

# **ACIP Anthrax Vaccine Work Group**

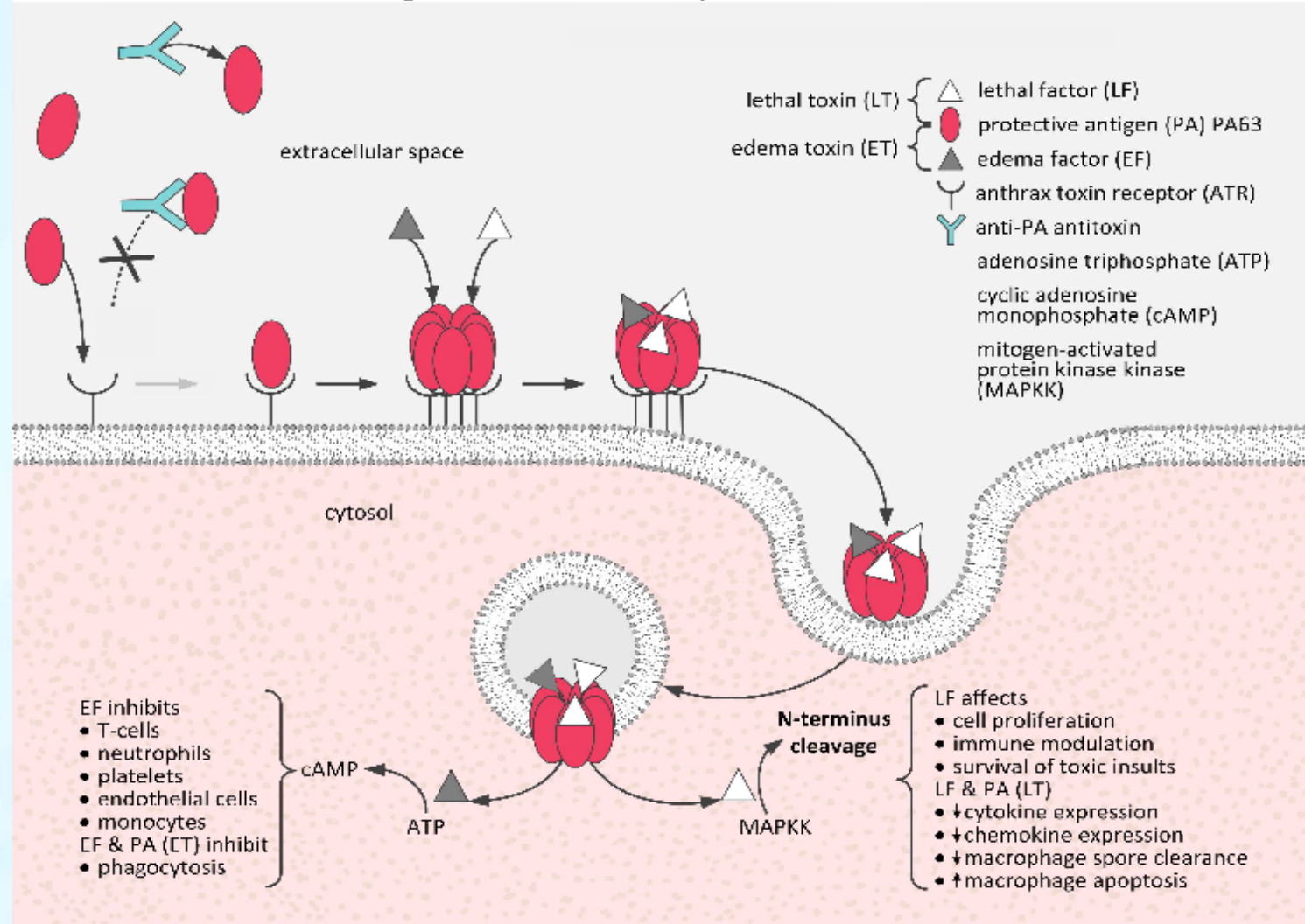
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# Outline

