Appendix A: Sample Research Abstract

Characterization of a liposomal copper(II)-quercetin formulation suitable for parenteral use

Kent TJ Chen[1,2*], Malathi Anantha[1], Ada WY Leung[1,3,4], Jayesh A Kulkarni[5,6], Gardenia GC Militao[1,7], Mohamed Wehbe[1,8], Brent Sutherland[1], Pieter R Cullis[6], Marcel B Bally[1,3,4,8]

[1]Department of Experimental Therapeutics, BC Cancer Research, Vancouver, British Columbia, Canada
[2]Department of Interdisciplinary Oncology, BC Cancer Research, Vancouver, British Columbia, Canada
[3]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[4]Cuprous Pharmaceuticals, Vancouver, British Columbia, Canada
[5]Department of Medical Genetics, BC Children's Hospital Research Institute, University of British Columbia, Vancouver, British Columbia, Canada
[6]Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, British Columbia, Canada
[7]Federal University of Pernambuco, Recife, PE, CEP:50.670-901, Brazil
[8]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada
*kchen@bccrc.ca

BACKGROUND
Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a naturally derived flavonoid that is commonly found in fruits and vegetables. There is mounting evidence to suggest that quercetin has potential anticancer effects and appears to interact synergistically when used in combination with approved chemotherapeutic agents such as irinotecan and cisplatin. Unfortunately, quercetin has shown limited clinical utility, partly due to low bioavailability related to its poor aqueous solutions (< 10 μg/mL).

METHODS
In this study, liposomal formulations of quercetin were developed by exploiting quercetin's ability to bind copper. Quercetin powder was added directly to pre-formed copper-containing liposomes (2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and cholesterol (CHOL) (55:45 M ratio)). As a function of time and temperature, the formation of copper-quercetin was measured.

RESULTS
Using this methodology, a final quercetin-to-lipid (mol:mol) ratio of 0.2 was achievable and solutions containing quercetin at concentrations of > 5 mg/mL were attained, representing at least a > 100-fold increase in apparent solubility. The resulting formulation was suitable for intravenous dosing with no overt toxicities when administered at doses of 50 mg/kg in mice. Pharmacokinetic studies demonstrated that the copper-quercetin formulations had an AUC0-24H of 8382.1 μg h/mL when administered to mice at 50 mg/kg.

CONCLUSIONS
These studies suggested that quercetin (not copper-quercetin) dissociates from the liposomes after administration. The resulting formulation is suitable for further development and also serves as a proof-of-concept for formulating other flavonoids and flavonoid-like compounds. Given that quercetin exhibits an IC50 of >10 μM when tested against cancer cell lines, we believe that the utility of this novel quercetin formulation for cancer indications will ultimately be as a component of a combination product.