

Supplemental Information

Targeting RNA adenosine editing and modification enzymes for RNA therapeutics

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Table S1: References from Figure 2

See attached excel file

Table S2: Effect of m6A demethylases (FTO/ALKBH5) in disease

See attached excel file

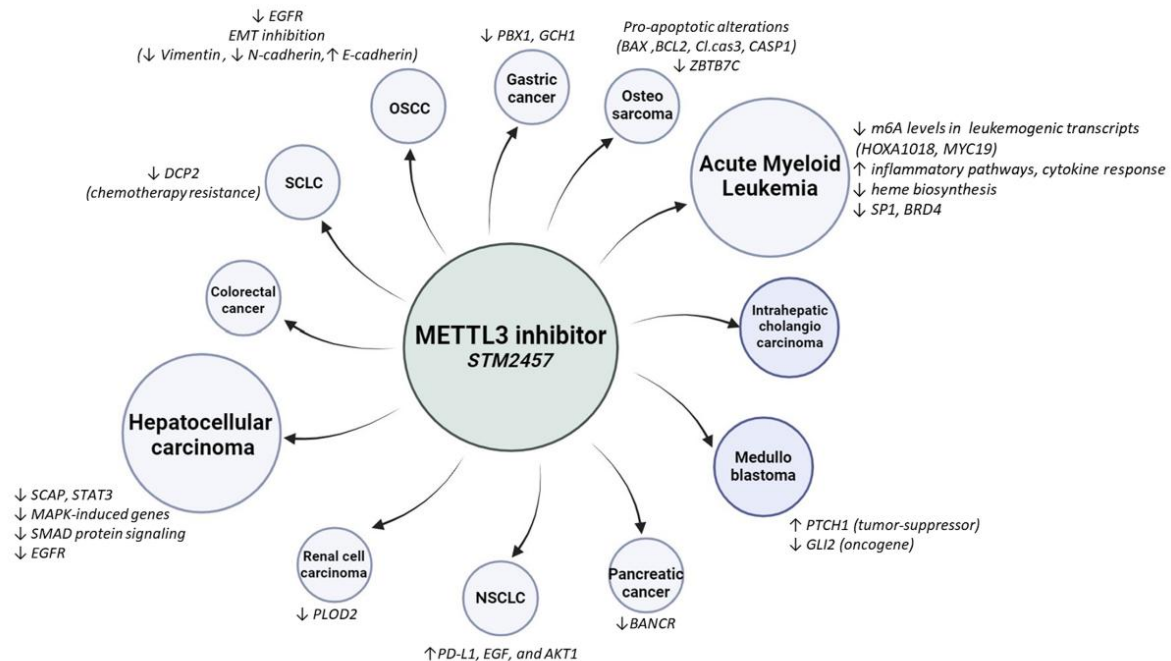
Table S3. Small molecule inhibitor against m6A readers						
Compound	Disease	Model	Effect of inhibition on disease outcome	Pathways affected by reader inhibition	Effect of reader inhibition on target transcript	Reference
JX5 (IGF2BP2 inhibitor)	T-cell acute lymphoblastic leukemia (T-ALL)	Immortalized human T lymphocyte cell line (Jurkat) Injection of Jurkat cells in M-NSG mice after irradiation	↓ proliferation and ↑ apoptosis <i>in vitro</i> ↓ splenomegaly and T-ALL expansion <i>in vivo</i>	n/a	↓ NOTCH1 expression	246
CWI1-2 (IGF2BP2 inhibitor)	Acute myeloid leukemia	CD34+ cells from AML patients Blast cells from MA9-induced leukemia mice	↓ colony forming ability <i>in vitro</i> ↓ self-renewal of LSCs/LICs <i>in vitro</i> ↓ leukemia engraftment <i>In vivo</i> ↓ leukemia onset → prolonged survival <i>In vivo</i>	↓ Gln uptake ↓ mitochondrial function → ↓ ATP production	↓ MYC, GPT2 and SLC1A5 mRNA stability and translation	247
Tegaserod (YTHDF1 inhibitor)	Acute myeloid leukemia	Leukemia monocyte cell line (THP-1) AML patient-derived CD34+ cells xenograft model mice using AML patient-derived CD34+ cells	↓ cell proliferation, G1 phase cell cycle arrest and ↑ apoptosis <i>in vitro</i> ↓ colony forming ability <i>in vitro</i> ↓ hepatosplenomegaly and leukemia cell infiltration in liver tissue → ↑ survival <i>In vivo</i>	n/a	↓ CCNE2 protein level but did not alter mRNA stability	248
DC-Y13-27 (YTHDF2 inhibitor)	Melanoma, colorectal carcinoma	MC38/B16 murine models Rag1 Knockout mice	↓ tumor growth when combined with anti-PD-L1 treatment and/or IR <i>in vivo</i>	↑ NF-κB signalling pathway	↓ c-MYC mRNA stability	249
Cucurbitacin B (CuB) (IGF2BP1 inhibitor)	Hepato-cellular carcinoma	Huh7 cells H22-derived tumors in BALB/c mice	↓ proliferation and ↑ apoptosis of cancer cells ↑ T-cell infiltration and ↓ tumor volume and weight <i>in vivo</i>	n/a	↓ c-MYC, KRAS, ARCKSL1, and FSCN1 mRNA stability	250

