ABSTRACT
Gastrointestinal stromal tumor (GIST) is characterized by activating mutations of the KIT or PDGFRA receptor tyrosine kinases and is driven by the intense cellular activity of Capet (CCCs), where KIT regulates its normal development and lineage specification. Despite the initial clinical success of imatinib, the majority of patients with advanced GIST develop imatinib resistance and die of their disease. The development of novel therapeutics that can improve clinical success of imatinib therapy and/or overcome resistance in GIST is important. Here, we demonstrate that ETV1 is required for GIST initiation and maintenance in vivo using compound genetically engineered mouse models (GEMMs). We have uncovered that ETV1 enhances KIT expression through direct binding to the KIT enhancers. Hence, ETV1 and mutant KIT form a positive feed-forward loop, which is enhanced by active MAPK signaling. Further, we demonstrate that inhibition of neither KIT nor ETV1 nor its downstream MAPK kinase signaling by MEK162, a MEK inhibitor, is sufficient to durably eradicate the GIST tumor. Interestingly, the combined targeting of the dual lineage inhibition of KIT by imatinib and ETV1 by MEK162 results in durable inhibition of the ETV1 protein and leads to significantly more enhanced inhibition of GIST growth than either single agent alone. Our observations demonstrate that ETV1 is a novel therapeutic target in GIST. Importantly, the dual lineage targeting of KIT and ETV1 by the combination therapy may form a more effective therapeutic strategy than imatinib alone in GIST clinical management.

METHODS
Genetic Engineered mouse modeling, tumor cell xenograft, Chromatin IP, Western blotting, Immunofluorescence, Immunohistochemistry.

RESULTS

Figure 1: ETV1 is required for the initiation of GIST development in vivo

Figure 2: ETV1 regulate KIT expression through binding to KIT enhancers

Figure 3: Dual inhibition of KIT and ETV1 synergistically induce apoptosis in GIST

Figure 4: Dual inhibition of KIT and ETV1 results in GIST xenograft tumor regression in vivo

Figure 5: Dual inhibition of KIT and ETV1 results in GIST GEMM tumor regression in vivo

CONCLUSION
- ETV1 is required for GIST tumor initiation and maintenance in vivo.
- ETV1 positively regulates KIT expression through binding to its enhancer.
- Targeting ETV1/KIT dual forward circuits by combined therapy of MEK162 and imatinib leads to more enhanced inhibition of GIST growth than either single agent in vitro and in vivo.

REFERENCE