Preclinical evaluation of TTRA-4201, a novel ferrous-iron reactive (FIRE) conjugate of the topoisomerase-I inhibitor exatecan

Abstract #366

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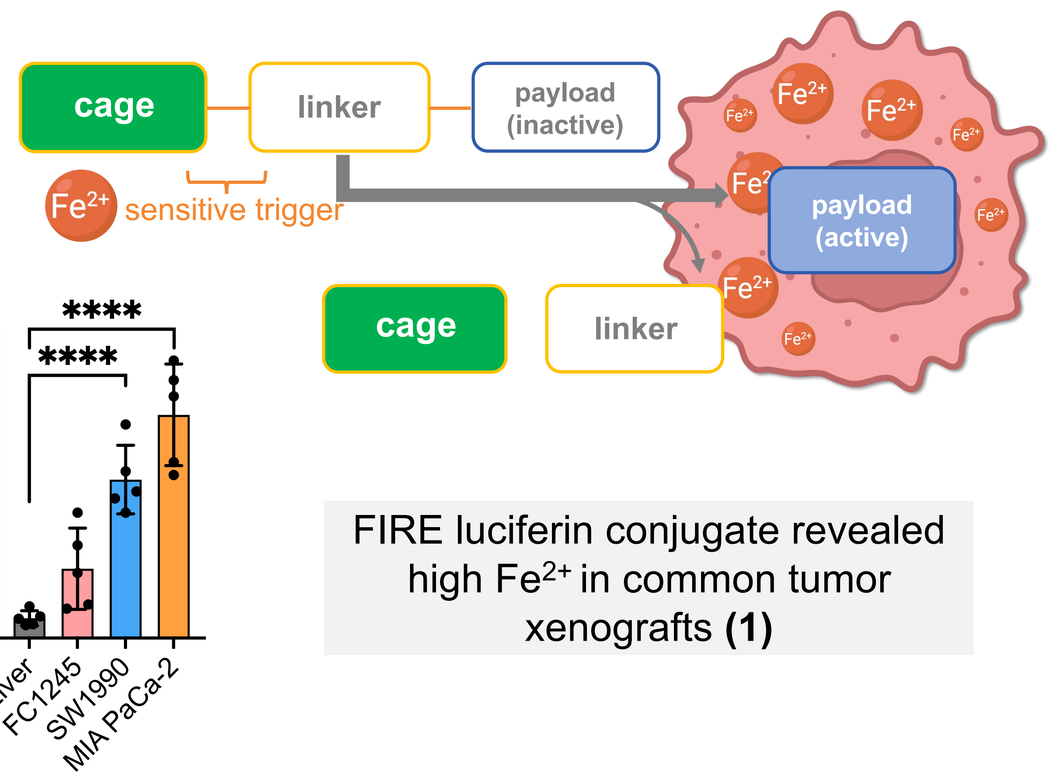
Background

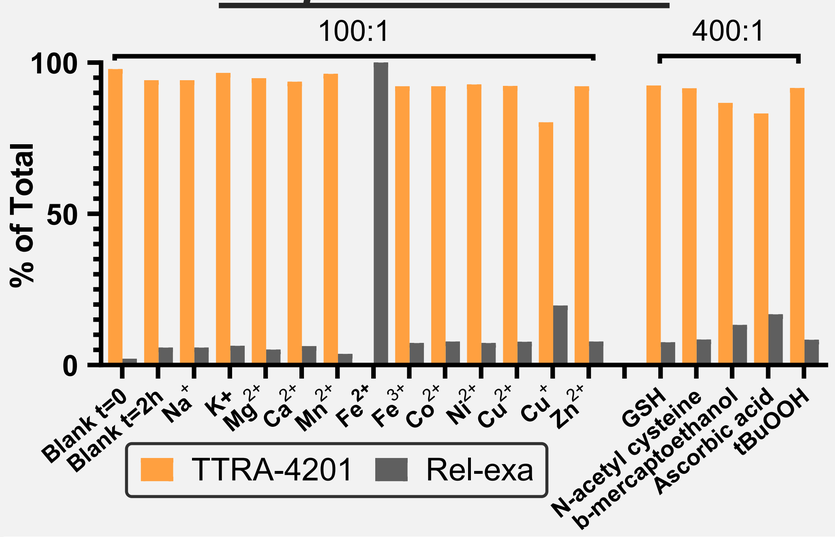
Non-mutational drivers of tumor progression have long been established since the Warburg dogma. Labile ferrous iron (Fe^{2+}) is the reactive form of iron which tumors use for growth. Our novel ferrous-iron reactive platform releases payload upon reaction with Fe^{2+} which presents at high levels in multiple tumor types.



