Acute Flaccid Myelitis, Enteroviruses and Vaccines

Cristina Cassetti, Ph.D.

Deputy Director

Division of Microbiology and Infectious Diseases, NIAID

June 19, 2020

National Institute of Allergy and Infectious Diseases

Outline

- Natural History Study
- Vaccines in Development
- NIAID Workshop on AFM Preparedness

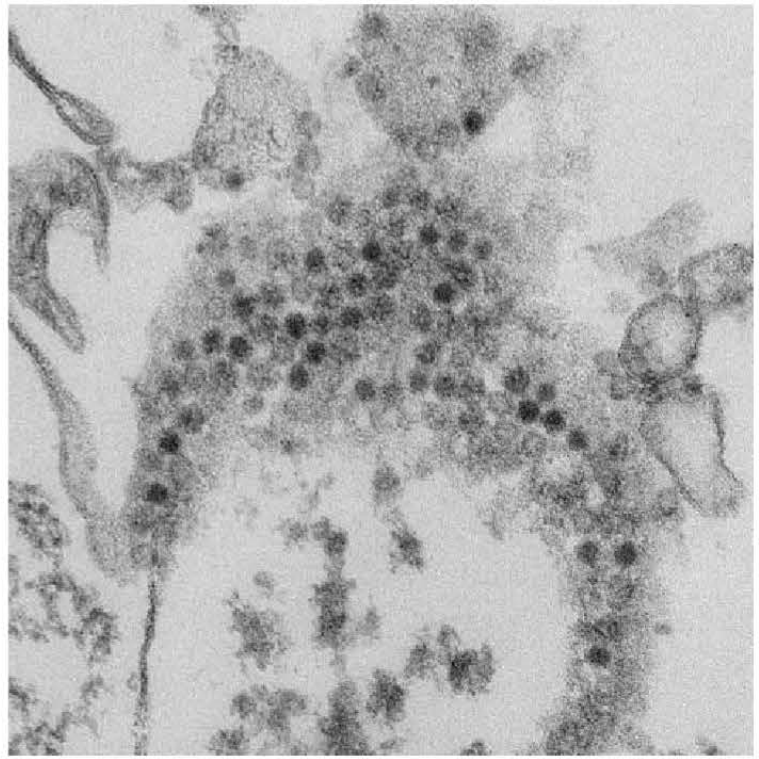
National Institute of Allergy and Infectious Diseases

July 23, 2019

News Release

NIH Awards Contract for Acute Flaccid Myelitis Natural History Study

- $10 million over 5 years to University of Alabama at Birmingham (UAB) to organize and implement an international, multi-site study
- UAB's David Kimberlin, MD is PI; Carlos Pardo-Villamizar, MD of Johns Hopkins is co-PI



