Ferrous Iron Reactive (FIRE) delivery of diagnostic or therapeutic agents

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Abstract #363

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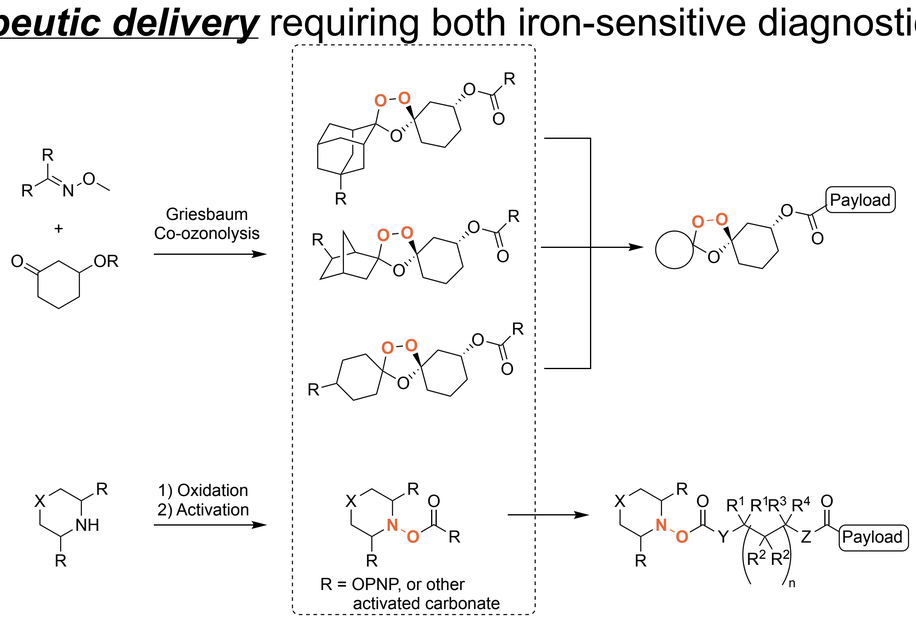
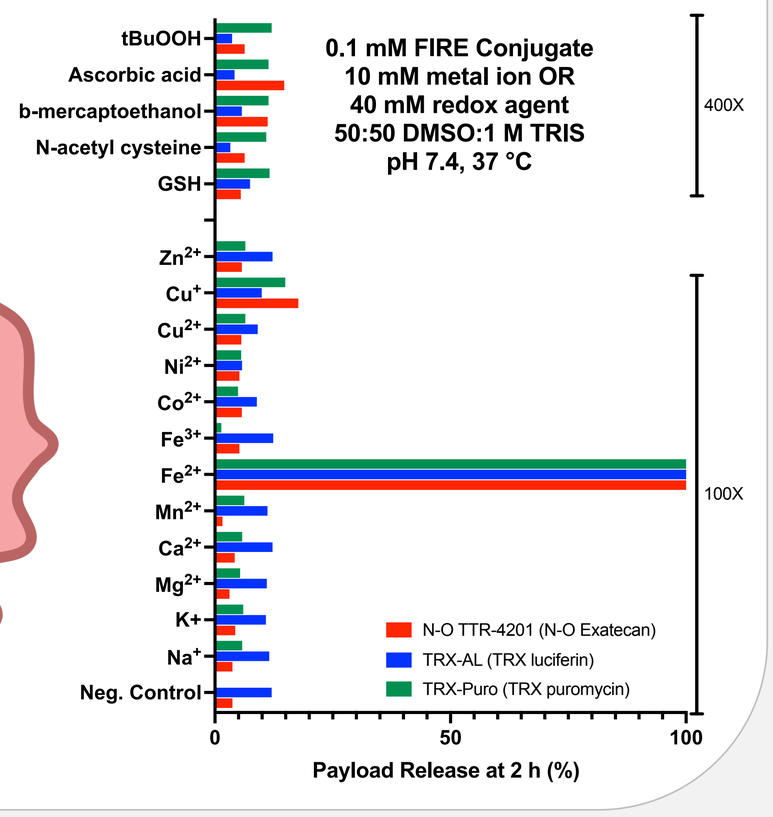
Leveraging intracellular ferrous iron to forge new medicines and tools

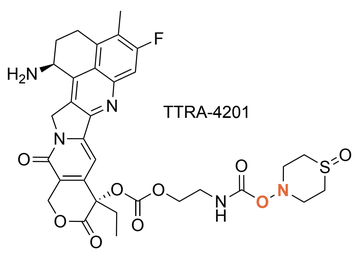
- Elevated levels of ferrous iron is a characteristic of many cancers
- The expansion of the labile iron pool is required to sustain rapid proliferation, leaving many of these cancerous tissues ferro-addicted
- The relatively higher concentration of labile ferrous iron presents an opportunity for ***selective therapeutic delivery*** requiring both iron-sensitive diagnostic tools and drug delivery systems

