A Novel Tumor-Activated Prodrug Strategy Targeting Ferrous Iron Is Effective in Multiple Preclinical Cancer Models

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Tanja Krainz

Current Literature Seminar

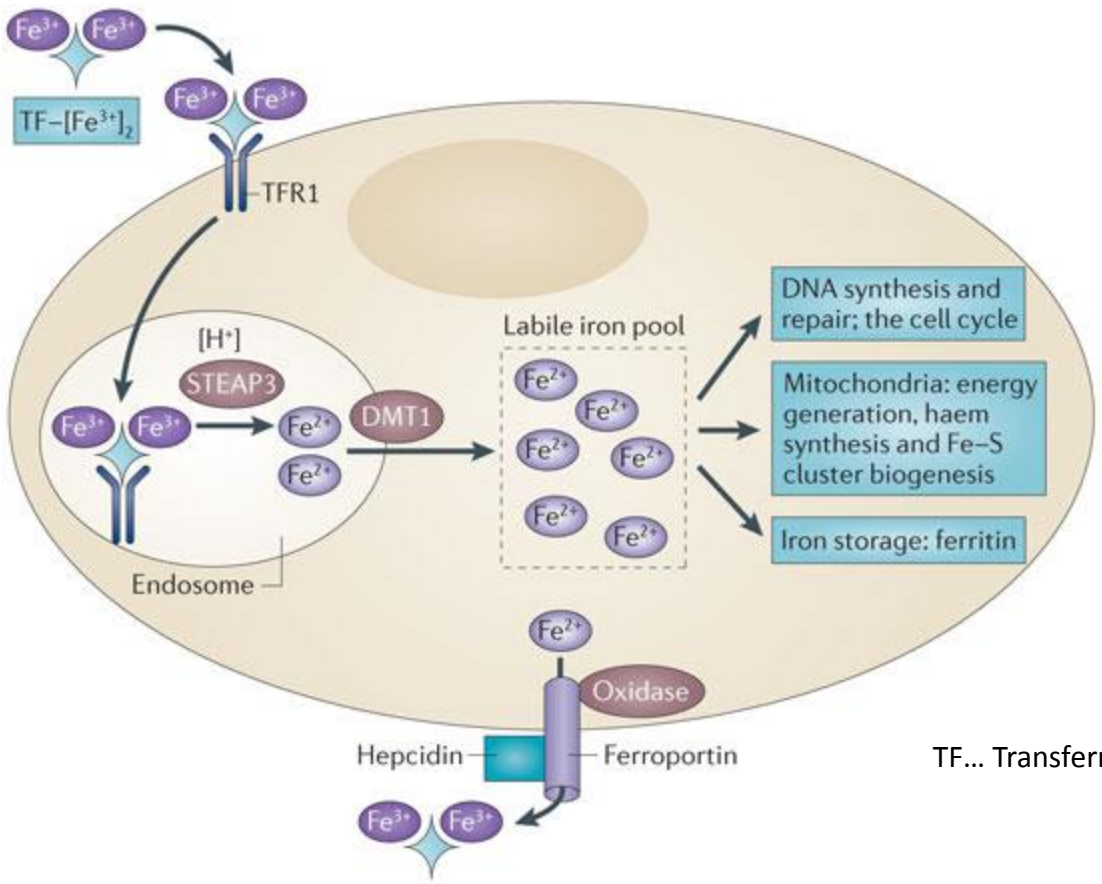
December 24, 2016

Iron and Cancer

Iron enables the function of

- Vital iron and haem-containing enzymes involved in respiratory complexes (mitochondrial enzymes)
- Enzymes involved in DNA synthesis and cell cycle
- detoxifying enzymes such as peroxidase and catalase