AS Fauci/NIAID

Natural History Study: Objectives

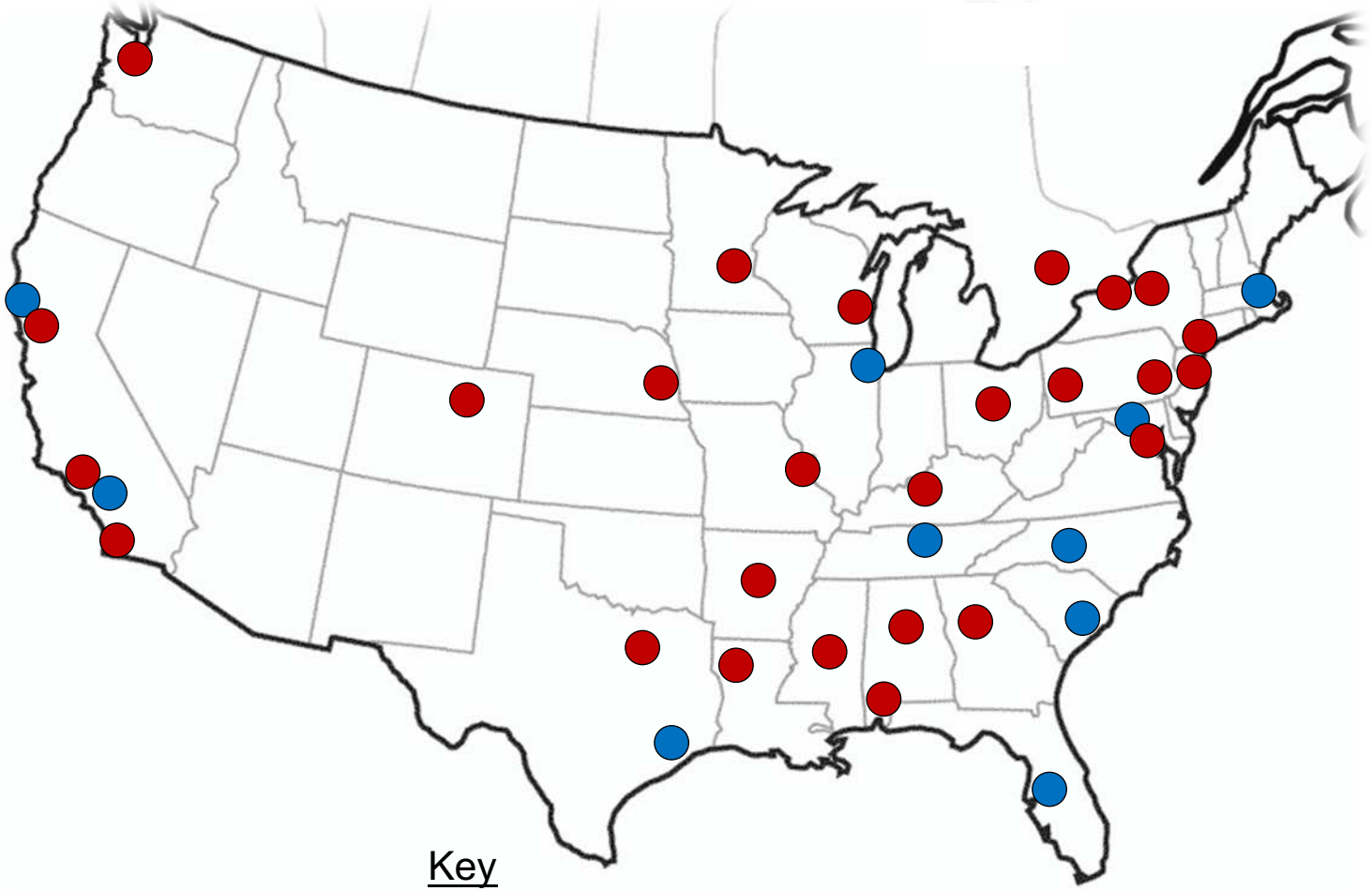
Primary:

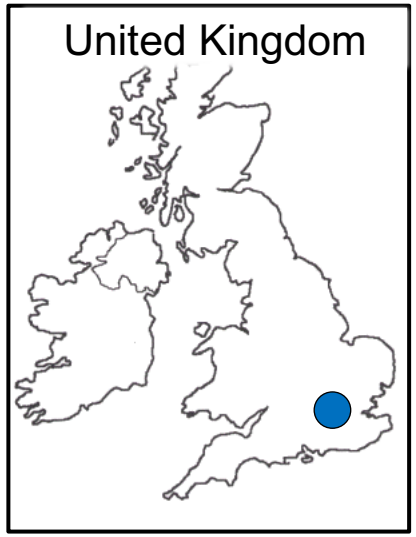
- To characterize the epidemiology and natural history of AFM in the first 12 months following enrollment.

Secondary:

- To describe the clinical diagnostic evaluations and therapeutic interventions for suspected AFM cases.
- To identify risk factors for development of AFM.
- To identify determinants of outcome of AFM.
- To describe the clinical characteristics of household contacts of patients being evaluated for AFM.