- ❑ Overview of anthrax antitoxins
- ❑ Studies on antitoxin use for postexposure prophylaxis (PEP)
  - Anthrax antitoxin for PEP and survival in animal models
  - Anthrax antitoxin effect on acquired immunity
  - Anthrax antitoxin use with anthrax vaccine adsorbed (AVA)
- ❑ Work group discussions
- ❑ Guidance on anthrax antitoxin use for PEP

# Anthrax Pathogenesis

Figure 1. Formation and Activity of Main Anthrax Toxins



## Background – Anthrax Antitoxins

There are currently three FDA approved anthrax antitoxins

### ❑ RAXIBACUMAB

- Initial U.S. Approval: 2012
- Human IgG1 $\lambda$  monoclonal antibody that binds the protective antigen (PA) component of *Bacillus anthracis* toxin

### ❑ ANTHRASIL (Anthrax Immune Globulin Intravenous (AIGIV))

- Initial U.S. Approval: 2015
- Purified human IgG containing polyclonal antibodies that bind the protective antigen (PA) component of *B. anthracis* lethal and edema toxins collected from individuals immunized with AVA

### ❑ ANTHIM (obiltoxaximab)

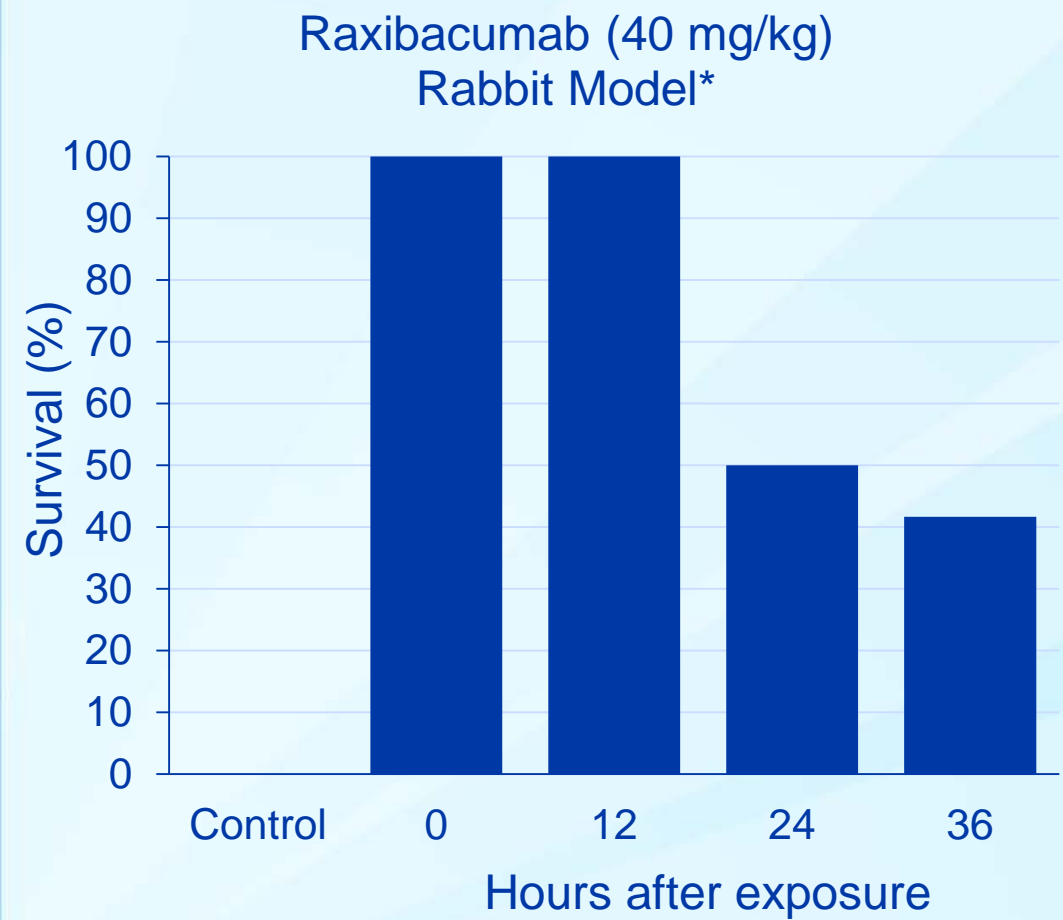
- Initial U.S. Approval: 2016
- Chimeric IgG1 kappa monoclonal antibody that binds the PA component of *B. anthracis* toxin