➢ **Iron is essential for cell replication, metabolism and growth**



TF… Transferrin

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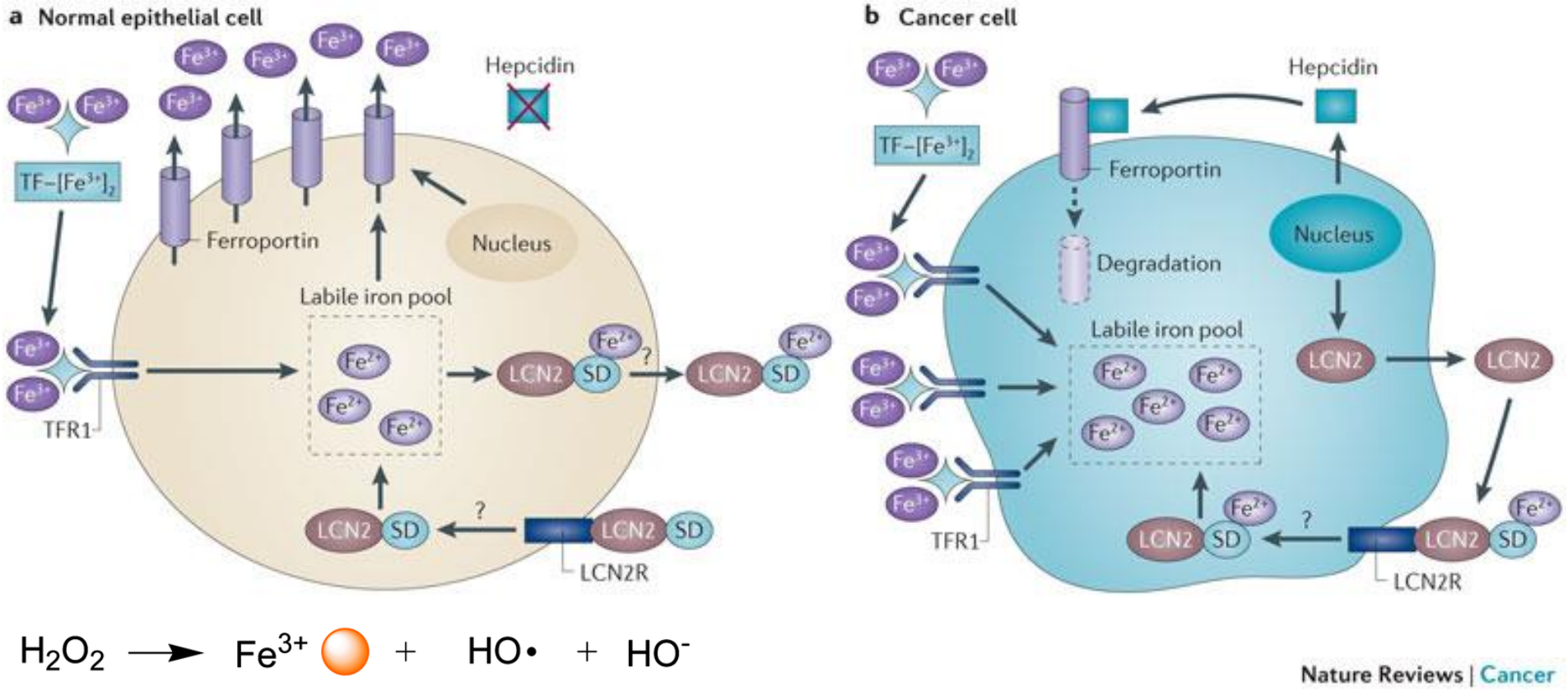
12/24/2016
Nat. Rev. Cancer, **2013**, *13*, 342-355

Iron (Uptake and Efflux) in Normal vs. Cancer Cells



$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO\bullet + HO^-$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HOO\bullet + H^+$$