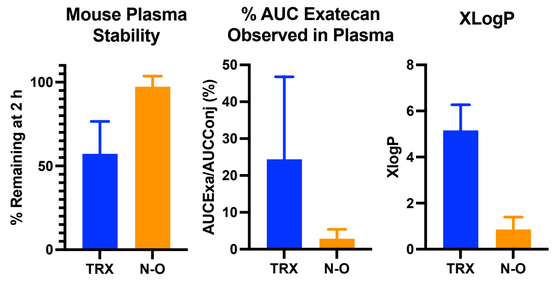


Trioxolane and N-O triggers show clear selectivity for Fe^{2+}



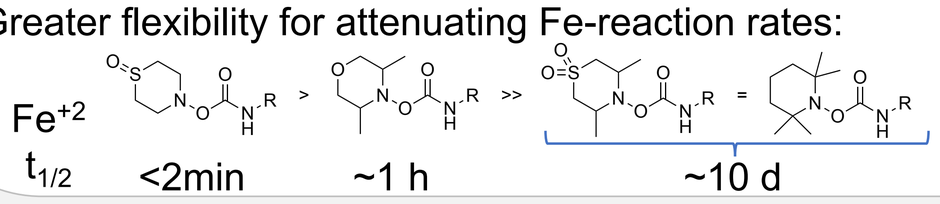
A novel Fe^{2+} reactive trigger group



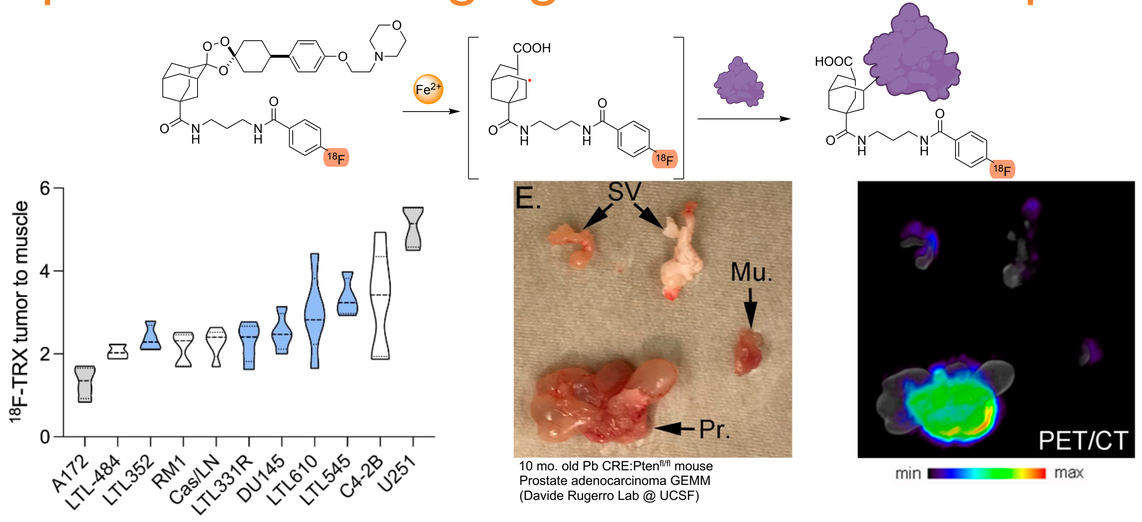


Advantages:

- **40% reduction in MW** compared to analogous TRX triggers
- **Reduced stereochemical complexity** simplifies development
- **Improved physical properties:** increased mouse plasma stability, reduced free circulating exatecan in PK, and improved XLogP
- Greater flexibility for attenuating Fe-reaction rates:



^{18}F-TRX enables oxidation-specific, quantitative imaging of the labile iron pool



Problem:

