

Project Title: Chromosome condensation and the regulation of cell development

Grant Awarded: \$50,000

Principal Investigator: Dr Aude Fahrer, Research School of Biology, The Australian National University

I would like to thank the Cancer Council ACT for supporting the research in my laboratory during the past year.

This research stems from our discovery of the "nessy" mutant mouse, which has a defect in a chromosome condensing protein. Surprisingly, we found that this defect leads to defective development of T cells: immune cells important for fighting infection and cancer. This is an important finding, linking the fields of chromosome structure and immunology.

Several key aspects of this project have direct relevance to cancer.

- Cancer arises due to the failure of the immune system to recognise cancer cells as foreign. This project studies the development of T cells.
- Cancer arises due to defective cell division. This project studies a complex critical for cell division; lack of this complex results in errors in chromosome separation. Chromosome errors, resulting from defective replication, are a common feature of many types of cancer.
- Condensins also have important roles in epigenetic regulation. Epigenetic (reversible) changes to DNA have now been shown to be important in the vast majority of cancers.
- Condensin II has recently been implicated in several cancers:
 - reduced levels have been associated with breast cancer;
 - increased levels have been associated with a favourable outcome in prostate cancer;
 - defects have been found in cases of pyrothorax associated lymphoma; and
 - condensin II binds to Rb protein. Rb is a key tumour suppressor gene; mutations in Rb are found in many types of cancers.

Cancer Council ACT funding has been instrumental in allowing us to pursue this research over the last 12 months. The work is carried out by exceptional research students whom I supervise at The Australian National University. Thus, as well as advancing the science, the funding allows research students to complete their research training. In the past twelve months, this grant has supported the research of two excellent B.Sc. (Hons) students; Ms Aleksandra Trajkovska (graduated with first class honours 2010) and Ms. Christina Salmon, who is currently completing her honours thesis. It has also supported the work of an outstanding Ph.D. student Mr. Laurence Wilson.

We have had a successful year, with advances on several fronts:

- We have identified alterations in the levels of important signalling molecules in mutant T cells.
- We are currently trying to confirm novel interactions between condensin and two proteins involved in cell division.
- We have submitted a publication describing twelve "splice" forms of our gene. (with acknowledgement to Cancer Council ACT in the manuscript). Splicing allows a single gene to be turned into several different forms of a protein, each with partly differing sequence. One of the forms we discovered is extremely unusual.
- Based on this work, we have searched the human genome for examples of other genes which can undergo similar splicing. We have identified over two thousand new protein forms, including many derived from cancer-associated genes. This important discovery will provide the basis for our next publication.

The work we have been carrying out aims to understand fundamental biology. This sort of basic research is extremely important as it will eventually lead to improved cancer treatments. Thanks to previous grants provided to my laboratory by Cancer Council ACT, I have been privileged to meet many of your volunteers. Doing so spurred me to look at other avenues of research, which could be of more immediate benefit to cancer patients.

This has led me to develop a new hypothesis for an immune-based cancer therapy which I have also published this year: "A proposal for a simple and inexpensive therapeutic cancer vaccine". Fahrer AM.

Immunol Cell Biol. 2011. We have recently started animal trials of this therapy. I hope it will feature in a future Cancer Council ACT report!

Thank you Cancer Council ACT for supporting my research!