Project Title: How exercise prevents obesity-related hepatocellular carcinoma: insights for chemoprevention of liver cancer
Grant Awarded: $200,000 over 2 years: $100,000 in 2016-17
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Fatty liver disease associated with obesity and diabetes, i.e. not due to alcohol, is common and contributes to a rapidly increasing rate of liver cancer (hepatocellular carcinoma or HCC) in Australia. In mice genetically predisposed to obesity, diabetes and fatty liver, the response to a single low dose of liver carcinogen early in life is accelerated onset of liver cancer at 6 months, rather than 9-12 months usual for lean male mice. The ultimate goal of this research is to identify the protective mechanisms so they can be harnessed in the form of drugs that lower the risk of liver cancer in overweight or diabetic persons.

During the first 3 months of 2017, we completed preliminary work using mice provided with an in-cage exercise wheel: this prevented early-onset liver cancer. This research is in the advanced stage of writing a manuscript to be submitted to a leading liver journal very soon.

The present research will clarify how exercise prevents liver cancer. To test whether JNK1 (a molecular signalling pathway) implicated in fostering persistent growth of altered liver cells is “switched off” by exercise, we have started breeding mice deficient in JNK1 protein with our fat (Alms1 mutant, foz/foz) mice. We have found that such Jnk1-/-. foz/foz mice do not develop the severe forms of fatty liver disease, non-alcoholic steatohepatitis or NASH. We anticipate that onset of liver cancer after carcinogen (diethylnitrosamine, DEN) injection at day 12 of life will be slow – 9-12 months despite equivalent obesity as ordinary foz/foz mice. The cross-breeding program to generate these mice is arduous and slow, but we anticipate having mice to conduct experiments come available over the next 3-4 months.

Meanwhile we have signed a material transfer agreement (MTA) with the Celgene company (San Diego) and received an adequate supply of the most selective and safe inhibitor of JNK1 yet developed (CC-003). We will soon administer CC-003 to DEN-injected foz/foz mice in an attempt to prevent early onset of liver cancer.