Application Summary

Application ID:	APP1162998	**Application Year:**	2018
Grant Type:	Project	**Grant Duration:**	1 years
Round:	2018_Project Grant_funding_commencing_2019		
Application Title:	ATF4-mediated control of life/death decisions in melanoma resistance		

Administering Institution:	Centenary Institute of Cancer Medicine and Cell Biology

Participating Institutions:	**Department**
Centenary Institute of Cancer Medicine and Cell Biology	Origins of Cancer Program

Research Team:

CI Role	CI Title & Name	Institution	Will CI be based in Australia?	Is this CI claiming a Career Disruption?
CIA	Doctor Yi Fang Guan	Centenary Institute of Cancer Medicine and Cell Biology	Yes	No

Associate Investigators:

Name
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Guide to Peer-Review Areas:	Cancer Biology, Molecular Biology, Biochemistry
Broad Research Area:	Basic Science
Field of Research:	BIOCHEMISTRY AND CELL BIOLOGY - Cell Metabolism
Research Keywords/Phrases:	cancer cell biology, metabolism, melanoma, amino acid transport, transcriptional regulation.

Synopsis:

Cancer cells use a variety of methods to adapt to cellular stresses imposed by their environment. One such mechanism is via Activating Transcription Factor 4 (ATF4), which is rapidly translated in response to cellular stresses including hypoxia, endoplasmic reticulum (ER) stress and nutrient deprivation. These pathways are known to be important in melanoma, which has the highest rate of ATF4 mutation of all cancer (cBioPortal data). ATF4 transcription initially attempts to repair the damage caused by the stress, which may include initiating increased amino acid and other solute transporters to restore nutrient levels, or autophagy induction to degrade unfolded proteins. However, under prolonged or severe stress insults, ATF4 transcribes genes encoding pro-apoptotic proteins (eg CHOP), ultimately resulting in apoptosis. Currently, it is unclear how ATF4 mediates these opposing transcriptional responses. There are no data on the quantitative and qualitative differences of signals derived from ER or nutrient stress, and whether they alter (1) ATF4 protein levels, (2) where ATF4 binds to DNA (chromatin immunoprecipitation and sequencing; ChIP-seq), (3) which proteins bind to ATF4 (rapid immunoprecipitation of endogenous proteins; RIME), or (4) the transcriptional outcome of ATF4 binding (mRNA-seq). Our preliminary data show that each stress results in different ATF4 protein levels, differential DNA binding sites and transcriptional output. We also have data showing novel binding partners of ATF4 using mass spectrometry (RIME). In this study, not only will we provide a complete profile of ATF4 expression and action under ER and nutrient stress, but we will test combinations of inhibitors and activators of ATF4 pathway components for their therapeutic potential and enabling rapid translation of our findings to the clinic.

Plain English Summary:

Cancer cells have the ability to switch on their adaptive response to survive and invade. One such adaptive response is mediated by a factor called ATF4 in response to stress or nutrient deprivation. This project will focus on understanding the differential responses of ATF4 to each stress type, balancing the decision between “survival” and apoptosis (cell death). We foresee that these studies will lead to the development of new therapeutic strategies that can combat drug resistance in m