**Molecular Characteristics of Repotrectinib That Enable Potent Inhibition of TRK Fusion Proteins and Broad Mutant Selectivity**

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**INTRODUCTION**

- Chronic myeloid leukemia (CML) and acute myeloid leukemia (AML) are treated with tyrosine kinase inhibitors (TKIs).
- TRK fusion proteins are targeted by TRK inhibitors.
- Repotrectinib (TPX-0005) is a broad-spectrum, multi-kinase inhibitor.

**METHODS**

- **Co-crystal structures of TPX-0005 bound to various TRK inhibitors**
- **Cell-based screening and in vivo tumor models**

**RESULTS**

- Repotrectinib demonstrates marked anti-tumor activity in xenograft tumor models harboring wild-type (WT) and mutant TRK.
- Repotrectinib is potent against the gatekeeper mutation (TRKA F589L) and activation loop mutation (DFG, TRKA TRK).

**CONCLUSIONS**

- Repotrectinib is highly potent against a wide variety of TRK mutations.
- Repotrectinib has been granted orphan drug designation for the treatment of patients with NTRK+ advanced solid tumors.

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