FORMULATION DEVELOPMENT OF A STABLE, ORALLY DELIVERED LIVE HUMAN NEONATAL ROTAVIRUS (RV3-BB) VACCINE CANDIDATE

Prashant Kumar, University of Kansas
prashant.kumar@ku.edu
Swathi Pullagurla, University of Kansas
Ravi S. Shukla, University of Kansas
Ashaben Patel, University of Kansas
Christopher Bird, University of Kansas
Ozan Kumru, University of Kansas
Sangeeta B. Joshi, University of Kansas
David B. Volkin, University of Kansas

Key Words: Rotavirus, Gastroenteritis, Neonatal rotavirus vaccine, RV3-BB, intussusception

Rotavirus is the most common cause of gastroenteritis among children under 5 years of age leading to ~200,000 deaths in 2013.[1] Rotavirus-attributed mortality can be significantly reduced by promoting global implementation of rotavirus vaccination by vaccine dosage cost reduction and optimizing vaccine efficacy in low-resource countries. Furthermore, a rotavirus vaccine administered at birth could prevent neonatal mortality and reduce the risk of intussusception [2]. An oral human neonatal rotavirus vaccine candidate (RV3-BB) has been developed from the human neonatal rotavirus strain RV3 (G3P[6]) [2], and a recently published Phase IIb clinical trial showed RV3-BB was efficacious in preventing severe rotavirus gastroenteritis via a neonatal or infant schedule in Indonesia[2]. The overall goals of this project are to develop and implement commercially viable bulk and drug product manufacturing processes of a stable liquid formulation for oral delivery (without pre-neutralization) that is affordable in the developing world (Fig. 1). The consortium working on this program is sponsored by the Bill and Melinda Gates Foundation between Batavia Biosciences, Murdoch Children's Research Institute, BioFarma, and The University of Kansas.

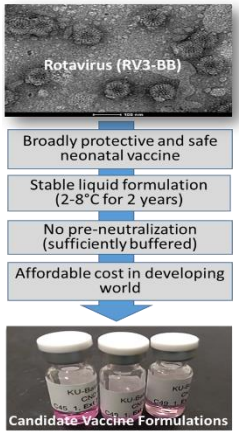

Fig. 1 – Considerations for the development of neonatal rotavirus vaccine (RV3-BB)

The formulation goals are to develop a refrigerator stable (i.e., 2 years, 2-8ºC) liquid formulation, based on the same RV3 strain, with no requirement to pre-neutralize gastric acid during administration. Analytical characterization of virus bulks and purified virus was performed in terms of potency, size, concentration, morphology, and physical stability. FFA and qPCR potency assays were developed and implemented for formulation development and stability evaluation. Optimization of various formulation parameters including pH and excipients to stabilize RV3 against various environmental stresses (thermal, agitation, and freeze-thaw) was performed. Excipient screening was first performed to evaluate the effect of individual excipients, followed by evaluation of various combinations. Rotavirus vaccines present a unique formulation challenge requiring careful balance of stabilizing the virus against low pH environments during oral delivery vs. long term storage stability. Accelerated and real-time stability studies with RV3 candidate formulations are in progress to elucidate the most stable formulation(s) that meet the aforementioned criteria (i.e., 2 year stability at 2-8ºC and withstand acid induced potency loss). Stability modelling studies based on extrapolation of accelerated and real-time stability data to predict long-term formulation stability are ongoing.

Acknowledgements:

This work is funded by the Bill and Melinda Gates Foundation.

Collaborators on the RV3 team:
(From Batavia, Netherlands) Femke Hoeksema, Ahd Hamidi, Alfred Luitjens, Christopher Yallop
(From BioFarma, Indonesia) Erman Tritama, BioFarma, Novilia Sjafri Bachtiar, Adriansjah Azhari
(From MCRI, Australia) Julie Bines

References:
1. www.who.int/immunization/monitoring_surveillance/burden/estimates/rotavirus/en/ (Accessed March, 2018).
2. J.E. Bines, et al. Human neonatal rotavirus vaccine (RV3-BB) to target rotavirus from birth. The New England journal of medicine 2018; 378 (8): 719-730.