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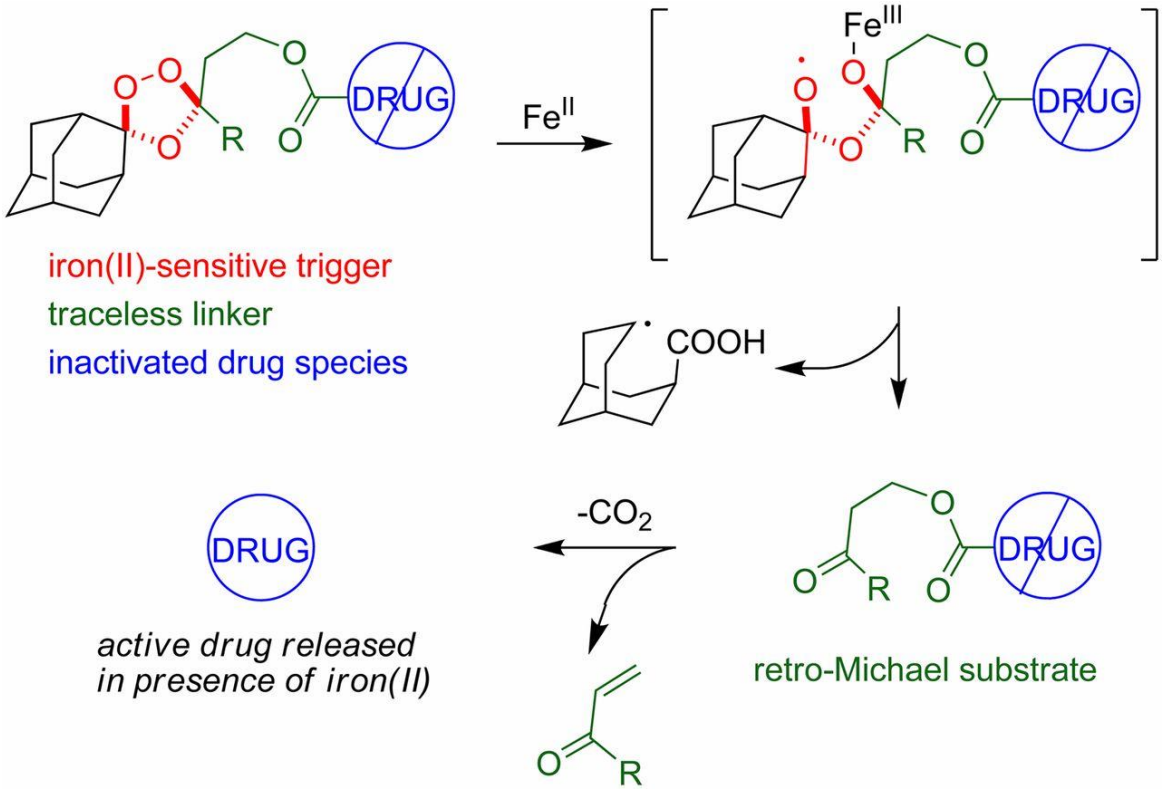
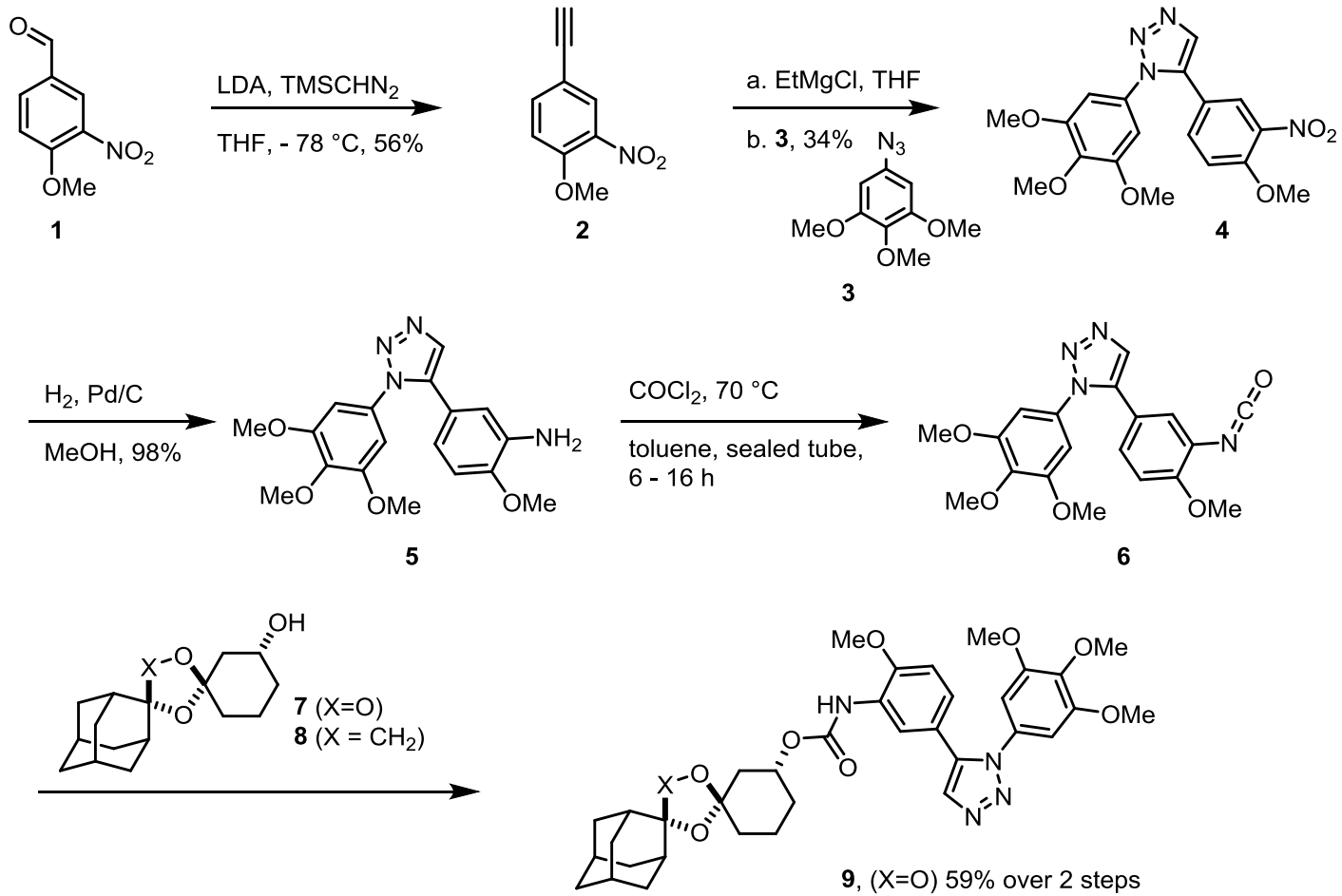
Fe(II)-Dependent Drug Delivery

