"Mitochondrial Dysfunction in Cancer"

Interim Report - June 2015

Overall Objectives: To determine whether differences in mitochondrial mass vary as a function of breast cancer sub-type and whether mitochondrial mass can be used to stratify patients for treatment and predict patient outcome. Secondly, to identify and validate drugs that modulate mitochondrial mass in tumor cells as a means to better treating specific sub-types of breast cancer.

Specific Aims

Aim 1: To determine how mitochondrial mass in primary human breast cancers correlates with tumor grade and clinical outcome.

Aim 2: To validate small molecule inhibitors of mitophagy in human breast cancer cells and in relevant mouse models that can be used to specifically kill breast cancer cells.

Results

Progress on Aim 1: We have successfully mined the tumor bank at the UChicago HTRC for patient breast cancer specimens and stained sections for both TOM20 (a mitochondrial marker) and Ki67 (a proliferative marker) and shown that interestingly, ER-negative breast cancers show significantly elevated mitochondrial mass compared to ER-positive breast cancers. We are currently assessing whether there are significant differences in mitochondrial mass in HER2+ tumors compared to other sub-types and if triple negative breast cancers shows significant differences in mitochondrial mass compared to ER-positive or HER2+ breast cancers. This work is still on-going and depends upon access to pathologist time for analysis of a statistically powered cohort of specimens of each sub-type but is moving consistently forward.

Progress in Aim 2: We carried out a high throughput screen for drugs that modulate mitochondrial mass and identified 16 drugs that increased mitochondrial mass in tumor cells and 4 drugs that decreased mitochondrial mass. In further analyses in which we performed a dose-response curve, we were able to narrow down our interest to 4 drugs that increase mitochondrial mass and 2 drugs that reduce mitochondrial mass (in a dose-dependent manner. In subsequent studies, we confirmed by other approaches (immunofluorescence for mitochondria and flow cytometry for Mitotracker) that both 2 of these lead compounds perform as predicted from the high throughput screen to alter mitochondrial mass. On-going work is examining the effect of these 2 drugs on a panel of breast cancer cell lines, as originally proposed.

In summary, the work continues as originally proposed and it is envisaged that work will be completed within the next 12 months.

Outcomes thus far: Publication of two peer-reviewed papers related to this work has been completed (Chourasia et al, Cancer & Metabolism, 2015; Chourasia et al, EMBO Rep. 2015).

Significantly, we are currently applying for the NCI Provocative Question initiative RO1funding using data obtained with Fletcher Scholar Award support that if successful should allow us to continue this project into the future. The timing of this initiative is fortuitous since a Provocative Question on "Mitochondria and Cancer" has not been issued previously.