## Background – Anthrax Antitoxins Indications

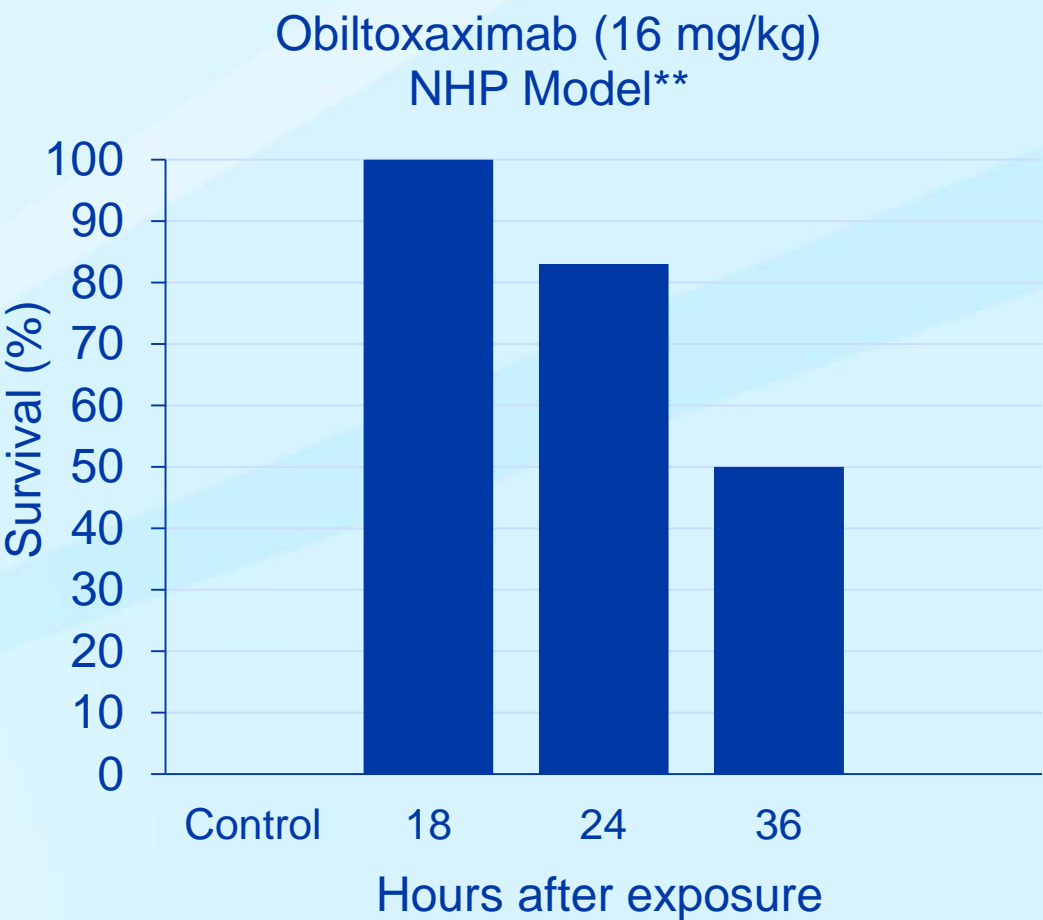
- ❑ Anthrax antitoxins all have an indication for the treatment of adult and pediatric patients with inhalation anthrax due to *B. anthracis* in combination with appropriate antimicrobials
- ❑ The monoclonal antitoxins, raxibacumab and obiltoxaximab, are also indicated for PEP of inhalation anthrax when alternative therapies are not available or are not appropriate
- ❑ Animal Rule – The effectiveness of the antitoxins for treatment and PEP of anthrax is based solely on efficacy studies conducted in animal models of inhalation anthrax

# **ANTHRAX ANTITOXIN USE FOR PEP**

# Anthrax Antitoxin PEP and Survival



\*Raxibacumab FDA Briefing Package (BLA 125349)



