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Laboratory And Pre-clinical Studies Of Parainfluenza Viruses

Project Number
1ZIAAI000327-39

Contact PI/Project Leader
BUCHHOLZ, URSULA

Awardee Organization
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Description

Abstract Text

In recent years, we have focused on using a PIV3-based vector to express RSV antigen, providing a bivalent vaccine against the two most important pediatric viral respiratory pathogens. The vector is one that we previously developed, called rB/HPIV3, which consists of bovine PIV3 in which the F and HN genes have been replaced by those of HPIV3. This results in a **chimeric virus** that is attenuated in non-human primates and humans due to the BPIV3 backbone, and which bears the neutralization and major protective F and HN antigens of HPIV3. Both the empty B/HPIV3 vector and B/HPIV3 expressing the unmodified RSV F protein were previously shown to be well-tolerated in infants and young children. Therefore, this vector appears to be in the desired range of attenuation. In work continuing from previous years, we continued to focus on expressing the RSV fusion F glycoprotein because it generally is considered to be the most important RSV neutralization and protective antigen. RSV F also is much more highly conserved among RSV strains than the attachment G protein, which is the other neutralization antigen and the second most important protective antigen. We continued to evaluate a number of strategies to optimize the immunogenicity of rB/HPIV3 expressing RSV F protein. This involved increasing both the quantity and the quality of the expressed RSV F antigen. Evaluation of several different positions for the RSV F gene in the vector genome identified the second gene position as generally being optimal. Evaluation of several versions of codon-optimization of the RSV F ORF identified the most efficient one, provided by GenScript (GS). The RSV F protein was modified with two missense mutations (called HEK) to be identical to an early-passage isolate of this RSV strain, which reduced fusion and stabilized the trimer. Two additional modifications in particular substantially increased the immunogenicity of vector-expressed F protein: (i) one modification was to increase the stability of the pre-fusion conformation of the F protein - the conformation that is the most effective in inducing RSV-neutralizing antibodies - by introducing mutations that have been reported by colleagues in the NIH Vaccine Research Center and elsewhere. The most successful mutations involved addition of a disulfide bond (called the DS mutation) in combination with two cavity-filling missense mutations (called Cav1). (ii) The other modification was to engineer RSV F to be efficiently packaged in the B/HPIV3 vector particle. This was done by replacing the transmembrane and cytoplasmic tail (TMCT) domains of RSV F with those of BPIV3 F. Each of these two modifications, DS-Cav1 and TMCT, resulted in a substantial increase in the induction of serum RSV-neutralizing antibodies, and in particular antibodies that neutralized RSV efficiently in vitro without added complement and thus are highly effective in neutralization. In work continuing from previous years, we constructed and evaluated more than 35 versions of rB/HPIV3-RSV-F in pre-clinical studies. These constructs included a variety of missense mutations identified by workers in the field as well as with deletion of the F cleavage site, resulting in a single chain protein. These studies resulted in the identification of two lead versions. One is called rB/HPIV3-F2/HEK/GS-opt/DS-Cav1 and has the following characteristics: insertion of RSV F at the second gene position (F2), an early-passage amino acid sequence (HEK), GenScript optimization (GS-opt), and the DS-Cav1 pre-F stabilization. The second lead version, called rB/HPIV3-F2/HEK/GS-opt/DS-Cav1/B3TMCT, is identical except that it also contains the TMCT modification. These candidates presently are being manufactured into clinical trial material for pediatric clinical evaluation. We also used HPIV3 as a vector to express the RSV fusion protein. One advantage is that rHPIV3 expresses all of the HPIV3 antigens compared to only two for rB/HPIV3. In addition, the use of rHPIV3 as vector should avoid excessive attenuation following addition of a modified RSV F gene, which may occur with rB/HPIV3. This project built on scientific insights obtained with B/HPVI3. To enhance its immunogenicity, RSV F was modified (i) to increase the stability of the prefusion (pre-F) conformation and (ii) by replacement of its transmembrane (TM) and cytoplasmic tail (CT) domains with those of HPIV3 F (H3TMCT) to increase incorporation in the vector virion. RSV F (+/- H3TMCT) was expressed from the first (F/preN) or the second (F/N-P) gene position of rHPIV3. The H3TMCT modification dramatically increased packaging of RSV F into the vector virion and, in hamsters, resulted in significant increases in the titer of high-quality serum RSV-neutralizing antibodies, in addition to the increase conferred by pre-F stabilization. Only F-H3TMCT/preN replication was significantly attenuated in the nasal turbinates by the RSV F insert. F-H3TMCT/preN, F/N-P, and F-H3TMCT/N-P provided complete protection against wt RSV challenge. F-H3TMCT/N-P exhibited the most stable and highest expression of RSV F, providing impetus for its further development.

Public Health Relevance Statement

Data not available.

NIH Spending Category

Genetics Immunization Infectious Diseases Lung Pediatric Vaccine Related

Project Terms

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Genes Glycoproteins Hamsters Human Human Parainfluenza Virus 2 Immunization In Vitro Infant Intranasal Administration Laboratory Study Lead Life Lower respiratory tract structure Missense Mutation Modification Molecular Biology

Read More

Details

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Name
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

City

Country

Department Type
Unavailable

Organization Type
Unavailable

State Code

Congressional District

Other Information

FOA

Study Section

Fiscal Year
2020

Award Notice Date

Administering Institutes or Centers
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DUNS Number

CFDA Code

Project Start Date

Project End Date

Budget Start Date

Budget End Date

Project Funding Information for 2020

Total Funding
$1,633,214

Direct Costs
$0

Indirect Costs
$0

Year	Funding IC	FY Total Cost by IC
2020	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$1,633,214

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Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	$1,633,214	Genetics; Immunization; Infectious Diseases; Lung; Pediatric; Vaccine Related;

Sub Projects

No Sub Projects information available for 1ZIAAI000327-39

Publications

No Publications available for 1ZIAAI000327-39

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Outcomes

The Project Outcomes shown here are displayed verbatim as submitted by the Principal Investigator (PI) for this award. Any opinions, findings, and conclusions or recommendations expressed are those of the PI and do not necessarily reflect the views of the National Institutes of Health. NIH has not endorsed the content below.

No Outcomes available for 1ZIAAI000327-39

Clinical Studies

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