Poster1:

SkQ1 treatment in a mouse model of ovarian cancer prevents early- and late- stage skeletal muscle weakness while modulating skeletal muscle calcium release.

Luca J. Delfinis[1], Shahrzad Khajehzadehshoushtar[1], Luke D. Flewwelling[1], Nathaniel J. Andrews[1], Madison C. Garibotti[1], Shivam Gandhi[1], Aditya N. Brahmbhatt[1], Brooke A. Morris[1], Bianca Garlisi[2], Sylvia Lauks[2], Caroline Aitken[2], Arthur J. Cheng[1], Jim Petrik[2] and Christopher G.R. Perry[1]†.

Affiliations
[1]School of Kinesiology & Health Science, Muscle Health Research Centre, York University, Toronto, ON, Canada
[2]Department of Biomedical Sciences, University of Guelph, Guelph, ON, Canada

Muscle weakness and wasting are defining features of ovarian cancer-induced cachexia, a disease that currently has no treatment. How ovarian cancer induces myopathy remains incompletely understood partly because of limited preclinical models that do not sufficiently recapitulate the disease in women. As skeletal muscle mitochondrial stress occurs in ovarian cancer, we determined the ability of a mitochondrial-targeted enhancer drug SkQ1 to prevent weakness and atrophy in a novel mouse model of this condition. C57BL/6J female mice were injected with $1x10^6$ epithelial ovarian cancer (EOC) cells underneath the ovarian bursa, generating a metastatic model of ovarian cancer. Mice received the mitochondrial-enhancing drug SkQ1 in their drinking-water (EOC-SkQ1) or standard drinking-water (EOC-Vehicle) while cancer developed for ~40 (Early-Stage; no apparent metastasis) and ~80 (Late-Stage; robust metastasis) days. Control mice were age matched, injected with saline and provided standard drinking-water. SkQ1 had heterogenous effects on complex I-stimulated mitochondrial H_2O_2 emission (mH_2O_2). In the tibialis anterior (TA), mH_2O_2 was increased in Late-Stage EOC-Vehicle mice vs control but decreased in EOC-SkQ1 mice vs EOC-Vehicle. Interestingly, in the diaphragm, mH_2O_2 was increased at Late-Stage in both EOC groups vs control, however, EOC-SkQ1 mH_2O_2 was further increased vs EOC-Vehicle. TA weakness and atrophy occurred in Early-Stage EOC-Vehicle vs control. SkQ1 partially preserved force production at Early-Stage in TA and diaphragm, and at Late-Stage in diaphragm, but did not prevent atrophy in either muscle. High-force muscle weakness linked to lower calcium release in Flexor Digitorum Brevis in EOC-Vehicle vs control was completely prevented by SkQ1 at Late-Stage. SkQ1 did not affect primary tumour size. A mitochondrial-targeted pharmaceutical improves force production independent of atrophy in mice with ovarian cancer. Thus, mitochondrial-targeted therapies warrant further research in cancer cachexia.

Lab website: Perry lab website