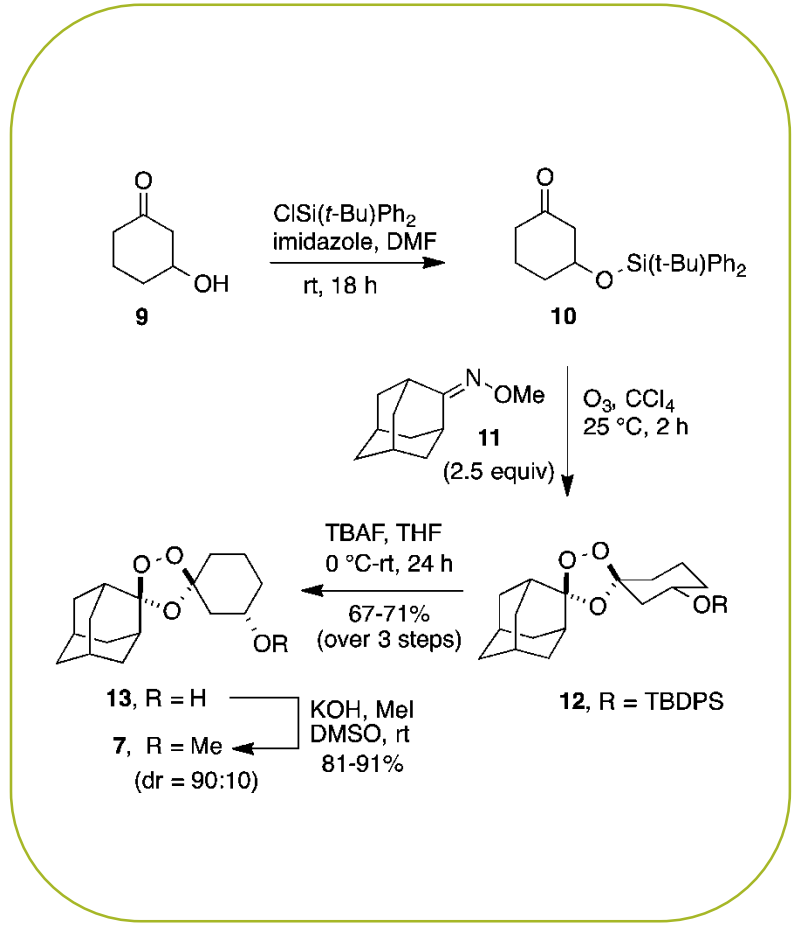


- Labile Fe(II) promotes Fenton chemistry
- Fenton reaction of a peroxidic prodrug coupled to release drug payloads

- Drug species can be conjugated via an amine or alcohol function, potentially allowing the intrinsic bioactivity and/or toxicity of the drug species to be blocked before Fe(II) dependent release at the desired side of action.

Synthesis of Microtubule Inhibitor





Org. Lett. **2014**, *16*, 5776-5779

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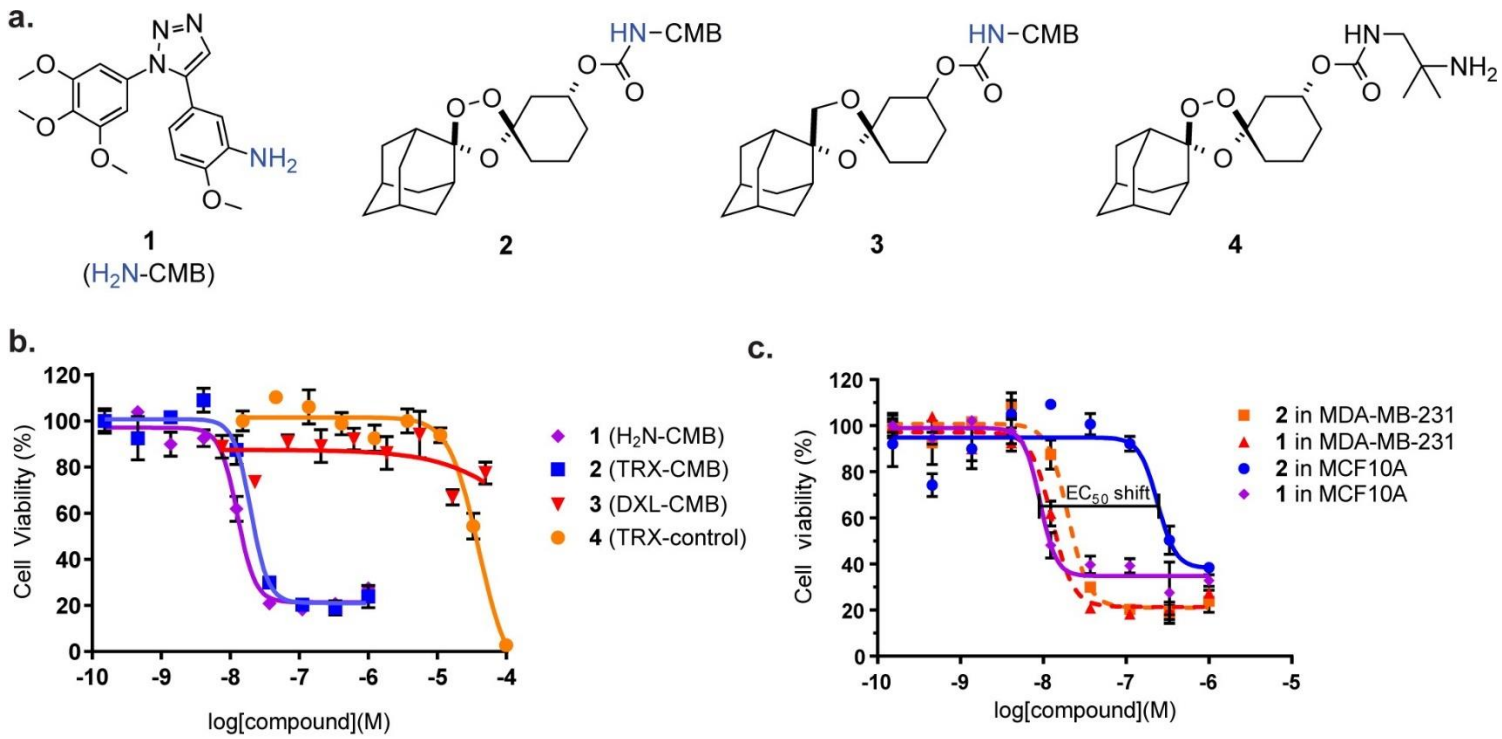
1/22/2017