AFM Study Sites





Key

- Activated sites
- Sites pending activation

Updated May 26, 2020

NIH National Institute of Allergy and Infectious Diseases

More Evidence for a Causal Role of Non-Polio Enteroviruses in AFM

nature medicine

Letter | Published: 21 October 2019

Pan-viral serology implicates enteroviruses in acute flaccid myelitis

Ryan D. Schubert, Isobel A. Hawes, [...] Michael R. Wilson

Nature Medicine **25**, 1748–1752(2019) | Cite this article

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio AN OPEN ACCESS JOURNAL PUBLISHED BY THE AMERICAN SOCIETY FOR MICROBIOLOGY

Research Article | Clinical Science and Epidemiol

Antibodies to Enteroviruses in Cerebrospinal Fluid of Patients with Acute Flaccid Myelitis

Nischay Mishra, Terry Fei Fan Ng, Rachel L. Marine, Komal Jain, James Ng, Riddhi Thakkar, Adrian Caciula, Adam Price, Joel A. Garcia, Jane C. Burns, Kiran T. Thakur, Kimbell L. Hetzler, Janell A. Routh, Jennifer L. Konopka-Anstadt, W. Allan Nix, Rafal Tokarz, Thomas Briese, M. Steven Oberste, W. Ian Lipkin

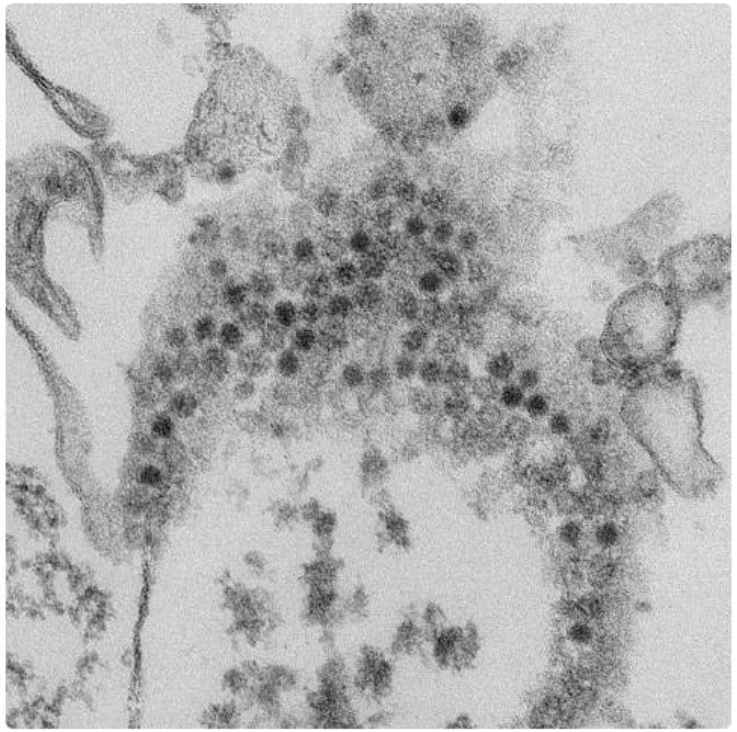
Christine A. Biron, Editor

DOI: 10.1128/mBio.01903-19 Check for updates

August 13, 2019

EV-D68 Vaccine Development at NIAID

- **Whole inactivated EV-D68 vaccine**:
  - Utilized NIAID contracts to obtain new isolates from CDC, develop serum-free cell lines for viral production, and optimize conditions for viral growth
  - Planning to award a contract in July to manufacture an inactivated EV-D68 vaccine and test in Phase I clinical trial
- **Virus-like particle (VLP) vaccine:**
  - Scientists at NIAID Vaccine Research Center (VRC) currently developing and characterizing VLPs expressed and self-assembled from EV-D68 structural protein sequences



