Discovering New Treatments for Asthma and COPD. The Use of the Human Viral Challenge Model with a Newly Manufactured and Characterised GMP Wild-Type Human Rhinovirus.

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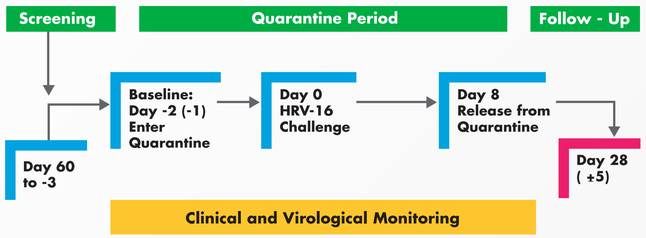
Abstract

Human Rhinovirus (HRV) infection is an important precursor to asthma and chronic obstructive pulmonary disease (COPD) exacerbations.
The Human Viral Challenge (HVC) model may provide a powerful tool in studying these and other chronic respiratory diseases. In this study, we have reported the production and human characterisation of a new Wild-Type HRV-16 challenge virus produced specifically for this purpose.

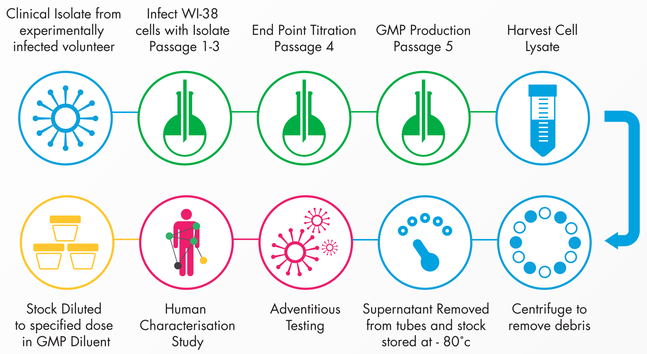
Background

Human Rhinovirus infections are frequently associated with the common cold and acute upper respiratory tract infection in humans. Although often considered trivial, they are associated with significant economic implications as well as being an important predisposing factor in sinusitis, otitis media, bronchitis and primary pneumonia. HRV is known to cause considerable morbidity in certain at-risk groups such as infants, the elderly, the immunocompromised, and those with chronic respiratory disease like asthma, COPD, and cystic fibrosis. At present, HRV is considered the number one cause of asthma exacerbations. Therefore, the use of HRV in a HVC Model can be an extremely powerful tool, not just to study HRV infection and disease, but also to investigate the mechanisms of exacerbation in patients with chronic respiratory disease and to conduct efficacy studies for new therapies in these disease areas.

HRV-16 Human Challenge Study Process



Summary of the HRV-16 Challenge Stock Production Process



Methods

The HRV-16 virus was isolated from a nasal wash sample taken from an 18 year old experimentally infected healthy female volunteer, who developed symptoms consistent with a respiratory virus infection two days post HRV-16 infection. The donor underwent extensive health screening. Following initial virus isolation by limiting dilution in the WI-38 cell line to create a Master Virus Seed Stock at hVIVO, a bulk stock was manufactured by passage in WI-38s under GMP conditions.

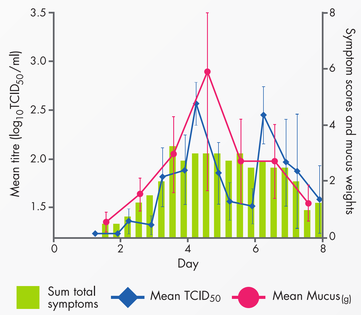
Viral identity was determined by Sanger sequencing and the infectious virus titre determined by $TCID_{50}$. The virus stock was screened for potential adventitious agents. All results confirmed the suitability of the HRV-16 GMP stock for use in HVC studies.

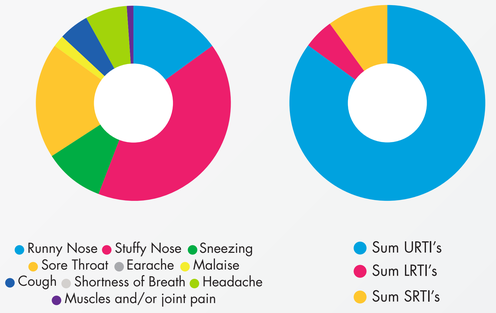
Conclusion

Our new Wild-Type HRV-16 stock is both safe and pathogenic given the disease profile that it induces, we are continuing with the development of the HRV-16 HVC models will enable us to progress further into asthmatic and COPD patient populations. Our HRV-16 stock has been produced in sufficient quantity to enable the same batch to be used throughout the development of the different planned models, thus building up an important body of safety and efficacy data.

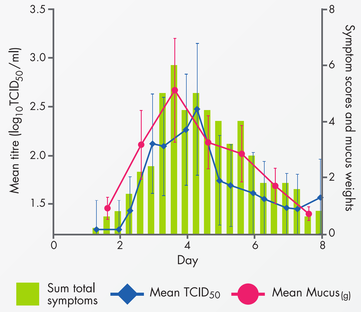
HRV Inoculum Dose Characterisation- Selected Dose Most Closely Mimics Natural Infection

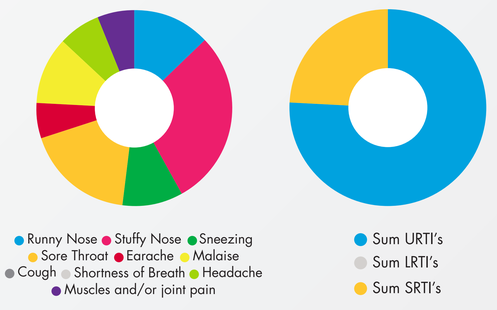
1 $TCID_{50}$



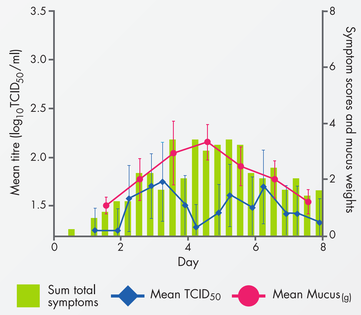


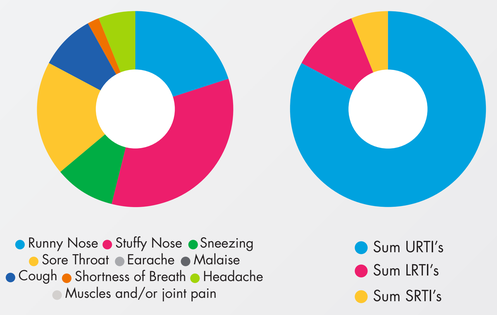
10 $TCID_{50}$





100 $TCID_{50}$





URTI: Upper Respiratory Tract Infection LRTI: Lower Respiratory Tract Infection SRTI: Systemic Respiratory Tract Infection

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