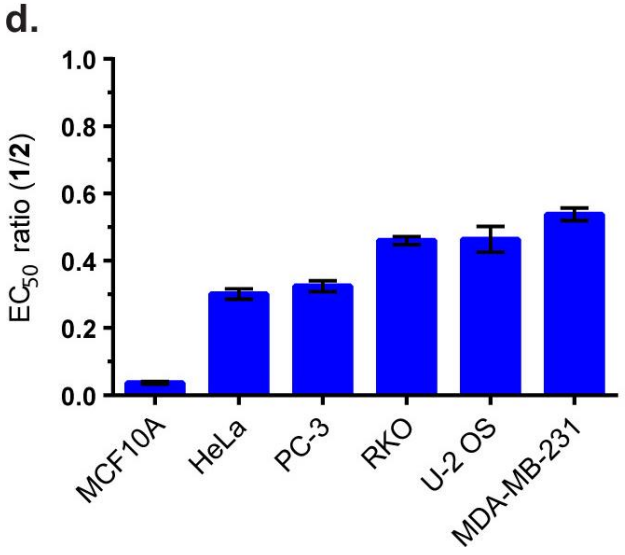
Design, Synthesis and Validation in Cell Culture of a Microtubule Toxin

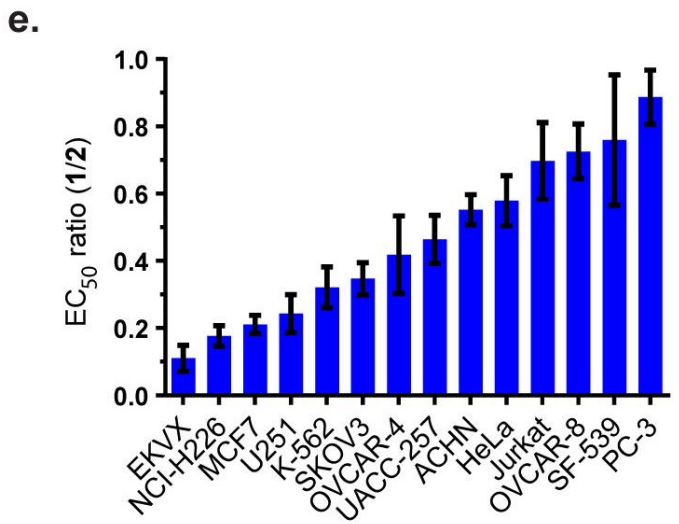


- **Drug release is both efficient and peroxide dependent**

Cytotoxicity in a Panel of Cancer Cell Lines

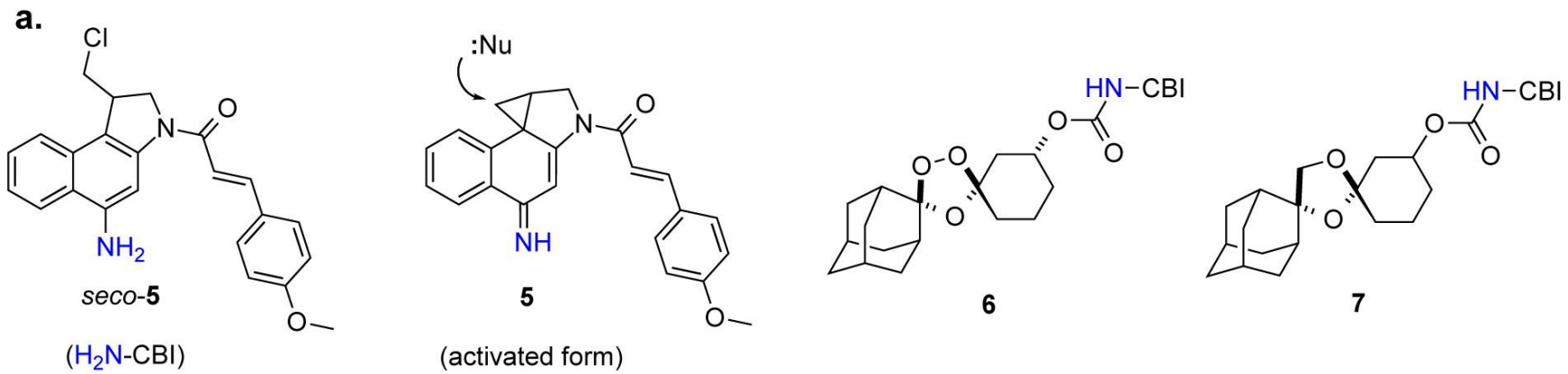
"**E_{50} ratio**" → Normalizing the activity of conjugate 2 to that of its cytotoxic payload 1 to compare efficiency of payload release from 2 across different cell lines



