# Novel Screening Platform to Identify Confirmation-Specific SHP2 Inhibitors

**NYU Langone** 

A novel screening platform to discover inhibitors targeting signaling active form ("on") conformation to overcome drug resistance in RAS-driven cancers and genetic disorders.

## Technology

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Researchers at NYU Langone Health have discovered that Src homology-2 protein tyrosine phosphatase (SHP2) signaling to RAS requires a specific conformation that can be mimicked by certain mutants of the catalytic cysteine, but not on phosphatase activity. They have developed a SHP2 mutant that remains in the open, signaling active conformation, allowing for high-throughput screening of inhibitors that specifically target SHP2 in its "on" state. SHP2 (encoded by *PTPN11*) is a critical regulator of RTK/RAS/MAPK signaling, and its aberrant activation drives multiple malignancies and developmental disorders. Current allosteric inhibitors only target SHP2 in its inactive ("off") conformation, limiting their therapeutic impact to malignancies/disorders driven by SHP2 in this conformation. This platform provides an innovative approach for identifying inhibitors of SHP2 in its active form, offering new therapeutic strategies for overcoming drug resistance and addressing unmet clinical needs in oncology and RASopathies.

#### **Development Stage**

A SHP2 mutant mimicking the open, signaling active state has been identified and functionally validated. Preliminary screens using this SHP2 mutant have been conceptualized.

#### Background

Activating SHP2 mutations contribute to oncogenesis and therapy resistance by sustaining hyperactive signaling. For example, activating germline mutations in PTPN11 account for ~50% of Noonan Syndrome cases, a disorder affecting 1 in 1,000–2,500 live births, leading to congenital heart defects, developmental delays, and increased cancer risk due to RAS/ERK pathway activation. Additionally, activating somatic mutations in PTPN11 are found in 35% of juvenile myelomonocytic leukemia (JMML) cases, 5-10% of pediatric B-cell acute lymphoblastic leukemia (B-ALL), and are the third most common oncogenic driver in neuroblastoma. SHP2 is also implicated in therapy resistance in EGFR-mutant lung cancer and other RAS-driven tumors, reducing the effectiveness of standard-of-care, first-line targeted therapies. For example, in non-small cell lung cancer (NSCLC) with EGFR mutations, tumors develop resistance to EGFR inhibitors (e.g., Osimertinib and erlotinib) by activating SHP2-mediated bypass signaling, which reactivates MAPK and PI3K pathways. Similarly, in KRAS-G12C-mutant cancers, SHP2 activation enables adaptive resistance to KRAS inhibitors (e.g., sotorasib and adagrasib) by sustaining downstream signaling. Current allosteric SHP2 inhibitors, such as the tool compounds SHP099 and RMC-4550, bind to the inactive ("off") conformation and fail to block constitutively active ("on") SHP2 found in resistant tumors. This limitation necessitates new therapeutic approaches

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## Category

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that specifically target SHP2 in its activated state to effectively treat malignancies and genetic disorders driven by hyperactive SHP2 signaling.

# Applications

**Drug Discovery:** Provides a high-throughput screening platform to discover novel inhibitors (antibodies, degraders, peptides, and small molecules) against constitutively active SHP2. Such inhibitors could be developed to treat drug-resistant RAS-driven cancers and RASopathies .

## Advantages

- New Therapeutic Potential: Allows for targeting of SHP2 in its activated state
- Means to overcome Drug Resistance: Identified inhibitors could block activated SHP2-driven survival pathways
- **Tailored Drug Screening:** Provides a platform for identifying conformation specific SHP2 inhibitors

# **Intellectual Property**

NYU has filed a U.S. provisional patent application covering the composition of an active SHP2 mutant variant, its method of use in screening platforms to identify inhibitors targeting SHP2 in its activated state, and the method of targeting activated SHP2 with therapeutic modalities for the treatment of cancer and RASopathies.