^^Obiltoxaximab FDA Briefing Package (Study AP301)

# Anthrax Antitoxin PEP and Acquired Immune Response

- ❑ Rechallenge of 21 surviving NHPs from a previous dose-ranging efficacy study
  - All survived with no evidence of reemergence of disease
  - Rechallenged again with 100 LD<sub>50</sub>s of *Bacillus anthracis* spores 11 months after the dose-ranging study
  - One hundred percent of the animals survived
- ❑ Rabbits were challenged with 200 LD<sub>50</sub>s of *B. anthracis* spores and treated with either obiltoxaximab, levofloxacin, or a combination of the two
  - Animals that survived were rechallenged 9 months later with another 200 LD<sub>50</sub>s dose
  - One hundred percent survived



## **Anthrax Mab Antitoxin PEP and AVA Co-administration**

- ❑ When AVA is co-administered with AIGIV, a polyclonal antibody, the development of protective immune response was significantly reduced
- ❑ Effect on the immunogenicity of AVA when co-administered with Mab anthrax antitoxins
  - First group received AVA at days 1, 15, and 29
  - Second group received the same AVA vaccine schedule plus a single intravenous 40 mg/kg dose of raxibacumab immediately prior to first dose of vaccine
  - The immune response at day 29 was non-inferior\* to that for AVA alone
  - Percentage achieving a  $\geq 4$ -fold increase in toxin neutralizing activity (TNA) titer from baseline at Week 26 after the first AVA dose was not different between the two groups

\*Non-inferiority was established if the ratio of anti-PA Ab titer GMCs for AVA compared to AVA plus raxibacumab at week 4 was less than 1.5

# Summary of Anthrax Work Group Discussions

- ❑ The anthrax Mab antitoxins, obiltoxaximab and raxibacumab, have an indication for use as PEP for inhalation anthrax when alternative therapies are not available or are not appropriate.
- ❑ The data show that anthrax antitoxin administered 12-18 hours postexposure to *Bacillus anthracis* spores can prevent 90-100% of disease in rabbit and nonhuman primate models. However, survival frequencies have been shown to be dependent on antitoxin concentration and time of administration postexposure.

# Summary of Anthrax Work Group Discussions

- ❑ Protection frequencies are significantly lower with increasing time to intervention after exposure:
  - At 36 hours postexposure, the survival frequencies in rabbits administered the maximum dose of raxibacumab (40 mg/kg) was 42%.
  - At 36 hours postexposure, the survival frequency in nonhuman primates administered the maximum dose of obiltoxaximab (16 mg/kg) was 50%
- ❑ Data suggest that anthrax Mab antitoxin does not interfere with the development of protective immunity
  - However, animals all received large dose spore inoculums. Whether antitoxin use in persons exposed to smaller dose spore inoculums would interfere with the development of an acquired protective immune response is unknown

# Summary of Anthrax Work Group Discussions

- ❑ Data on immune response support the co-administration of raxibacumab and AVA on the currently approved dose schedule
  - No data on immune response are available for co-administered raxibacumab and AVA on a dose-sparing schedule
- ❑ No data on immune response are available for co-administered obiltoxaximab and AVA on either a normal or dose-sparing schedule
- ❑ Data suggest that the co-administration of AIGIV and AVA significantly diminishes the immune response to AVA

## Anthrax Antitoxin Use for PEP

- ❑ In situations where no alternatives for PEP are available after exposure to *B. anthracis*, obiltoxaximab or raxibacumab may be considered to help prevent inhalation anthrax.
  - The predicted effectiveness of obiltoxaximab or raxibacumab are based solely on efficacy studies conducted in animal models of inhalation anthrax
- ❑ Data indicate that AVA can be co-administered with raxibacumab for PEP without impacting immunogenicity
  - Similar data are not currently available for obiltoxaximab. It is thus unknown if obiltoxaximab would impact the immunogenicity of AVA when co-administered
- ❑ AIGIV *does not* have an indication for PEP use, and the co-administration of AIGIV with anthrax vaccine has been shown to significantly reduce the development of protective immune response to AVA in a rabbit model.

# **DISCUSSION**