FIRE luciferin conjugate revealed high Fe^{2+} in common tumor xenografts **(1)**

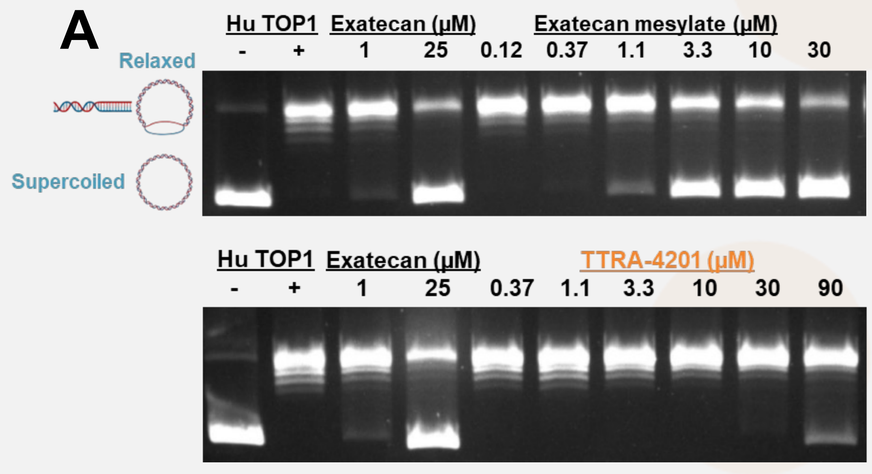
TTRA-4201 is a FIRE conjugate of exatecan – to date, unmodified exatecan has not been approved in the US due to its narrow therapeutic index

TTRA-4201 is selectively uncaged in the presence of Fe^{2+}



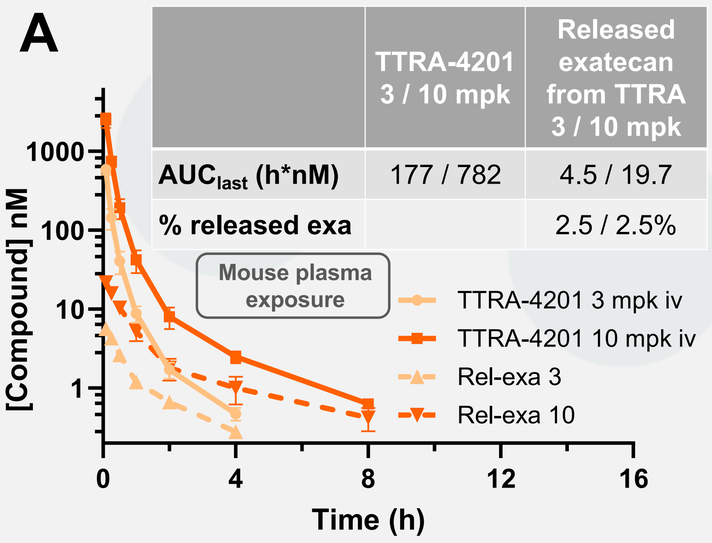
Exatecan release from TTRA-4201 was profiled in the presence of multiple metal ions for 2h to assess specificity of trigger release

TTRA-4201 does not bind to topoisomerase I and is potent in a 3D cellular assay

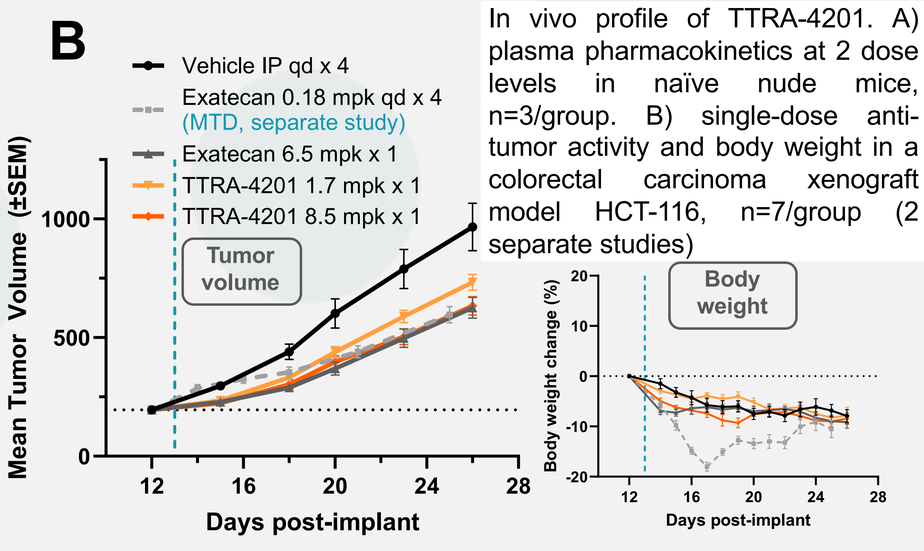


A) Functional activity of human topoisomerase I as measured by relaxation of supercoiled DNA (inhibition = more supercoiled DNA). B) Potency against cell viability was measured in a 72h 3D HCT116 CTG assay (inset, image of spheroid); Performed in replicates, 500 cells/well. Potency-shift may be a result of exatecan release kinetics

