Research profile for applicants

Name of DKFZ research division/group:	***Regulatory Genomics and Cancer Evolution (B270)***
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RESEARCH PROFILE AND PROJECT TOPICS

The Odom laboratory is dedicated to answering ambitious and interdisciplinary questions bridging genetics, genome regulation, cancer biology, and evolution. One focus of my laboratory has been the extensive and rapid turn-over of tissue-specific transcription factor binding, CTCF insulator elements, polymerase occupancies, and enhancer activities among mammalian species – as well as the mechanisms underlying this. Another focus is the molecular and transcriptional mechanisms underpinning mammalian ageing, by exploiting the power of single-cell transcriptomics. Most recently, we have used chemical carcinogenesis to study the earliest steps of tumour genome evolution and clonal expansion, as well as the conservation of these mechanisms across mammalian space.

This project will disentangle the genetic and hormonal determinants of sex differences shaping tissue function and cancer development, using liver as a model. We will analyse the homeostatic differences in single-cell transcription and chromatin within pre-adolescent P15 mouse liver between XX and XY genotype mice, which have always had a second sex chromosome, versus XmO mice, which have never had one. In addition the Xenium spatial biology system will be deployed to dissect tissue architectural differences between genotypes. To fully distinguish sex chromosome from hormone-driven effects, we will exploit the four core genotype model where the Sry has been deleted from chromosome Y and inserted into chromosome 3, producing males and females of both genotypes, XX and XY.

We will also deploy knockout mouse models where sex chromosomes are either directly evicted or are over-silenced by inducing Xist via a transgene in liver hepatocytes. This aspect of the project will be undertaken in collaboration with Edith Heard and James Turner at the Crick Institute. To evaluate the in vivo function of specific X- and Y-linked genes in mature tissues, we will use single-gene knockout mice, as well as an epigenetic modulation system within hepatocyte-derived organoids ex vivo to enable the silencing of X- and Y-linked genes.

in combination. Comparison of these knockout strategies will reveal which X- and Y-linked genes are required acutely versus chronically, and reveal functional vulnerabilities caused by their loss in mature tissues.

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