TG02, a brain penetrant multi-CDK inhibitor inhibits growth in MYC-driven glioblastoma

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Abstract

MYC is a central driver of tumorigenesis in many malignancies, including the universally lethal glioblastoma (GBM). However, developing direct inhibitors of MYC has proven challenging. One appealing alternative strategy to target MYC-driven cancers is to interfere with the signaling program necessary to facilitate MYC-dependent transcription. Cyclin-dependent kinase 9 (CDK9) has emerged as an attractive candidate through its function as a critical regulator in the transcriptional elongation of MYC and its target genes. Using a panel of patient-derived GBM cells, here we demonstrate that CDK9 inhibition with the brain-penetrant multi-CDK inhibitor TG02, potently suppresses GBM cell growth. Importantly, the anti-GBM efficacy of TG02 strongly correlates with MYC expression and appears to be independent of methylation status, suggesting a critical role for CDK9 in MYC-driven GBMs. These preliminary results indicate that CDK9 may be an actionable therapeutic target in GBM with aberrant MYC signaling and, importantly, the clinical stage oral small molecule, TG02, is an appealing drug candidate for GBM with elevated signaling and, importantly, the clinical stage oral small molecule, TG02, is a potent multi-CDK inhibitor with IC50 in the low nm range.

Background

- Globlastoma is the most lethal and the most malignant primary brain tumor with a median survival of 15 months
- MYC is known to be deregulated in a wide variety of cancers including glioblastomas and its constitutive expression is an established driver of tumorigenesis
- The MYC/MAX heterodimer lacks necessary binding pockets, which makes the MYC oncprotein an undruggable driver
- MYC is known to promote transcriptional elongation by recruiting P-TEFb to RNA Polymerase II, and causing phosphorylation at Ser 2 (Figure 1)
- A cyclin-dependent kinase, CDK9, is required for the aberrant proliferation of MYC-overexpressing tumors. CDK9 promotes transcriptional elongation via phosphorylation of RNA Pol II
- TG02 is a novel multi-kinase inhibitor developed by Tragara Pharmaceuticals
- TG02 is blood-brain barrier penetrant, and exhibits a half maximal inhibitory concentration below 10nM for CDKs 1, 2, 3, 5, and 9

Hypothesis and Approach

TG02 inhibits cell growth in GBM through CDK9-mediated transcription elongation in tumors with highly expressing MYC protein levels
- Determine a correlation between protein expression and half-maximal inhibitory concentration (IC50)
- Determine the effect of TG02 in a patient-derived orthotopic xenograft GBM model

Primary GBM cells show variable sensitivity to TG02

Fig. 2 A) Patient-derived neurospheres recapitulate GBM diversity B) TG02 is a potent multi-CDK inhibitor with IC50 in the low nm range

MYC protein levels inversely correlate with TG02 IC50

Fig. 3 Primary GBM cells show variable sensitivity following TG02 treatment. A) Half-maximal inhibitory concentrations of 31 patient-derived GBM cell lines following 72 hours of TG02 treatment. B) Percent growth inhibition following 72 hours of 40nM TG02 treatment

Fig. 4 Myc protein levels inversely correlate with IC50 of TG02. A) Western blot showing wide range of MYC and CDK9 protein levels in 10 patient-derived spheres B) MYC protein levels inversely correlated with TG02 IC50, but not CDK9.

Fig. 6 Toxicity and Pharmacokinetics of TG02. A) Mice treated with 40mg/kg TG02 3 times/week did not display fluctuations in body weight in one month of treatment B) Tissue distribution of TG02 after a single administration under fed condition at 75 mg/kg.

Future Directions

- Evaluate in vivo activity of TG02 in MYC high vs MYC low orthotopic patient-derived xenograft models

Conclusions

- Inhibition of CDK9 with TG02 has potent, but heterogeneous activity in a subset of primary GBM samples
- Expression of MYC, but not CDK9, correlates with sensitivity
- Sensitivity to TG02 does not correlate with MGMT methylation status
- Preliminary results show activity of TG02 in an intracranial GBM model with high MYC expression

Acknowledgements

- We thank Dr. Linda Liu (UCLA) and Dr. William Yong (UCLA)
- Nathanson Lab members
- Tom Estok (Tragara Pharma)