ABSTRACT
Site-specific delivery of oncology drugs using nanoparticle technology has been a decades-long goal. IT-141 and IT-147 are polymer micelles that encapsulate a drug (i.e. polymer-drug conjugates without covalent bonds) hydrophobic therapeutic moieties in the core of the micelle. IT-141 incorporates SN-38, the active moiety of irinotecan, in its core with a weight ratio of 2:1. IT-147 shows increased pharmacokinetics in rat plasma, increased maximum tolerated dose (MTD) and improved anti-tumor efficacy in HCT116 and HT-29 xenograft models over irinotecan in all studies. IT-147 contains the polymer micelle drug core and is not thought to be utilized as a prodrug through hydrolysis. The polymer-drug conjugates are unstable at low pH, providing a mechanism for environment-dependent micelle stability and subsequent drug release. Furthermore, these micelles in vivo possess relative activity constants suitable to provide contrast in magnetic resonance imaging (MRI). The magnetic relaxation value (T2) was 1.6 x 10^-6 m/s² and the spin-lattice relaxation value (T1) were 50-80 ms⁻¹. Small molecular complexes of iron not typically provide sufficient MRI contrast. Because contrast is not observed with individual iron complexes, and the MRI contrast is directly related to the properties of the iron-stabilized nanoparticle, only nanoparticle conjugates provide contrast in MRI. When these iron-stabilized micelles were administered to tumor bearing xenograft mice, increased contrast in the tumor is observed, peaking between 24 and 48 hours. MRI was performed with IT-141 in HCT116, HT-29, and A549 subcutaneous tumor models. IT-141 contrast imaging was performed in HCT116 and HCT116/RH444 subcutaneous and MCF-7 orthotopic tumor models. Our technology has produced stable micelles that encapsulate therapeutic moieties in include SN-38, daunorubicin, epirubicin, Doxorubicin, paclitaxel, docetaxel, and ametoprin with improved pharmacokinetics, decreased toxicity and increased efficacy. The MRI imaging results hold potential for use in the clinic where delivery of the chemotherapeutic-loaded nanoparticle can be monitored non-invasively.

RESULTS
- IT-141 and IT-147 increase pharmacokinetics and improve anti-tumor efficacy over respective free drugs.
- IT-141 encapsulates SN-38, the active metabolite of irinotecan, non-covalently. IT-141 increases plasma pharmacokinetics of SN-38 over SN-218 from irinotecan and improves anti-tumor efficacy in HCT116 xenograft model.
- IT-141 encapsulates SN-38, the active metabolite of irinotecan, non-covalently. IT-141 increases pharmacokinetics and improves anti-tumor efficacy over free drug in HCT116 xenograft model.

CONCLUSIONS
- IT-141 encapsulates SN-38, the active metabolite of irinotecan, non-covalently. IT-141 increases plasma pharmacokinetics of SN-38 over SN-218 from irinotecan and improves anti-tumor efficacy in HCT116 xenograft model.
- IT-147 encapsulates SN-38, the active metabolite of irinotecan, non-covalently. IT-147 increases pharmacokinetics and improves anti-tumor efficacy over free drug in HCT116 xenograft model.
- Iron-stabilized polymer micelles encapsulate hydrophobic cancer therapeutics non-covalently.
- Iron-stabilized polymer micelles show significantly improved anti-tumor efficacy over free drug.
- Iron-stabilized polymer micelles hold potential as imaging biomarker.

MRI imaging holds potential for use in the clinic by non-invasive monitoring of the nanoparticles and potential predictor of response.

HYPOTHESIS
Hypothesis: Iron containing core of micelles (-15 nm) is comparable in size with iron oxide nanoparticles. Relativity values for iron-stabilized micelles are similar to iron oxide nanoparticles. We believe that the size of the iron containing cores imparts superparamagnetic properties.

Transaxial view of contrast signal from IT-141 in HCT116 subcutaneous tumor over time.

Coronal contrast signal from IT-141 in HCT116 subcutaneous tumor over time.

Histograms represent median contrast per ROI predose and at 24 hours in HCT116, HT-29, and A549 tumors.

Coronal images compare predose signal from IT-147 to contrast signal in tumor at 48 hours.

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IT-141 and IT-147, iron-stabilized micellar nanoparticles for therapeutic and diagnostic applications