

Presenting Author Name

Joanna Joe

Phonetic spelling of your (full) name

jo-ann-uh jo

Presenting Author Category

Masters Student

Supervisor Name

Geoffrey Hicks

GBD Audio File

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Headshot

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Short Bio (100 words)

I am a third year Masters student in Biochemistry and Medical Genetics in the lab of Dr. Geoff Hicks. Through my research I have developed an interest in CRISPR- based gene editing and therapies, double stranded break repair and translational research. When I'm not in the lab, I enjoy travelling, hiking and spending time with my little siblings and dog (preferably on a beach).

Research Category

Basic Science

Abstract Title

Atm restoration prevents cancer and neurological outcome of A-T

Authors

Name	Role	Profession
Joanna Joe	Presenting Author	Graduate
Molly Pind		
Alicia Chan		
Paul Mathews		Full Professor
Geoffrey G Hicks		Full Professor

Background

Ataxia Telangiectasia (AT) is a pediatric autosomal recessive neurodegenerative disorder caused by a deficiency in the AT Mutated (ATM) protein. AT is marked by progressive motor dysfunction, immune deficiency, and cancer predisposition. We have developed a novel Atm-deficient mouse model with a clinically relevant nonsense mutation in the Atm gene, and notably, the first model to exhibit the ataxia

phenotype. Using this model, we tested novel small molecule read-through (SMRT) compounds, which restore low levels of Atm production and offer therapeutic benefits. However, before clinical trials, the direct mechanism of Atm restoration behind the therapeutic effect needs to be confirmed.

Objective

In this pre-clinical study, we aim to show that restoring even low levels of Atm production in vivo will improve outcomes associated with Atm deficiency.

Methods

To test this hypothesis, we will generate an inducible murine expression model of AT. The model is created by adding an estrogen receptor 2 ligand-binding domain (ERT2-LBD) upstream of the Atm gene such that Atm translocation into the nucleus is tamoxifen-inducible. The mouse genome is edited using an Easi-CRISPR strategy with ssDNA as a template. Successful integration will be validated using H2AX phosphorylation as an indicator of an active Atm signalling pathway.

Results

The first set of mice were born in April and PCR analysis using allele-specific primers shows integration of the ERT2-LBD at the 5' end in at least three mice. Samples are being sequenced for confirmation. A second round of mice were born in September and long read sequencing will be used to verify integration.

Conclusion

This model will help determine whether restoration of even low levels of Atm protein directly has therapeutic effects on cancer and immune deficiency phenotypes. Our collaborators will also study the effects of Atm restoration on ataxia. This is the final pre-clinical step before SMRT compounds can enter clinical trials.