Development of a drug and device for an efficient alveolar delivery of a neutralizing monoclonal antibody to treat pulmonary intoxication to ricin

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The high toxicity of ricin and its ease of production have made it a major bioterrorism threat worldwide. However there is no efficient and approved treatment for ricin inhalation poisoning, though major improvements have been made in terms of (ricin intoxication) diagnosis, and therapeutic strategies. We describe for the first time the development of an anti-ricin neutralizing monoclonal antibody (IgG 43RCA-G1) and a device allowing its rapid and effective delivery into the lungs for an application in humans. The antibody is a full-length IgG and bound to ricin A-chain subunit with a high affinity (KD=53 pM). Its local administration into the respiratory tract of mice 6 hours after ricin pulmonary intoxication allowed the rescue of 100% of intoxicated animals. Specific constraints for use in operational conditions and aerosolization stresses associated with protein aggregation and loss of activity were overcome by formulating the drug as a dry-powder that is solubilized extemporaneously in a stabilizing solution to be nebulized. Although regulatory studies are required, the inhalable formulation of IgG 43RCA-G1 did not induce any pulmonary inflammation in mice. A mesh nebulizer was customized to improve IgG 43RCA-G1 deposition into the alveolar region of human lungs, where ricin aerosol particles mainly accumulate. The drug & device also comprises a semi-automatic reconstitution system to facilitate its use and a unique holding chamber to maximize the aerosol delivery in the deep lung. *In vivo* studies in non-human primates showed that drug delivery with the device resulted in a high concentration of IgG 43RCA-G1 into the airways for at least 6 hours after local deposition, which is consistent with the therapeutic window, and in a limited passage into the bloodstream.
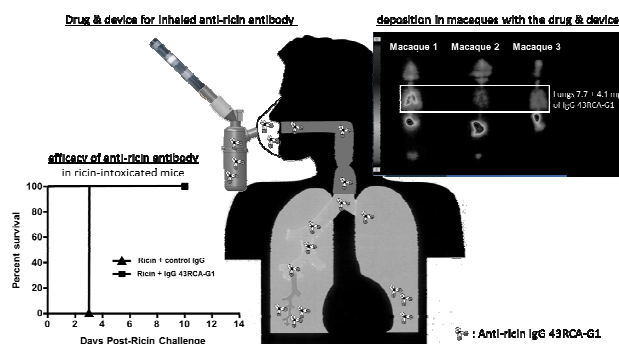

Figure 1. : Scheme of the development of a drug and device and the proof of concept principle for an anti-ricin mAb delivered by aerosol