The targeted cytotoxic prodrug, AQ4N, persists in the spleen, large intestine, and subcutaneous tumors.

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Background

- AQ4N (b/anxantrone) is a prodrug of a potent topoisomerase II inhibitor, AQ4.
- Systemic toxicity of AQ4N is minimized due to lack of systemic bioreduction to AQ4.
- AQ4N selectively accumulates in tumors, lymphoid tissues, GI tract and pancreas, where it is bioreduced to AQ4.
- Toxicology studies in mice, rats, and monkeys indicated systemic bioreduction to AQ4.
- AQ4N is being studied in human Phase I studies in the US and Europe.

Methodology

- ~40 male CB17 SCID mice irradiated per study
- After 2 days, 10^6 BXPC-3 (pancreatic cancer) cells were injected subcutaneously (SC) in right flank
- Tumors grew to 160 ± 59 mm^3 prior to dosing
- Single IV injection of 14C-AQ4N at 20 mg/kg (120 Ci/kg)
- After 2 days, 10^6 BXPC-3 (pancreatic cancer) cells were injected subcutaneously (SC) in right flank
- Mice were sacrificed at time points (3 mice/time) up to 14 days post dose.
- Control mice plasma with spiked 14C-AQ4N used to generate standard curve for assessing radioactivity in tissue extracts.
- Two studies:
  1) AQ4N 14C labeled in the benzene ring
  2) AQ4N 14C labeled on the methyl groups of the tertiary amine.

Summary

- High levels of AQ4N radioactivity are observed initially in the plasma, kidney, liver, lungs, and large intestine 2 weeks after a single dose.
- AQ4N radioactivity persists at high levels in the spleen and plasma after single dose.
- Consistent high exposure was observed in spleen, large intestine, liver and kidney.
- Tumors had 5-10 fold higher exposure than plasma after single dose.
- A study assessing the metabolites of AQ4N (no 14C) is underway using LC/MS/MS analysis of all tissues.

![AQ4N in Tissues at 336 hrs](image1)

![AQ4N Cmax in Tissues](image2)

![AQ4N Exposure Profile](image3)

![AQ4N Tissue Kinetics](image4)