SER-201, a novel polyoxazoline conjugate of irinotecan with improved efficacy in five mouse xenograft models

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ABSTRACT SUMMARY
Polyoxazoline (POZ) polymers with side chain pendants were prepared and the oncology drug, irinotecan, was attached to each pendant. SER-201 has a 20kDa POZ polymer backbone with an average of ten irinotecan molecules. Female athymic mice (Ncr:Nu) were implanted with human cancer tumor fragments of HT-29 (colorectal), NCI-H460 (non small cell lung), MDA-MB231 (breast) and A2780 and IGROV-1 (ovarian). Irinotecan and SER-201 were intravenously dosed to the mice q4d x 3, at doses of 40, 60 and 90mg/kg and the tumor size was measured twice a week for 40 to 60 days following the first dose. Results of these measurements show that SER-201 has significant tumor growth inhibition and regression when compared to irinotecan. These observations were consistent with all the tumor models tested.

INTRODUCTION
Polyethylene glycol, polyglutamic acid and hydroxypropyl methylacrylate are polymers that have been successfully tested as drug delivery vehicles of small molecule oncolytics. We have developed another class of polymers called polyoxazoline (POZ) with different molecular architectures. These patented polymers are of high quality and have side chain pendants for the attachment of small molecular weight drugs, as shown in the cartoon below:

In this presentation we introduce POZ as a drug delivery vehicle that can successfully deliver irinotecan, a topoisomerase I inhibitor used to treat colorectal and other solid tumors. We show that SER-201 has superior efficacy and safety profiles when compared to irinotecan alone.

EXPERIMENTAL METHODS
Polyoxazoline polymers with a molecular weight of 20kDa and an average of ten pendant side chains were prepared and purified by proprietary methods. Irinotecan was coupled to a small molecule ester linker and then attached to each pendant arm by ‘click chemistry’. The resulting molecule, SER-201, was tested for solubility, purity, and drug loading. Tumor fragments (30-40mg) of HT-29, NCI-H460, A2780 and IGROV-1 cell lines were implanted subcutaneously in the right flank of female athymic Ncr:Nu mice. In the case of the MDA-MB231 study, 2x10⁷ cells were inoculated in the right flank. All the tumors were allowed to grow to an average tumor weight of 150mg. The treatment groups received 40, 60 or 90 mg/kg of irinotecan or equivalent doses of SER-201. Each treatment group (n=10) received a total of three intravenous doses administered every fourth day (q4dx3). Vehicle controls were dosed according to the same schedule. Animals were weighed and tumor volumes measured twice weekly following the first drug administration. Animals exhibiting poor condition due to tumor progression were euthanized accordingly. Anti-tumor activity was measured as changes in tumor weight, tumor growth inhibition, tumor regression and duration of regression. Tolerability was measured as body weight loss and deaths due to drug toxicity. All study protocols were reviewed and approved by an in-house institutional animal care and use committee.

RESULTS AND DISCUSSION
SER-201 was >99% pure, and soluble in water and 5% dextrose solution. The drug loading was confirmed by Reverse Phase chromatography to be 17% by weight. Gel filtration chromatography and MALDI confirmed the molecular weight of the polymer and H¹-NMR confirmed the number of ‘click’ pendants on the molecule.

Significant anti-tumor activity was observed in the SER-201 treated groups when compared to the irinotecan groups.

The figures below show that SER-201 inhibited tumor growth in all five tumor models when compared to controls. The inhibition was in a dose dependent manner. Tumor growth inhibition due to irinotecan did not reach statistical significance and was not dose dependent.
Tumor growth delay (T-C value) was significantly longer for SER-201 compared with irinotecan in all the xenograft models and especially with the HT-29, MDA-MB231 and IGROV-1 tumors (p<0.001). In the case of the NCI H460 and A2780 tumors, significant differences were observed at the higher dose of 90 mg/kg. Cisplatin had no effect in the A2780 xenograft model.

In the HT-29 xenograft study, SER-201 at doses of 60 and 90 mg/kg resulted in complete tumor regressions in some of the animals, while none were observed with irinotecan at any dose level. In the MDA MB231 study, SER-201 had complete tumor regressions in 7 out of 10 animals and at all doses tested.

All doses of SER-201 and irinotecan were well tolerated with no significant loss in body weight. No deaths due to drug toxicity occurred with either compound.

CONCLUSION
SER-201 is a viable polymer-drug compound for the treatment of solid tumors.

REFERENCES