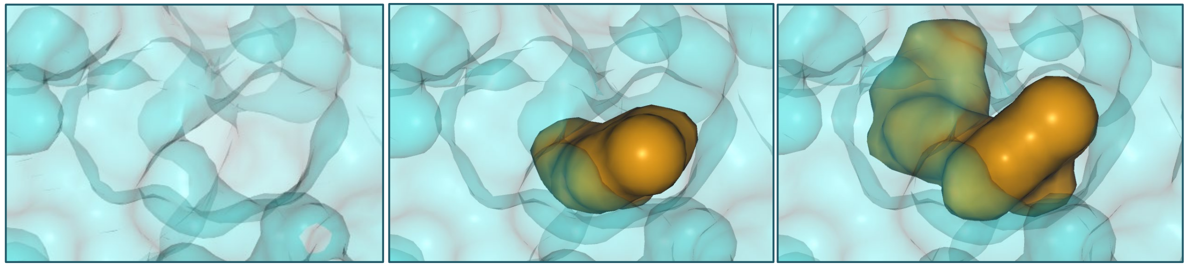
SHP2 Fragment Screen

- **Fragment screen was carried out on two constructs**
  - Closed autoinhibited C-terminal truncated form having catalytic + both SH2 domains
  - Phosphatase domain only form
  - Screened using ligand-observed NMR and X-ray crystallography
- **No hits obtained for phosphatase-only construct**
- **Multiple hits obtained for C-terminal truncated form**
  - >70 structurally validated hits bound in tunnel-like site
  - Additional sites identified
- **Tunnel site does not exist for other phosphatases: high selectivity potential**



SHP2 Fragment Hit to Early Lead Compound

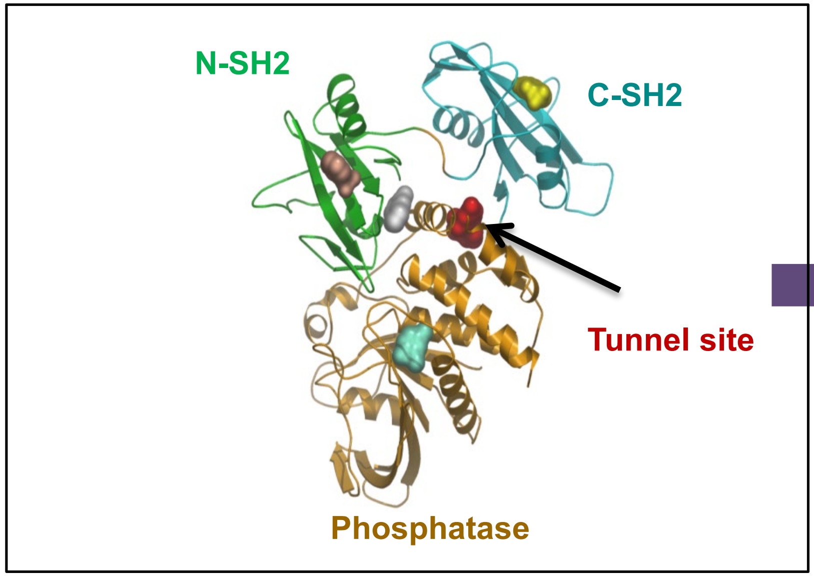
- Example of a millimolar-affinity fragment hit binding to tunnel site

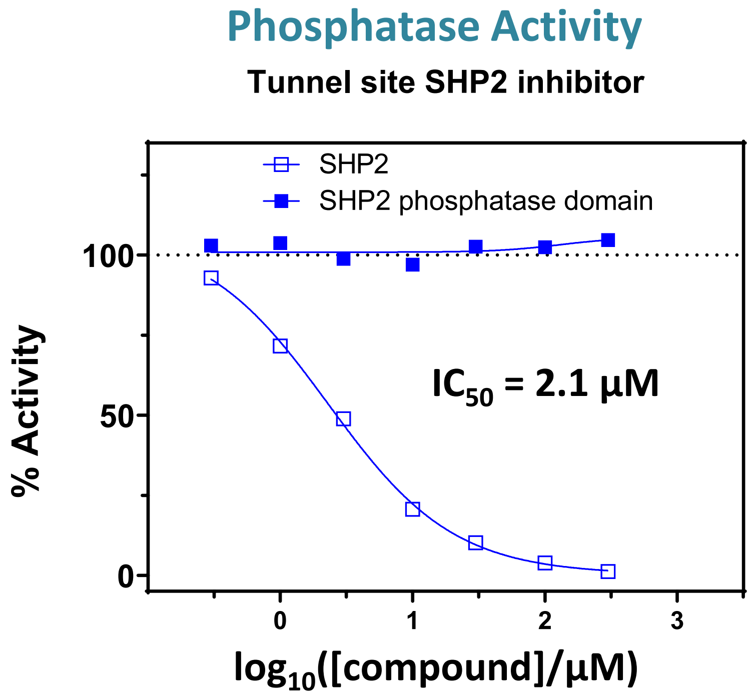


Apo Tunnel Site	Fragment	Early Lead
SHP2 ITC K_D/µM	1000	1.1
Ligand Efficiency	0.34	0.39

- Isothermal titration calorimetry (ITC) used to characterise affinity of weakly binding compounds
- Structure-guided growing of fragment hit into adjacent pockets gave an Early Lead with ~ 1000-fold increase in affinity

SHP2 Enzyme Inhibitory Activity Demonstrated



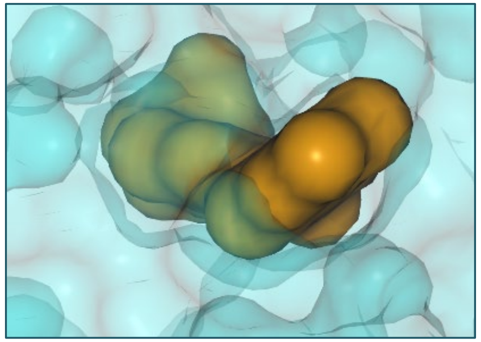


- Early Lead inhibits activity of C-terminal truncated construct expressing N-SH2, C-SH2 and catalytic domains
- No inhibition of phosphatase catalytic domain-only construct
- Promising starting point for further optimization

Summary and Current Project Status

- **Novel allosteric SHP2 inhibitor series identified using fragment-based drug discovery**

- **Lead series has subsequently been optimised to single-digit nanomolar-affinity orally bioavailable preclinical candidate using structure-led design**
  - No inhibitory activity versus catalytic-domain-only construct
  - No inhibition across a panel of 20 phosphatases, including closest relative SHP1



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