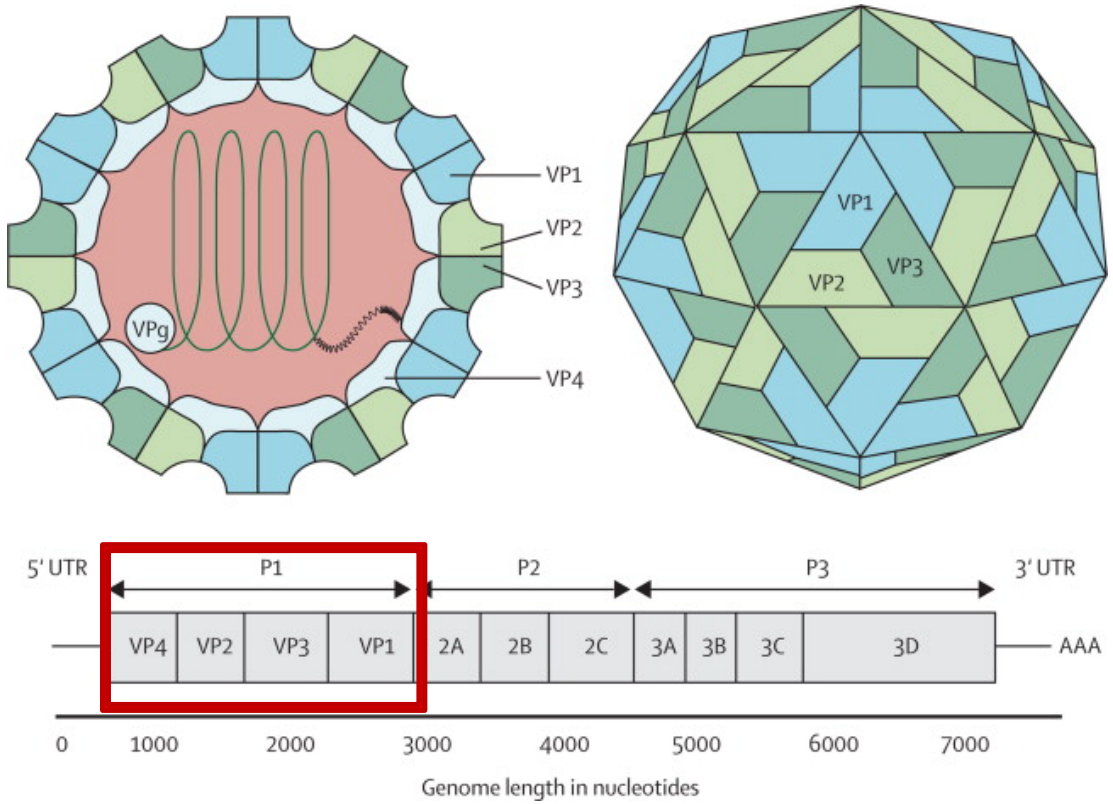
This thin section transmission electron microscopic image reveals numerous, spheroid shaped Enterovirus-D68 (EV-D68) virions, which are members of the family Picornaviridae.

Credit: Credit: CDC/Cynthia S. Goldsmith, Yiting Zhang

NIH National Institute of Allergy and Infectious Diseases

VRC Virus-like Particles (VLP) Vaccine

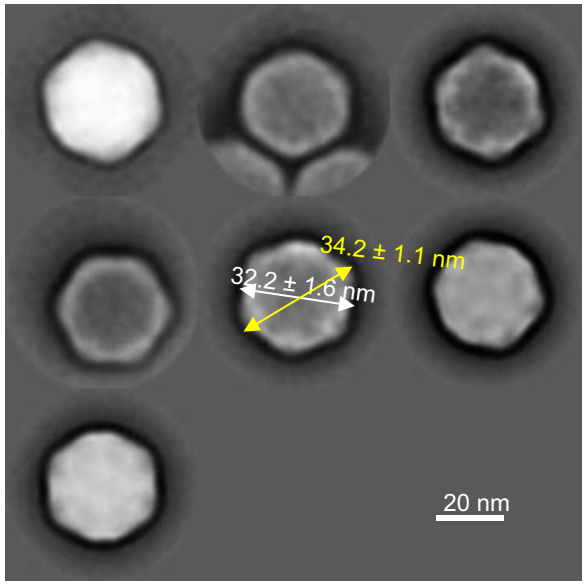
- Utilizing mammalian and bacterial expression systems
- Orderly antigen arrays are immunogenic
- Quaternary epitopes preserved
- Structures available
- Licensed VLP products
- Protein engineering may provide basis for generalizable design



