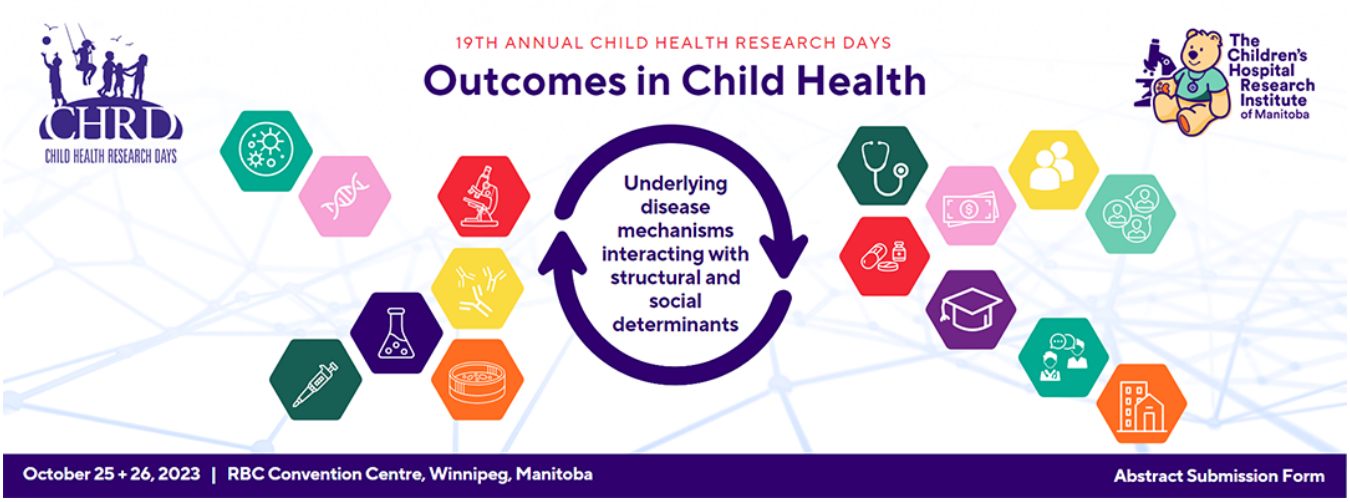

CHRD 2023: Abstract Submission Form

Submitter Name
Júlia Amanda Cerato

Presenter Name
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Presenter Status
PhD Student

Research Category
Basic Science

Role in the project
Design
Perform Experiments
Analyze Data
Write Abstract

Title
Dabrafenib impairs respiratory syncytial virus infection of respiratory epithelial cell

Background
Respiratory syncytial virus (RSV) is the leading cause of hospitalization due to pediatric viral respiratory tract infection, responsible for 200,000 infant deaths worldwide. There are no effective antiviral therapy or clinically approved RSV vaccines for infants. Therefore, understanding RSV-host interaction is crucial for developing new therapies. RSV infection induces airway epithelial cell and alveolar macrophage necroptosis, enhancing disease pathogenesis. We have demonstrated that the pharmacological inhibition of necroptosis proteins impairs RSV replication in vitro. Dabrafenib has been shown to selectively inhibit receptor-interacting protein kinase 3 (RIPK3), a central necroptosis protein, and ameliorated tissue injury in different disease models

Objective
Thus, we will assess dabrafenib drug repurposing to treat RSV infection in vitro.

Methods
MTT assay was used to evaluate cell viability after drug treatments in non-infected A549 cells. A549 cells were infected with RSV-GFP (24h, 0.5 MOI) and treated with dabrafenib (75 μM), immediately before, 24h before, or 24h after infection. To understand the autophagy role, A549 cells were treated with bafilomycin or 3MA for 1h prior infection. Infection rate and fluorescence intensity were quantified by immunofluorescence.

Results
To analyze the effect of dabrafenib on A549 cell viability, we tested increasing concentration (25, 50, 75, 100 μM) for different time points (24, 48, and 72 h). Dabrafenib did not alter A549 cell viability throughout 72h at all concentrations tested. We also tested cell viability effects of bafilomycin (10 nM) and 3MA (10 mM) for 24h. None of the drugs presented cytotoxic effects on A549 cells. Importantly, the pre-, post-, and concomitant dabrafenib treatments significantly decreased RSV infection rate ($p<0.001$) and fluorescence intensity ($p<0.001$). Moreover, autophagy inhibitors decreased RSV infection rate ($p<0.0001$) and fluorescence intensity ($p<0.001$).

Conclusion
Dabrafenib treatment significantly impairs RSV replication in vitro, suggesting that RIPK3 is necessary for viral replication. Furthermore, autophagy is also required for RSV replication.

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