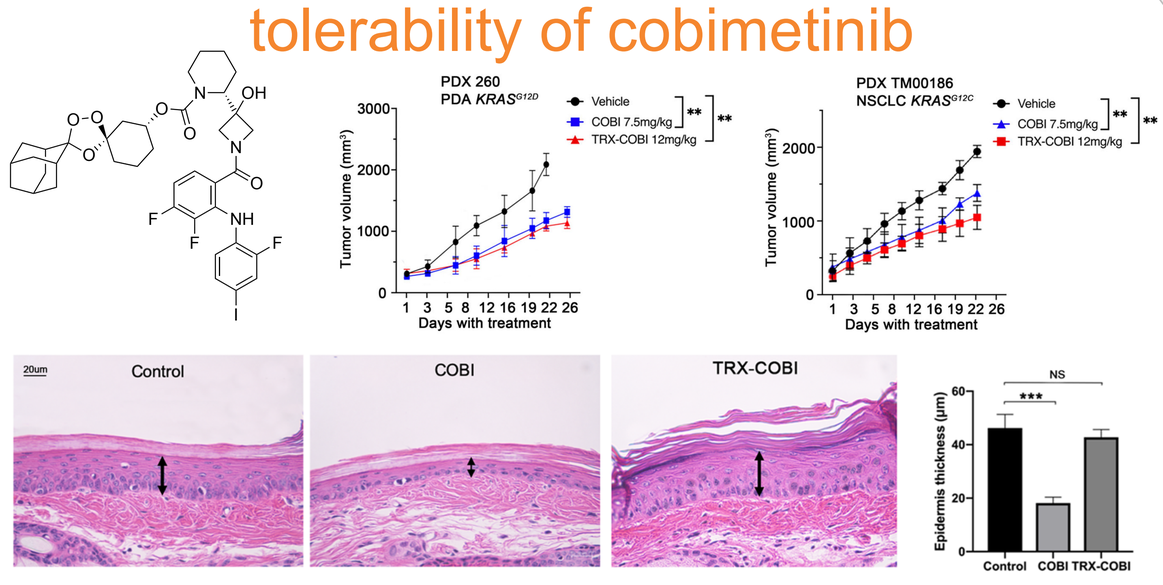
- Existing probes for labile iron pool lack redox specificity, require laborious ex-vivo analysis, or require transgenic animals

Solution:

- ^{18}F incorporated into an iron-reactive TRX conjugate
- Fe^{2+} promoted cleavage generates a reactive, carbon-centered radical on the radiolabeled portion of the molecule
- The radical then rapidly reacts with a biological macromolecule resulting in a covalent sequestration of the PET-emitting fragment
- Biodistribution studies in several xenograft models showed preferential response in tumors that exceeded the response observed in the liver, the major organ for iron storage and regulation

Ref: ACS Cent. Sci. 2019, 5, 727−736

Iron mediated delivery improves tolerability of cobimetinib



Problem:

- Targeting MEK with allosteric inhibitors of MEK1/2 is hampered by dose-limiting toxicities observed in the eye, skin, and gut
  - Tolerated dosing is limited to ~25% of approved dose

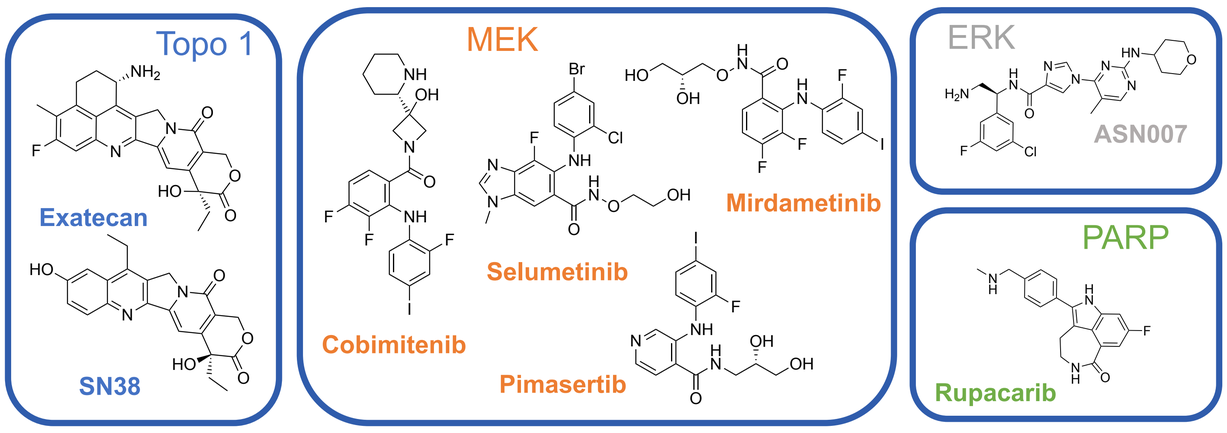
Solution:

When MEKi cobimetinib was conjugated to TRX FIRE platform (TRX-COBI) and dosed in equimolar quantities to unconjugated COBI:

- Equivalent tumor growth inhibition was observed in PDX models
  - Equivalent reduction in phospho-ERK was also observed
- After dosing 20 days, skin samples from mice were analyzed
  - COBI treated animals showed ~50% reduction of epidermal thickness compared to vehicle
  - TRX-COBI treated animals showed minimal epidermal thinning

Ref: J. Exp. Med. 2022 Vol. 219 No. 4 e20210739

The FIRE platform has broad payload compatibility



Visit Abstract 366 for a detailed look at TTR-4201 designed for FIRE delivery of exatecan