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Generation of a polycistronic universal influenza virus vaccine based on rare species adenoviral vectors

Project Number
1R21AI146529-01

Contact PI/Project Leader
COUGHLAN, LYNDA

Awardee Organization
ICAHN SCHOOL OF MEDICINE AT
MOUNT SINAI

Description

Abstract Text

SUMMARY: Influenza A viruses (IAVs) cause serious respiratory illness in humans, with ~250,000-500,000 deaths per year globally. In addition to seasonal epidemics, the ongoing **pandemic** threat posed by new, emerging, reassortant influenza viruses, for which humans are immunologically naive, represents a major public health concern. Current influenza vaccines are impacted by several issues. These include, the elicitation of narrow, strain-specific immune responses, an over-reliance on egg-based manufacturing methods, a protracted production process (>6 months), the need to predict in advance which strains will circulate in forthcoming seasons and the minimal induction of cellular and humoral immune responses to multiple influenza antigens (Ags) simultaneously. The sub-optimal performance of seasonal influenza vaccines in recent years has accelerated interest in developing a universal influenza virus vaccine, capable of providing broad and long- lived protection against seasonal and **pandemic** subtypes. Strategies to achieve this include refocusing immune responses towards highly conserved epitopes on influenza virus antigens such as the stalk of the major surface glycoprotein, hemagglutinin (HA), the neuraminidase (NA) or the internal nucleoprotein (NP). My research aims to develop an alternative, optimized, universal influenza vaccine platform which will overcome issues associated with current vaccines using three approaches. (1) Firstly, I will optimize polycistronic Ag expression cassettes, in which multiple IAV Ags are expressed simultaneously. These will include bi- or tri-cistronic Ag cassettes featuring headless HAs from group 1 or group 2 IAVs in combination with NA and/or NP. I will augment/broaden immune recognition of headless HA or NA by targeting Ags to host-derived extracellular vesicles (EVs) including exosomes in vivo. This will be achieved by engineering fusion-Ag constructs to tether Ag to a protein domain enriched in exosomes. Exosomes are nano-sized EVs which play important roles in the regulation of immune responses, due to their ability to present Ag, in addition to MHC and co-stimulatory molecules, to T- and B-cells. (2) Secondly, I will engineer these Ag constructs into non- replicating, rare species adenoviral (Ad) vectored vaccines, which have established protocols for clinical manufacturing, can be thermostabilized with minimal losses to immunogenicity under cold-chain free conditions and have demonstrated safety and immunogenicity in infants, adults and the elderly in clinical trials. (3) Finally, I will comprehensively evaluate and phenotype the magnitude and profile of these universal influenza vaccines in single-shot regimens. These data will provide valuable information for the design of subsequent prime:boost regimens and for challenge experiments in the future. In summary, the universal influenza vaccine platform described in this proposal would be well-suited to stockpiling for **pandemic** preparedness, and could provide heterologous protection following a single shot, which may be sufficient to ease the burden on the healthcare system in the early phase of an emerging **pandemic**.

Public Health Relevance Statement

PROJECT NARRATIVE: Influenza A virus is a serious pathogen of great clinical and economic impact, with high mortality in susceptible populations. My research aims to develop a novel, "universal" vaccine for influenza which has the potential to elicit broad and cross-reactive immune responses as a result of combining several approaches: (i) the selection of optimized, highly conserved influenza A virus immunogens and expression of them in combination within a single vaccine, (ii) increasing the immune recognition of these immunogens by targeting them to host-derived exosomes in vivo and (iii) the delivery of optimized antigens by novel rare species adenoviral vectored vaccines, a vaccine platform which has demonstrated safety and immunogenicity in humans.

NIH Spending Category

Biodefense	Biotechnology	Emerging Infectious Diseases	Immunization	Infectious Diseases
Influenza	Pneumonia & Influenza	Prevention	Vaccine Related	










Project Terms

Adenovirus Vector	Adjuvant	Adult	Animal Model	Antibody Formation	Antigen Targeting
Antigens	B-Lymphocytes	Biological Assay	Bronchoalveolar Lavage	CD8B1 gene	Cavia
Cells	Cessation of life	Cleaved cell	Clinical	Clinical Protocols	Clinical Trials
Cold Chains	Combined Vaccines	Communicable Diseases	DNA	DNA cassette	Data
Elderly	Enzyme-Linked Immunosorbent Assay	Epidemic	Epitopes	Escherichia coli	Ferrets
Engineering	Flow Cytometry	Future	Generations	Genome	Healthcare Systems
Hemagglutinin	Immune	Immune response	Immunity	Immunoglobulin A	Immunoglobulin G
Immunologics	In Vitro	Individual	Infant	Infection	Influenza
Influenza A virus	Intramuscular	Lead			


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Name COUGHLAN, LYNDA 		Not Applicable	Name GORDON, JENNIFER L
Title ASSISTANT PROFESSOR			Contact jennifer.gordon2@nih.gov
Contact lynda.coughlan@mssm.edu			
Organization			
Name ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI		Department Type MICROBIOLOGY/IMMUN/VIROLOGY	State Code NY
City NEW YORK		Organization Type SCHOOLS OF MEDICINE	Congressional District 13
Country UNITED STATES (US)			

Other Information

FOA PA-18-858		Administering Institutes or Centers NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES		Project Start Date	06-August-2019
Study Section Special Emphasis Panel[ZRG1 IMM-R (90)]		DUNS Number 078861598	CFDA Code 855	Project End Date	31-July-2021
Fiscal Year 2019	Award Notice Date 06-August-2019			Budget Start Date	06-August-2019
				Budget End Date	31-July-2020

Project Funding Information for 2019

Total Funding \$254,250	Direct Costs \$150,000	Indirect Costs \$104,250
Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	\$254,250

NIH Categorical Spending

[Click here for more information on NIH Categorical Spending](#)

Funding IC	FY Total Cost by IC	NIH Spending Category
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES	\$254,250	Biodefense; Biotechnology; Emerging Infectious Diseases; Immunization; Infectious Diseases; Influenza; Pneumonia & Influenza; Prevention; Vaccine Related;

Sub Projects

No Sub Projects information available for 1R21AI146529-01

Publications

No Publications available for 1R21AI146529-01










Patents

No Patents information available for 1R21AI146529-01

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No Outcomes available for 1R21AI146529-01

Clinical Studies

No Clinical Studies information available for 1R21AI146529-01

News and More

Related News Releases

No news release information available for 1R21AI146529-01

History

No Historical information available for 1R21AI146529-01

Similar Projects

No Similar Projects information available for 1R21AI146529-01