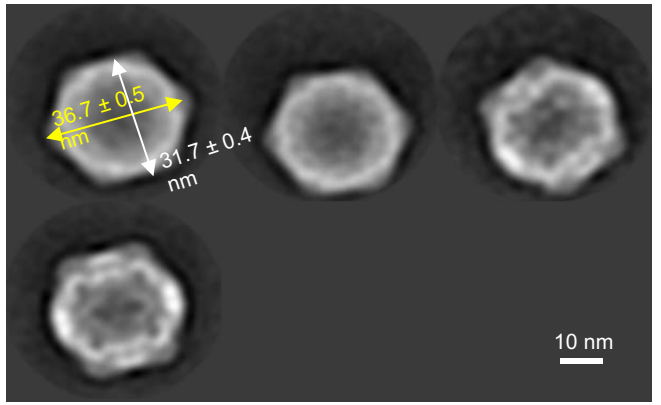
National Institute of Allergy and Infectious Diseases

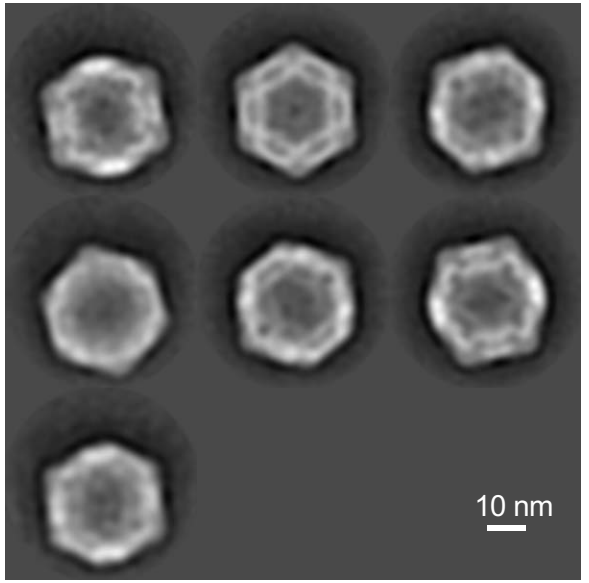
EV-D68 Virus and Virus-Like Particle

Virus



VLP



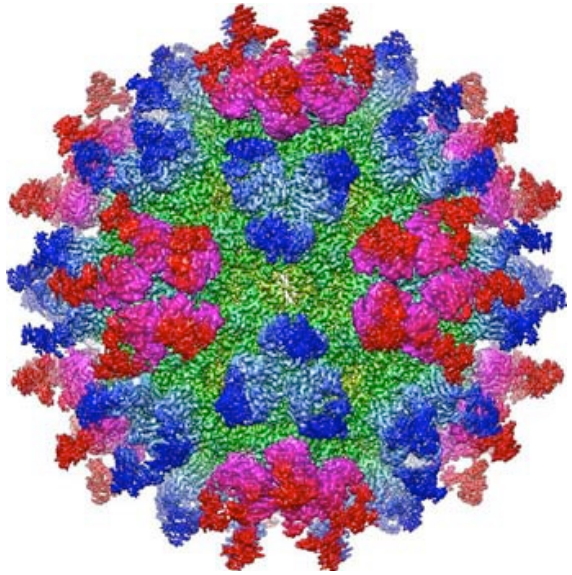


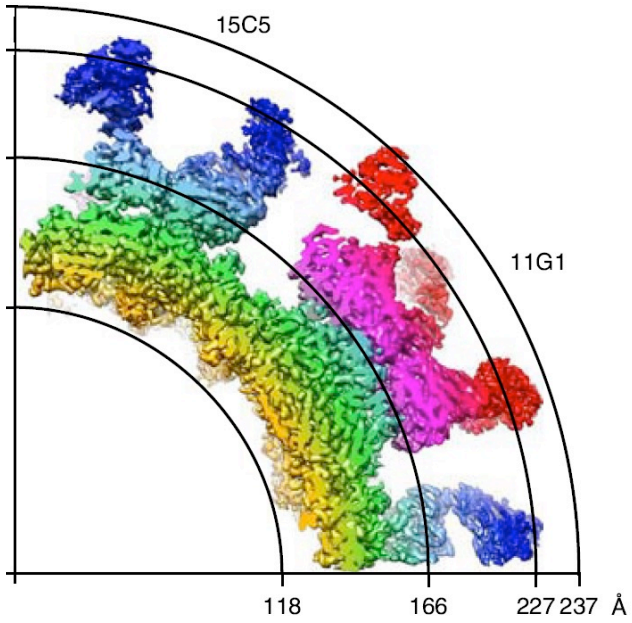
Cyro-EM 2D class averages

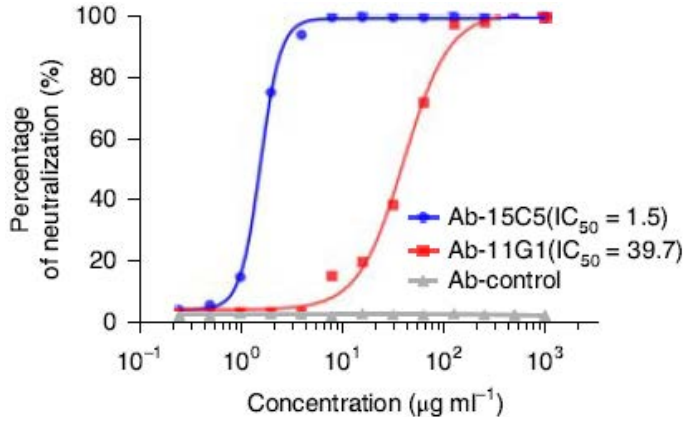
Vaccine Research Center, NIAID, NIH
Wei Shi, Lingshu Wang, Yaroslav Tsybovsky

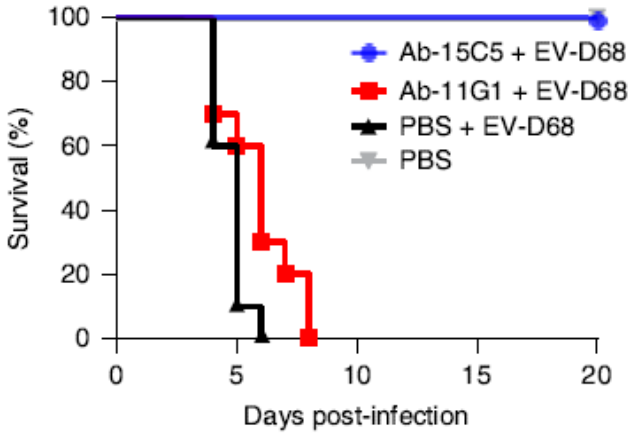
NIH National Institute of Allergy and Infectious Diseases

EV-D68 Mechanism of mAb Neutralization









- **mAb 15C5 binds across VP2 and VP3 at 3-fold axis**
- **Triggers shift to A-particle**
- **Causes premature genome release**

- **mAb 11G1 binds across VP1 at 5-fold axis**

Zheng Q, …, Graham BS, Cheng T, Li S, Xia N. Atomic structures of enterovirus D68 in complex with two monoclonal antibodies define distinct mechanisms of viral neutralization. Nat Microbiol. 2019; 4:124-133.

