# TET2 Modulators for the Treatment of Cancer and Inflammatory Diseases

**A series of small molecule modulators (agonists and antagonists) of TET2 for potential use as therapeutics for rare hematological diseases.**

### Technology Overview

The inventors, in collaboration with NYU's internal drug development accelerator (Therapeutic Alliances), have discovered a series of small molecule modulators of TET2 for potential use as therapeutics. These "hit" compounds (agonists and antagonists) were identified from a ~250,000 compound high throughput screen and were recently validated in activity determination assays.

Previously, the inventors discovered that targeted restoration of TET2 is sufficient to block aberrant self-renewal of pre-leukemic stem cells. As described in *Cimmino et al. Cell 2017*, restoration of endogenous TET2 expression (using a transgenic RNAi mouse model) reversed aberrant self-renewal in TET2-deficent cells. Additionally, they found that restoration of TET2 expression promoted DNA demethylation, differentiation, and cell death. Lastly, they found that genetic or pharmacological restoration of TET2 activity confers an emergent vulnerability in leukemia cells, rendering them more sensitive to PARP inhibitors. Taken together, these results suggest that the restoration or enhancement of TET2 activity is a promising therapeutic strategy for the treatment of hematological diseases with TET2-deficiencies.

### Current Drug Development Stage

**Hit-to-Lead stage:** Hit compounds (confirmed by resynthesis/testing) are currently being validated in cellular LC/MS assays for functional efficacy.

### Background

TET2 is one of the most frequently mutated genes in hematopoietic malignancies, such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). As a member of the ten-eleven-translocation (TET) protein family, TET2 is α-ketoglutarate- and Fe2+-dependent dioxygenase (α-KGDDs) that oxidizes 5-methylcytosines (5mCs) to 5-hydroxymethylcytosine (5hmC) and promotes locus-specific reversal of DNA methylation. Truncations or mutations in the TET2 catalytic domain, which negatively affect co-factor binding, lead to impaired 5mC oxidation and consequent DNA hypermethylation. Mutations in TET2 are associated with an increased risk of MDS progression and poor prognosis in AML. Therefore, therapeutic strategies that restore or enhance TET2 activity, thereby limiting DNA hypermethylation, are expected to be efficacious treatments for TET2-deficent hematological cancers. Conversely, antagonists of TET2 may have potential utility in enhancing CAR-T and immune checkpoint therapy. Further, TET2 modulators (agonists and antagonists) may have potential utility in controlling Treg function. As of present, no TET2 modulators have been FDA approved or are in clinical development.

### Applications

**Technology ID**

AIF01-09

**Category**

Life Sciences/Biochemicals & Small Molecules
Life Sciences/Therapeutics/Oncology
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- **Leukemia and pre-leukemic diseases with TET2-deficiency**
  - Clonal hematopoiesis (CH)
  - Myeloproliferative neoplasms (MPN)
  - Myelodysplastic syndrome (MDS)
  - Chronic myelomonocytic leukemia (CMML)
  - Acute myeloid leukemia (AML)
  - Acute lymphoblastic leukemia (ALL)
- **Other cancer subtypes**
  - Neoplasms with decreased TET2 expression and consequent DNA hypermethylation
- **CAR-T and immune checkpoint therap**y
- **Modulation of Treg function** - applicable to both cancer and autoimmune diseases

### Benefits

- Validated disease target  TET2 mutations represent “pre-leukemic lesions” that enable the progression of hematological malignancies.
- Clear pharmacological mechanism of action  Restoration of TET2 expression is sufficient to block aberrant self-renewal of pre-leukemic stem cells.
- Target location  TET2 is a cytoplasmic protein expected to be accessible to small molecule pharmacological intervention.

### Intellectual Property

Provisional patent application pending

### References

1. Cimmino L, Dolgalev I, Wang Y, et al. , https://pubmed.ncbi.nlm.nih.gov/28823558/