The Centre for Blood Research Seminar Series

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THE CENTRE FOR BLOOD RESEARCH

Wednesday, October 24, 2018

LSC 3 | 12:00 - 1:00PM

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"CRISPR for Gene Therapy and Novel Mouse Models"

Gene therapy is undergoing a successful revival for disorders with unmet therapeutic needs, with seven therapies having received approval by the FDA or EU. Increasing this excitement is CRISPR, a genome-editing approach to directly correct disease-causing mutations. Aniridia is a rare syndrome; best known for iris hypoplasia visible in the child's eyes at birth. However, aniridia is actually a panocular disorder in which patients are born with poor vision that typically progresses to complete vision loss by adulthood. Aniridia is caused by mutations in the gene paired box 6 (PAX6), and currently, there is no cure or successful long-term l treatment.

We are exploring the possibility of treating aniridia with a gene-editing therapy directed at correcting the causative Pax6 mutation. Typically for gene therapy development, the first step is to "cure" a mouse. To support this effort we have generating a novel mouse model of aniridia in which we used CRISPR to add a FLAG tag to the 5' end of a Pax6 gene, which already carried the Sey (small eye) mutation. We initiated ex-vivo correction of the Pax6 mutation in mouse embryonic stem cells. Excitingly, our best guide RNA and single stranded donor corrected the Pax6 mutation in 29% ± 7% (SEM) of the cells. More recently, we have successfully used this CRISPR strategy to correct the Pax6 mutation in vivo in zygotes of "aniridic" mice, repairing the germline mutation and restoring vision in the mouse model of aniridia. Finally, we have coined the term CHuMMMs (CRISPR humanized-minimally mouse models), to describe a new kind of mouse model we are making in which the CRISPR therapy binds human DNA in the mouse genome.

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