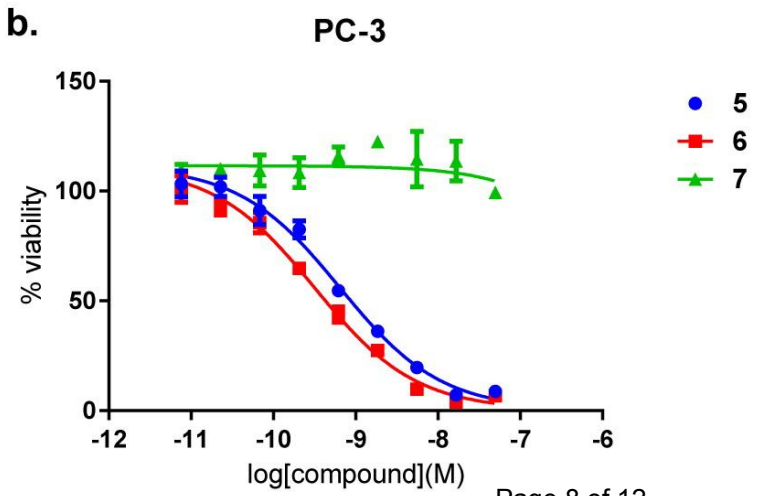


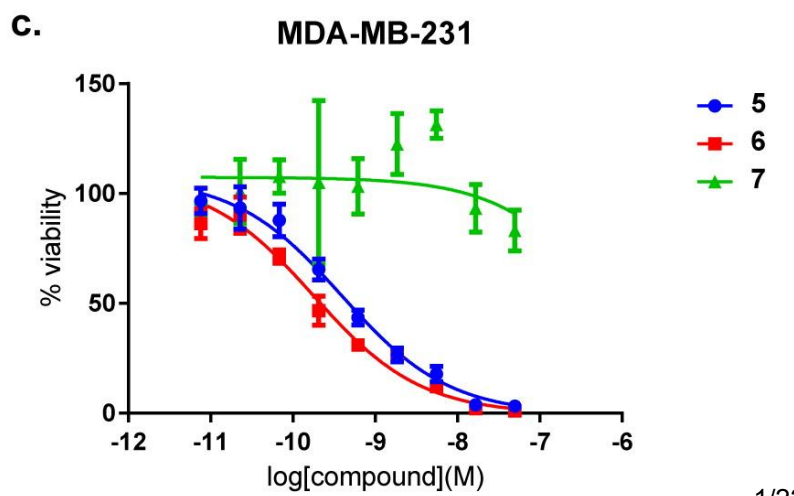
In Vivo PK/PD Studies of Duocarmycin Conjugate

Duocarmycin isolated from Streptomyces bacteria. Known for extreme cytotoxicity. Extremely potent antitumor antibiotics

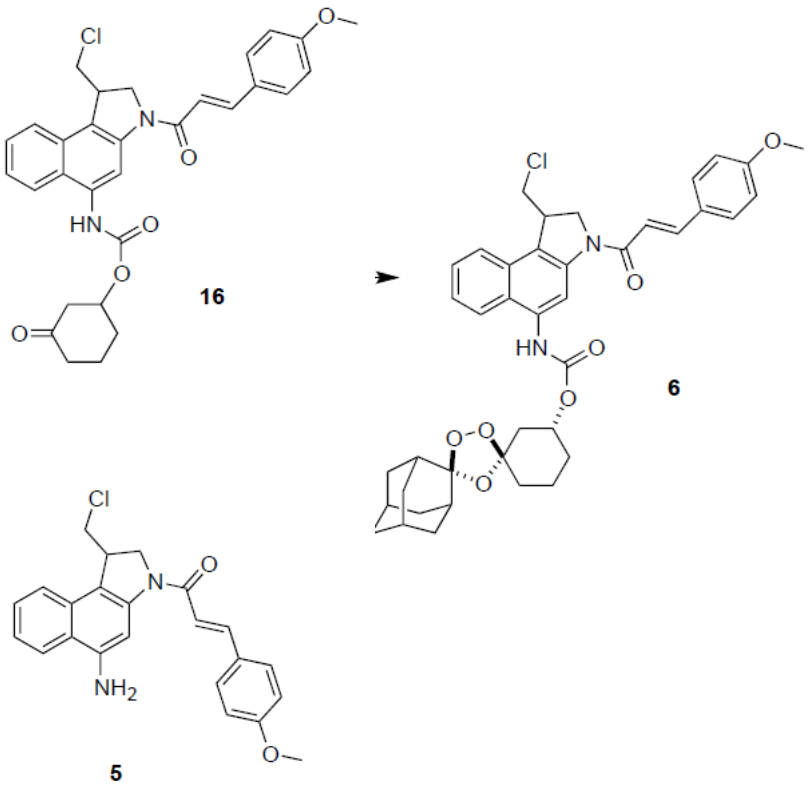


	T1/2 [h]	Clearance [mL min-1 kg-1]	Volume of Distribution [L/kg]
5	3.8	20	6.7
6	20.4	31.3	55

