

CBC Reviews.

Profs. McNerney (U of C) and Feng (NU).

Determining the role of CUX1 in genome architecture

The PIs are well established researchers in their respective areas, and the work represents an excellent collaboration with complementary expertise.

The goal of the work is to study the roles of HOX-family transcription factor CUX1 in DNA folding and tumor suppression. Several lines of evidence support the hypothesis that CUX1 functions in the formation and maintenance of DNA looping.

In aim 1 three different human AML cell lines will be established with inducible degron tagged CUX1 genes as CUX1 is a haploinsufficient tumor suppressor. CUX1 protein will be knocked down to different extents and CUX1 genomic binding sites will be correlated with nascent RNA transcription.

In aim 2 a time course Hi-C study will be performed on the three modified cell lines following different extents of CUX1 protein knockdown. The expectation is that there will not be large effects on TAD domains, but instead there will be a decrease in enhancer-promoter looping. Particular attention will be given to genes involved in hematopoietic differentiation.

The studies will then be extended to hematopoietic stem cells.

The experiments are well designed and address interesting questions.

My main concern is that the work is a logical progression from the 2017 NAR paper published by the McNerney group. In that paper siRNA was used to knockdown CUX1. In the present work that will be replaced with acute depletion using an inducible degron. RNAseq will be replaced with nascent RNAseq. A significant advance will be the correlation of CUX1 depletion with temporal changes of Hi-C patterns. Given the expertise of the groups, the past paper and the initial preliminary results, this might already be appropriate for national funding.