**FINAL PROJECT REPORT**

***Date: 31st January 2013***

***Name:***

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***Project Title:***

Chemotherapy response in an obese mouse model with colorectal cancer

**Please copy the "Specific Objective(s)" statement, entered on your application form, in the space below.**

**Aim 1:** Compare tumours grown in normal weight and obese mice. (month 1-8)

Specific objective 1.1: Determine tumour growth rate of tumours in normal weight and obese mice

Specific objective 1.2: Analyse mouse plasma for obesity-related factors by ELISA

Specific objective 1.3: Analyse tumours for obesity-related factors by IHC and Western blotting

**Aim 2:** Compare response to chemotherapy of tumours grown in normal weight and obese mice. (month 3-12)

*Specific objective 2.1:* Determine maximum tolerated dose of 5-FU, oxaliplatin and irinotecan in obese tumour-bearing mice

*Specific objective 2.2:* Determine tumour cell response by FACS analysis and clonogenic assays 24h after in vivo dosing with 5-FU, oxaliplatin and irinotecan

*Specific objective 2.3:* Determine tumour growth delay following in vivo dosing

**Briefly describe how successful you were in achieving the stated objective(s). If the objective(s) was not achieved, explain why that is the case and describe what you did manage to achieve.**

**Aim 1:**

*Specific objective 1.1:* Achieved, but it took much longer to achieve a difference in mouse weight between normal and Western Style diet-fed mice (1 week in literature vs 6 months in our study).

BALB/c mice were fed either a 'Western style' diet or normal mouse chow following weaning. Animals were weighed weekly until 6 months of age, and their food consumption was monitored over a two week period. Both groups were implanted subcutaneously with $10^6$ cells from the mouse CT26 colorectal cancer cell line. Growth of tumours was monitored using daily calliper measurements. Animals were sacrificed when tumours reached maximum size, blood was taken, and organs and tumours excised for analysis.

Mice on Western style diet increased in weight faster, and at a more variable rate, than mice on normal diet, with no significant difference in final body weight. Mice on Western diet consumed less (69% by weight) than those on normal diet. Organ weights (heart, kidney, lung, liver) were similar between the two groups, but gonadal fat pads weighed notably more in the Western diet group. Gonadal fat weight increased with mouse weight and rate of mouse growth. All tumours reached maximum size within three weeks of implantation, with tumours in the Western diet group growing at a more variable rate than tumours in the normal diet group. There was no difference in final tumour weight between the groups.

Data was presented at the New Zealand Society of Oncology Meeting, 11-12th May 2011, in Auckland (Developing an obese mouse model of colorectal cancer, Dachs, Gabi, Dyer, Arron, Bothwell, Jennifer, Gunningham, Sarah, Currie, Margaret, Willis, Jinny, Robinson, Bridget).

*Specific objective 1.2:* Partially achieved; plasma from mice fed Western diet and normal diet was analysed using a protein array, and still requires further analysis.

*Specific objective 1.3:* Ongoing; tumours and organs have been collected and fixed or frozen, but not yet analysed due to disruptions from earthquakes, lack of laboratory access and recent move back to original building.

**Aim 2:**
*Specific objective 2.1:* Achieved; mice were treated with different doses of 5-FU, and no difference in drug tolerance was observed between mice on Western diet and those on normal diet.
*Specific objective 2.2:* Ongoing; due to lack of laboratory access post-earthquake, tumours from treated animals were collected and frozen, instead of analysed by FACS and clonogenic assays, and molecular analysis of tissues is still ongoing.
*Specific objective 2.3:* Not achieved due to lack of laboratory access post-earthquake and length of time required to achieve *1.1*; molecular analysis from *2.2* will be used as end-point instead.

**Briefly describe any interesting outcomes which might not have been considered in your original objectives (if any).**

We observed a range of responses in mice fed on Western diet; some mice remained slim, some had similar growth rates to mice on normal diet, and some became obese. Preliminary protein array data of plasma from these animals indicated substantial differences in the levels of obesity-related factors which were more pronounced than differences between the groups of mice on normal vs. Western diet. These findings will be further investigated to determine what effect they may have on tumour biology.

**Please note:**
This is not the final report as we have a time-only extension until June 2013. A final, updated report will be sent at that time.
The earthquakes since September 2010 have severely disrupted our study. Our main building and its laboratories was closed for almost two years, and temporary accommodation had to be found, and frequently changed and often closed at short notice. Although we have recently been able to move back into our main building (end January 2013), our animal facilities are still located at Lincoln, making studies challenging.