NIH National Institute of Allergy and Infectious Diseases

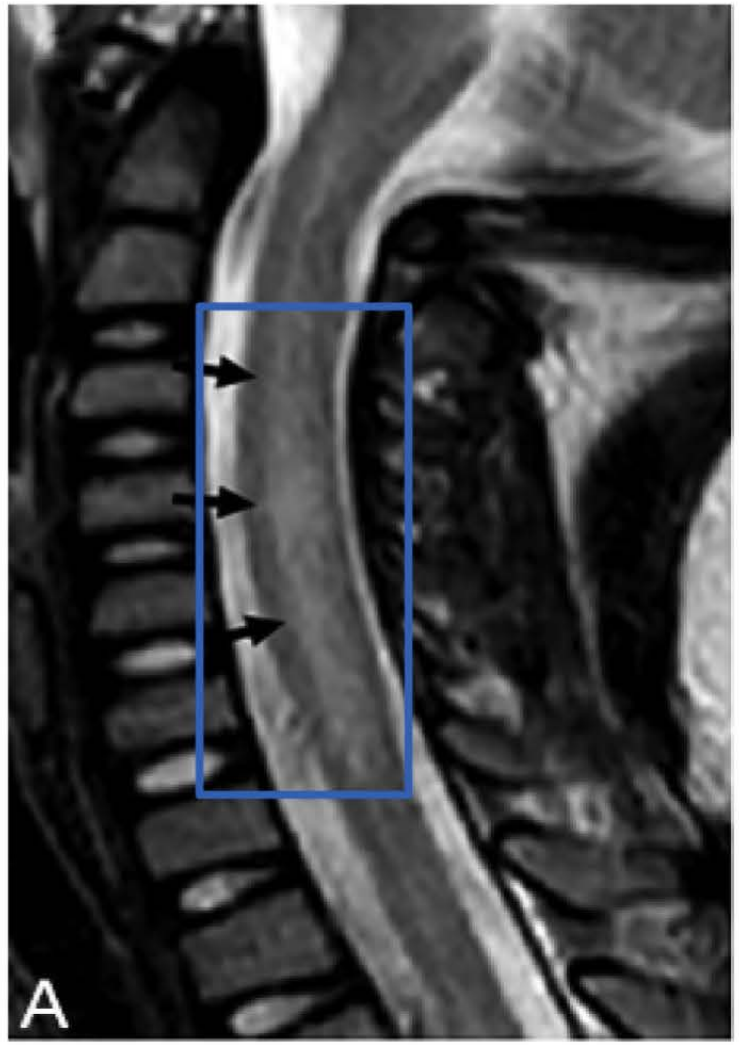
VLP vaccine summary

- VLP vaccine development
  - Produced from bacteria or mammalian cells
  - Stable and similar in size and shape to virus
  - Immunogenic and protective in mice
  - Highly neutralizing mAbs bind to the VLPs
- Work in progress
  - Serological assays
  - mAb discovery and mapping
  - Determine optimal immunogen structure
  - Protein engineering to improve expression and stability
  - Explore cost-effective manufacturing and delivery approaches

NIAID Workshop on AFM Preparedness

- February 19-20, 2020, Rockville, MD

- Objectives:
  - Determine research priorities
  - Catalyze development of countermeasures
  - Generate discussion regarding use of countermeasures



JA Maloney et al., *Am J Neuroradiol* (2015).

Research gaps/opportunities

- Changes in epidemiology in US
- Pathophysiology of non-polio enterovirus mediated AFM
  - Role of direct viral infection of cells vs. immune mediated damage
  - Mechanism of viral spread to the CNS
  - Genetic predisposition to AFM?
- Vaccines
  - Inactivated vaccines for other enteroviruses have been licensed (Polio-Salk, EV71)
  - Challenge of clinical trial design for a vaccine given current epidemiology of AFM
- Therapeutics
  - Promising broad-spectrum anti enteroviral drugs that target viral polymerase, protease, and ATPase
  - It will be challenging to get drugs into the CNS and lungs.
  - More than 1 target may be needed to minimize drug resistance development.
  - mAbs are promising for potential prophylaxis and treatment of AFM

A novel proposal: Antibody treatment for AFM

Matthew R. Vogt, MD, PhD.

Pediatric Infectious Diseases Fellow
Monroe Carell Jr. Children's Hospital
Vanderbilt University Medical Center