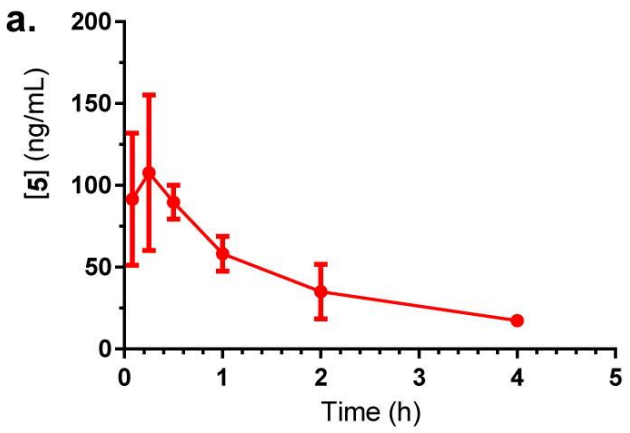


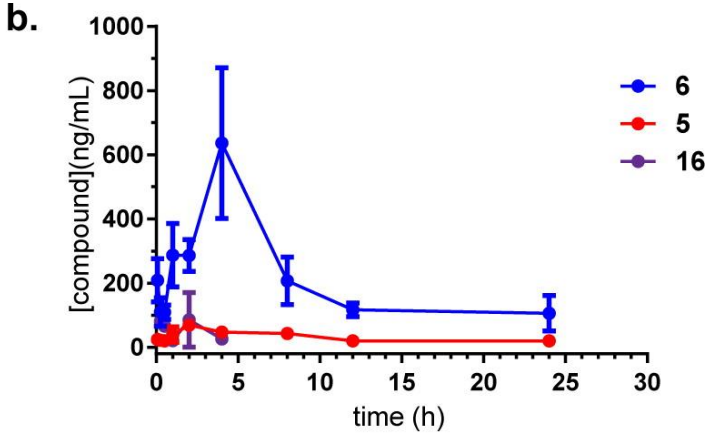


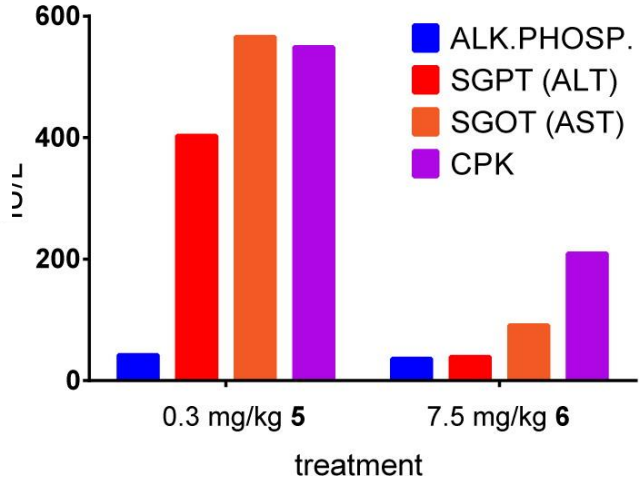
PK Profile and *In Vivo* tolerability

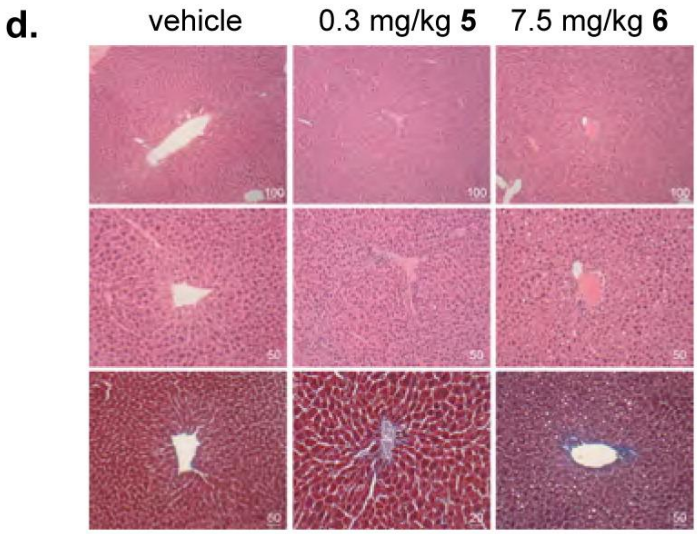


Plasma concentrations







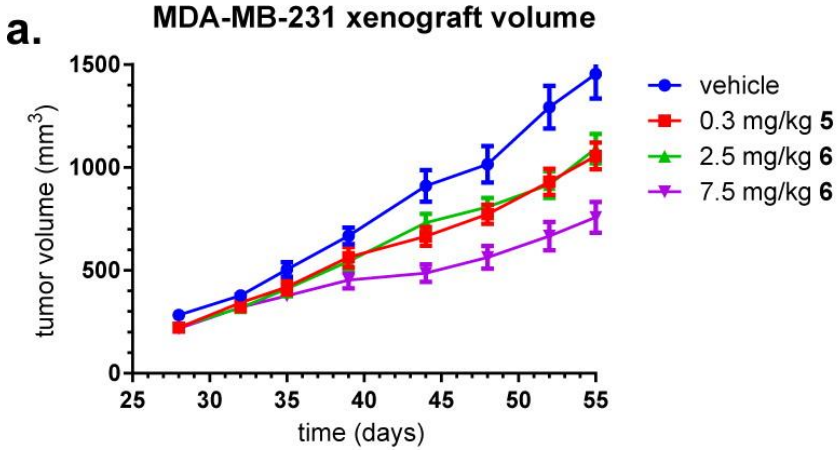


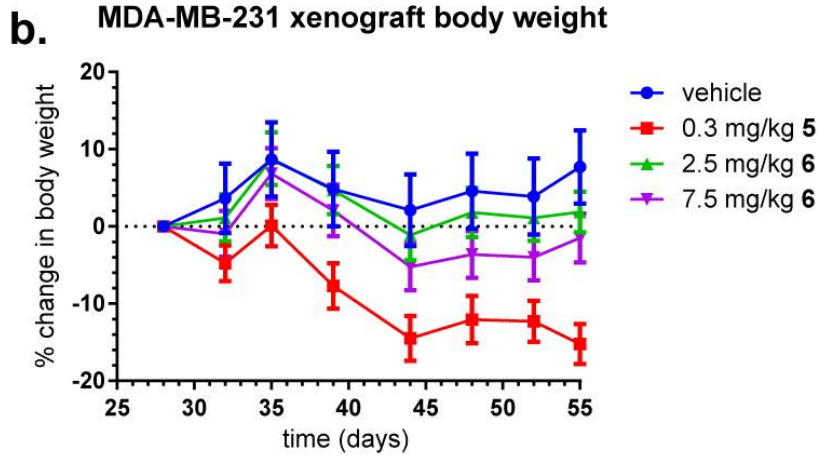
Mouse liver samples

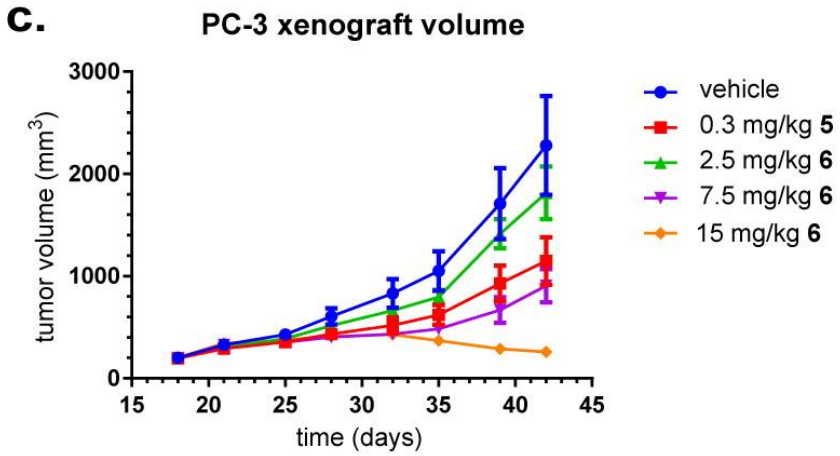
Xenograft Studies

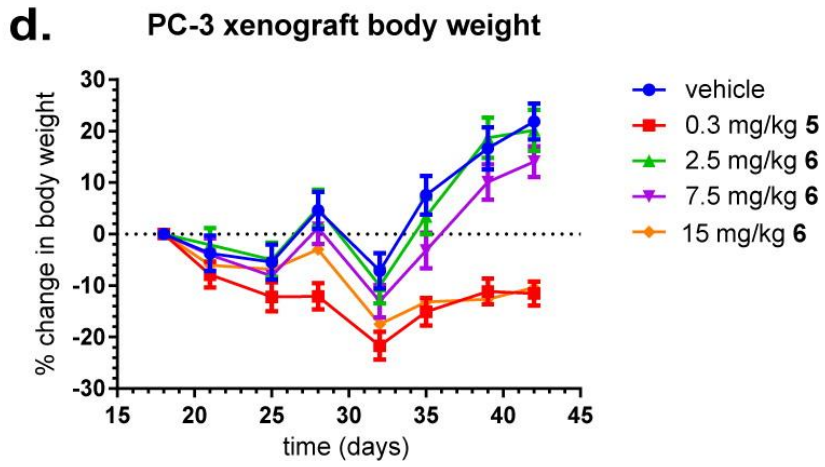
MDA-MB-231 xenograft bearing female SCID-beige mice

IP administration on Q4d schedule(3 total doses)









Conclusion

- Trioxolane-mediated Fe(II)-dependent drug delivery acts as a new approach for cell/tissue selective drug targeting
- Two prototypical trioxolane drug conjugates bearing cytotoxins with distinct mechanisms of cellular toxicity
- Confirmed that intrinsic cytotoxicity of these agents can be decreased in conjugated forms (and yet fully realized following cell or tumor selective release at their intended side of action)

1	15	15	39
H	P	P	Y
Hydrogen	Phosphorus	Phosphorus	Yttrium
1.008	30.974	30.974	88.906

67	3	66	16
Ho	Li	Dy	S
Holmium	Lithium	Dysprosium	Sulfur
164.930	6.941	162.50	32.066