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

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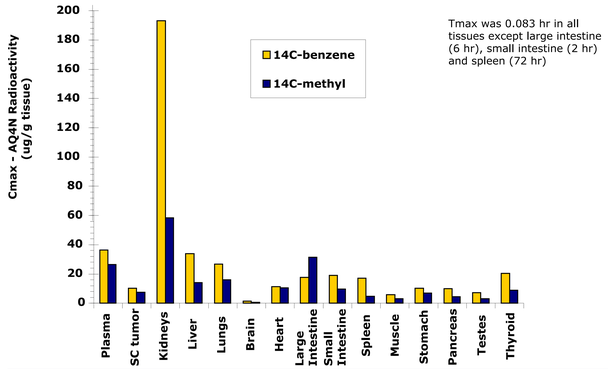
## Background

- AQ4N (banoxantrone) 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 lymphoid atrophy, lymphopenia, urthelial degeneration and tubular neuropathy in the kidney
- AQ4N is being studied in human Phase I studies in the US and Europe

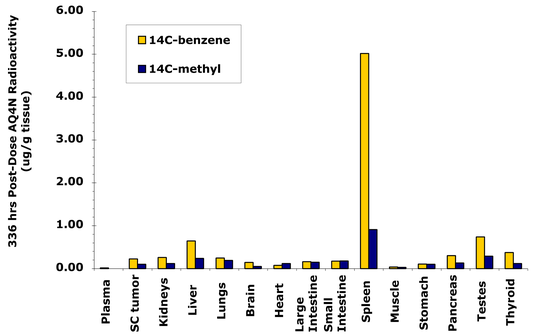
## Methodology

- ~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 $^{14}$C-AQ4N at 20 mg/kg (120 µCi/kg)
- Mice were sacrificed at time points (3 mice/time) up to 14 days post dose.
- Control mice plasma with spiked $^{14}$C-AQ4N used to generate a standard curve for assessing radioactivity in tissue extracts and plasma.
- Two studies:
  1) AQ4N $^{14}$C labeled in the benzene ring
  2) AQ4N $^{14}$C labeled on the methyl groups of the tertiary amine.

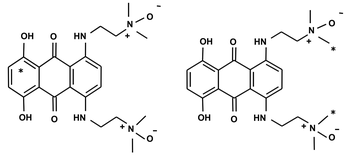
## AQ4N Cmax in Tissues




## AQ4N in Tissues at 336 hrs




## AQ4N Exposure Profile



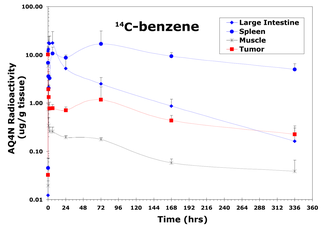
| Tissue | $^{14}$C-benzene Exposure (µg/mL(or g)•hr) | $^{14}$C-methyl Exposure (µg/mL(or g)•hr) |
|---|---|---|
| Plasma | 14.1 | 14.0 |
| SC Tumor | 142.0 | 79.0 |
| Spleen | 1592.0 | 986.0 |
| Large Intestine | 652.8 | 813.0 |
| Liver | 2089.0 | 530.0 |
| Kidney | 632.5 | 249.0 |
| Brain | 82.8 | 68.0 |
| Pancreas | 268.9 | 133.0 |
| Small Intestine | 375.6 | 431 |
| Stomach | 76.3 | 65 |
| Lungs | 549.0 | 274 |
| Heart | 65.4 | 104 |
| Testes | 145.0 | 102 |
| Thyroid | 115.0 | 65 |

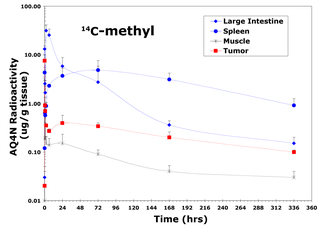
- Tumor exposure 5-10 fold plasma exposure
- Consistent high exposure in spleen and large intestine, suggesting intact AQ4(N) species present

**Terminal Half-Life in Selected Tissues**

| Tissue | $^{14}$C-benzene $t_{1/2\beta}$ (hr) | $^{14}$C-methyl $t_{1/2\beta}$ (hr) |
|---|---|---|
| SC Tumor | 777.6 | 162.4 |
| Spleen | 1581.7 | 366.4 |
| Large Intestine | 63.0 | 133.0 |

## AQ4N Tissue Kinetics




## Summary

- High levels of AQ4N radioactivity are observed initially in the plasma, kidney, liver, lungs, and large intestine
- AQ4N radioactivity persists at high levels in the spleen 2 weeks after a single dose
- Consistent high total 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 $^{14}$C) is underway using LC/MS/MS analysis of all tissues

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