Project Title: Mechanisms and targets of protein synthesis dysregulation in cancer
Grant Awarded: $600,000 over 3 years: $200,000 in 2019-20
Principal Investigators: Prof Thomas Preiss, John Curtin School of Medical Research, The Australian National University.

Final report
Work on this project commenced in early 2017 as a collaboration primarily between the Canberra-based Preiss and Hannan groups, with involvement of the Melbourne-based co-investigators as required. Our Cancer Council ACT funded work concluded with the end of 2019. Thus far, two publications (see below) have directly arisen from this project.

The dysregulation of messenger RNA (mRNA) translation into protein by ribosomes, caused by altering the activity of eukaryotic translation initiation factors (eIFs), can mediate oncogenic transformation. Based on this, eIFs are considered promising clinical anti-cancer drug targets. However, it is poorly understood what mRNAs are dysregulated, how this is controlled, and importantly, exactly which of these processes are critical for the development of cancer.

This project has provided the groundwork to explore the mechanisms by which eIFs drive oncogenesis, which mRNAs are critical in terms of their dysregulation, and how translation inhibitors might serve as prototypical anti-cancer drugs. Key to this was an adaptation of our Translation Complex Profile sequencing (TCP-seq) method from yeast to mammalian cells. TCP-seq is the only high throughput sequencing-based method that can directly assess the initiation phase of mRNA translation. We have been able to record multiple datasets in triplicate from human cell lines, as well as mouse Eμ-Myc 4242 lymphoma cells. These included treatments with inhibitors targeting different translation initiation stages (cap attachment, scanning, start codon recognition). These inhibitors are also candidate anti-cancer drugs, and differential resistance of translation to these compounds revealed in our data allowed us to identify subsets of initiation pathways important for malignancy. Already, we have been able to complete a major study revealing new aspects of the initiation mechanism and the roles of cancer-related eIFs within it. The resulting paper has just been accepted by the leading journal Molecular Cell. Several of the TCP-seq datasets are currently being bioinformatically analysed and interpreted. This, and the preparation of at least one more manuscript with a direct cancer-therapy focus, will be completed in the coming twelve months, funded by other internal sources.

Publications:
Shirokikh, N. E. & Preiss, T. Translation initiation by cap-dependent ribosome recruitment: Recent insights and open questions. **WIREs RNA** 30, e1473 (2018). *An in-depth review of the translation initiation mechanism, the process we are targeting to better understand/treat cancer.*

Wagner S*, Herrmannová A, Hronová V, Sen N, Ingolia NT, Hinnebusch AG, Shirokikh NE, Preiss T*, Valášek LS*. Selective Translation Complex Profiling Reveals Staged Initiation and Co-translational Assembly of Initiation Factor Complexes. **Mol Cell**, accepted 01/06/20 * Co-corresponding authors.