TTRA-4201 exhibits in vivo stability and anti-tumor activity in a xenograft model of colorectal carcinoma

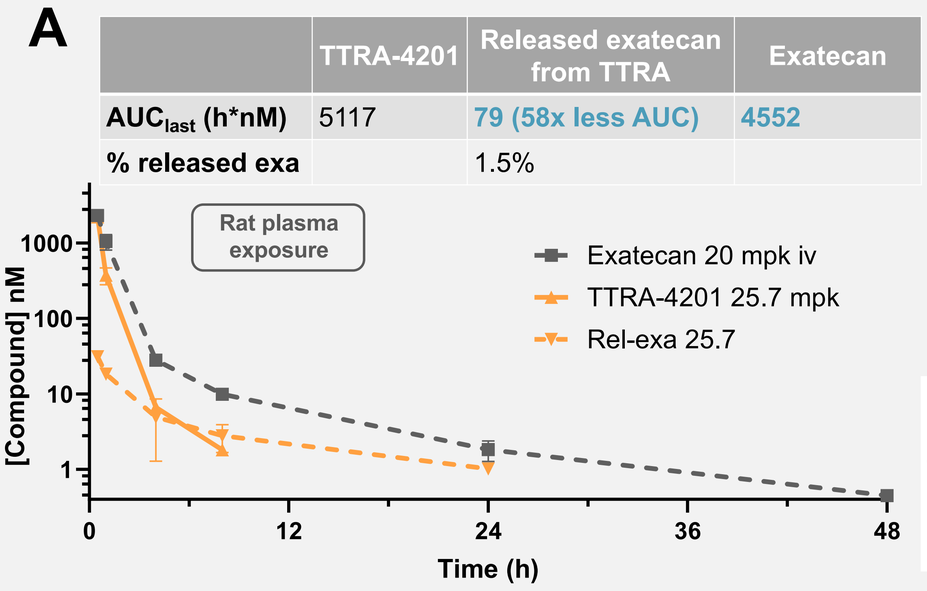


	TTRA-4201 3 / 10 mpk	Released exatecan from TTRA 3 / 10 mpk
AUC_{last} (h*nM)	177 / 782	4.5 / 19.7
% released exa		2.5 / 2.5%

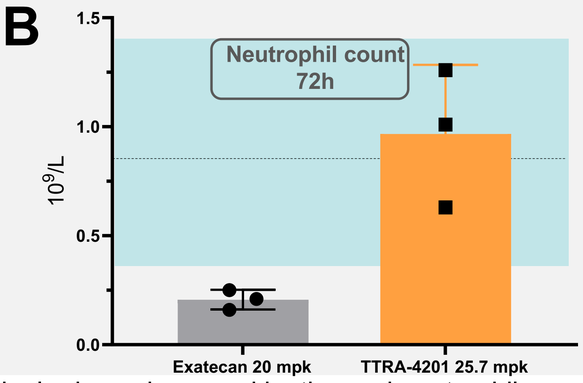


In vivo profile of TTRA-4201. A) plasma pharmacokinetics at 2 dose levels in naïve nude mice, n=3/group. B) single-dose anti-tumor activity and body weight in a colorectal carcinoma xenograft model HCT-116, n=7/group (2 separate studies)

Plasma exposure of released exatecan from TTRA-4201 is > 50-fold less than equimolar exatecan in rat, and does not elicit neutropenia

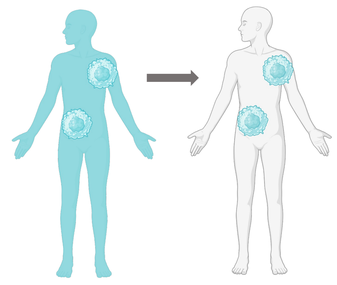


	TTRA-4201	Released exatecan from TTRA	Exatecan
AUC_{last} (h*nM)	5117	79 (58x less AUC)	4552
% released exa		1.5%	



Single dose pharmacokinetics and neutrophil assessment in male Sprague Dawley rats. A) plasma exposure of TTRA-4201, released exatecan, and equimolar exatecan, n=3/group. B) neutrophil counts at 72h, shaded area represents published reference range (He Q et al. *PLoS One* 2017), n=3/group

Conclusions



TTRA-4201 is a potent FIRE conjugate of exatecan that does not bind to topoisomerase I and results in markedly less exatecan in peripheral plasma. This may lead to a higher therapeutic index in the clinic, to access a substantial solid tumor patient population. Further optimization is in progress to nominate a development candidate.

Visit our FIRE Platform poster to learn more about the chemistry abstract #363

(1) Gonciarz et. al. *Cell Chem Biol* 2023 Vol. 30 No. 11

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