Table S4: Ongoing clinical trials in RNA editing therapy									
NCT number	Type	Status	Condition	Intervention	Sex	Age	Phase	Design (Allocation, Intervention model, masking, primary purpose)	Completion (estimation)
NCT05584111	Interventional	Active	Advanced Malignancies	STC-15: METTL3 inhibitor	All	Adult, Older Adult	1	Non-randomized, sequential assignment, open Label, treatment	5/2025
NCT06186492	Interventional	Recruiting	Alpha-1 Antitrypsin Deficiency	WVE-006: A-to-I RNA editing oligonucleotide for SERPINA1 mRNA	All	Adult, Older Adult	1	Randomized, sequential assignment, double, treatment	12/2024
NCT06405633	Interventional	Recruiting	Alpha-1 Antitrypsin Deficiency	WVE-006: A-to-I RNA editing oligonucleotide for SERPINA1 mRNA	All	Adult, Older Adult	2	Non-randomized, sequential assignment, open Label, treatment	07/2025
NCT06677307	Interventional	Recruiting	Alpha-1 Antitrypsin Deficiency	KRRO 110: A-to-I RNA editing oligonucleotide for SERPINA1 mRNA	All	Adult, Older Adult	2	Randomized, sequential assignment, double, treatment	12/2026
Data retrieved from the website www.clinicaltrials.gov . Last assessed on 7th of February 2025.									

Figure S1

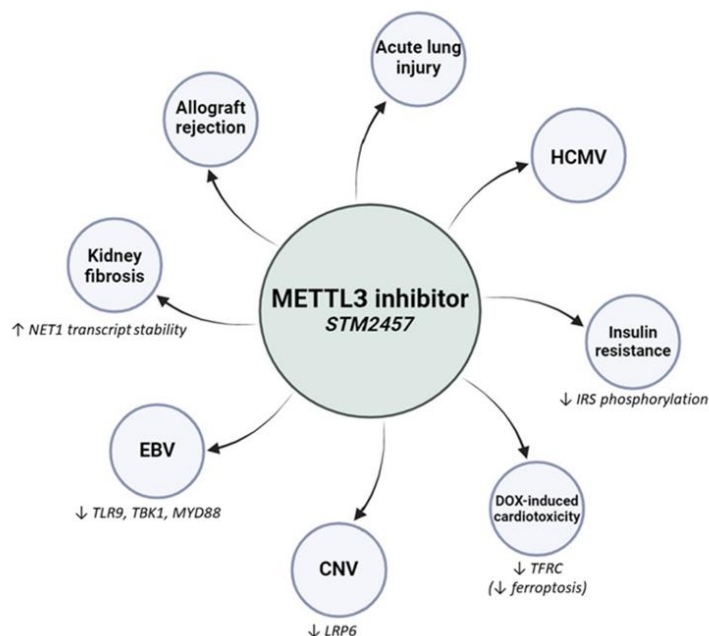
A

METTL3 inhibitors in cancer models



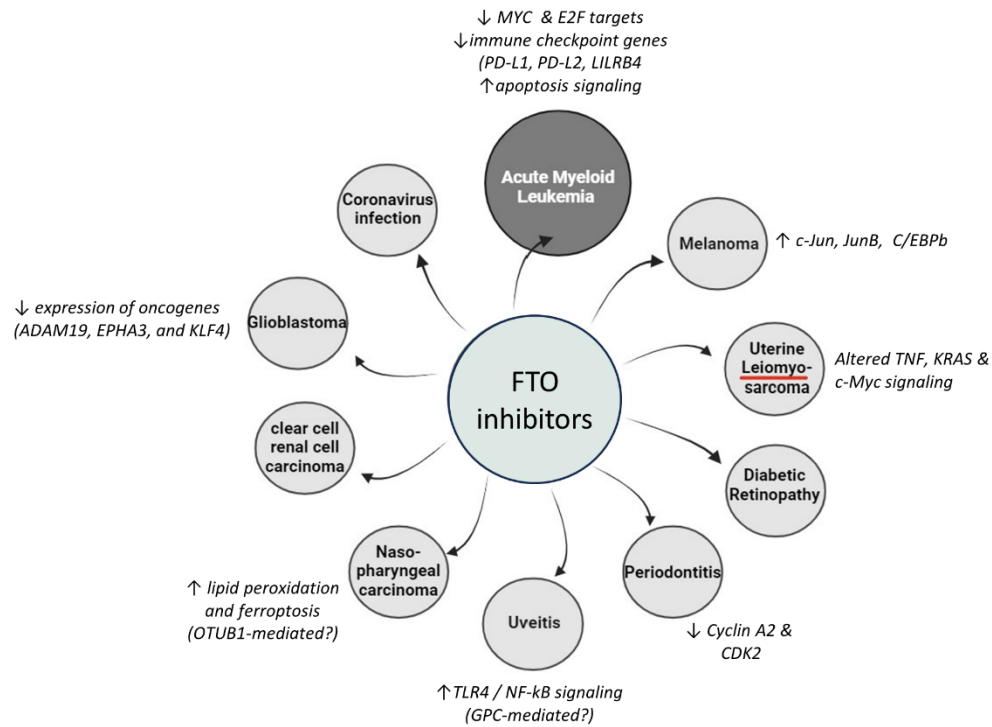
B

METTL3 inhibitors beyond cancer



Graphical representation of studies with *in vivo* targeting of METTL3 by the small molecule inhibitor STM2457 in different types of cancer (A) or other diseases (B). The size of each circle denotes number of studies available (larger circle size corresponds to more studies). Text in *italics* denotes the major molecular targets or processes affected by STM2457 treatment. Part of the figure was created with BioRender.com.

Figure S2



Graphical representation of studies with *in vivo* targeting of FTO by small molecule or chemical inhibitors. The size of each circle denotes number of studies available (larger circle size corresponds to more studies). Text in *italics* denotes the major molecular targets or processes affected by treatment with the FTO inhibitors. Part of the figure was created with BioRender.com.

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