Nebulization of Antibodies Against Ricin Poisoning by Inhalation: Drug and Device Development

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CONTEXT & BACKGROUND

Castor beans also called Ricin is a toxin classified as a priority of biological agents by the French Defense Ministry. Ricin risk is mainly associated to aerosol diffusion. Vaccines showed limited efficacy to induce neutralizing antibody in a pulmonary ricin intoxication (Pincus S.H. et al., 2011), while the local delivery of recombinant neutralizing antibodies raised against the A subunit of ricin (Poi M.A. et al., 1996; Guo J. et al., 2006), such as the 49RCA antibody developed by IRBA (Pelat T. et al., 2009) led to animal survival up to 6 hours after intoxication. Thereby the antibodies represent a promising therapeutic approach and an alternative to the systemic route for the delivery of local-acting monovalent antibodies (Mabs). Recently, the CEPR (INSERM U1100/EA6005) in Tours, specialized in the aerosol delivery of drugs, has demonstrated the feasibility and the clinical interest of delivering antibodies through the airways as an aerosol to treat lung affections (Maillet A. et al., 2008; Maillet A. et al., 2011) and showed that mesh nebulizers are the most reliable devices to efficiently administer liquid formulations of Mabs into the lungs and limit formation of massive insoluble subvisible aggregates.

**Ricin: Biological toxin with high potential of bioterrorism**

- [Ricin] per beans 1 to 10 % (injection of 3 castor beans = death)
- Lethal dose in Human through inhalation: 1 to 10 µg/kg (10x lower than ingested ricin)

**Vaccines:** Limited efficiency if inhaled ricin

- Therapeutic approach proposed:
  - Aerosolization with neutralizing monoclonal antibody (lgG 43RCA, IRBA)
  - Local delivery of 43RCA protected mice against pulmonary intoxication to ricin

- Objective for treatment of 5 DSCI inhaled ricin > 4.5 mg of 43RCA in lung

PROJECT OBJECTIVES

1) To develop a drug formulation capable of maintaining the integrity and affinity of an anti-rinch antibody during aerosolization

2) To develop a new aerosol generating device able to administer 4.5 mg of antibody to the deep lung region.

**DEVICE DEVELOPMENT**

- Formulation
- Lyophilization
- Nebulization

**DRUG DEVELOPMENT**

- mAb formulation:
  - Frozen Anti-rinch mAb
  - PBS 1×: 15 mg/mL
  - Nebulizer:
  - VMD 4 µm
  - Alveolar deposition: 10 %

**Results/Aggregates**

- mAb 10 mg/mL; Histidine 25 mM; pH 5.8

**Requirements**

- Affinity formulation = affinity initial state
- Nebulization: Add Polysorbate 20

**In-vivo studies**

- No toxicity of the formulation
- Monkeys pulmonary deposition: 13 % ± 7 %
- mAb 10 mg/mL; Histidine 25 mM; pH 5.8; P502 10 %; NaC1 135 M

**Regulatory**

- Antibody reconstructive system
- Controller
- Face mask
- Nebulizer
- Inhalation chamber

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