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Title: *ASSESSMENT OF THE EFFICACY OF THERAPEUTIC ANTIBODIES AGAINST* ASPERGILLUS FUMIGATUS

Abstract :

Invasive pulmonary aspergillosis is an airborne infection caused by *Aspergillus* fungus. Its high mortality rates are in part due to the limits of the therapeutics. In contrast to antibiotics, the amount of antifungal drugs is very limited. Furthermore, they are expensive, and their use is associated with severe side effects. Therefore, new therapeutic approaches are expected. Therapeutic antibodies offer curative options in numerous diseases, since they are able to both neutralize / inhibit pathogen growth (*via* their Fab fragment) and to stimulate the immune response of the host (*via* their Fc fragment). However, there are currently only two approved therapeutic antibodies in the field of infectious diseases: palivizumab prescribed to prevent severe outcomes caused by respiratory syncytial virus in newborns, and raxibacumab directed against the anthrax toxin. Many others are under development.

A surface antigen has been recently characterized on the cell wall of *A. fumigatus*, which is the most virulent species among the genus *Aspergillus*. This antigen plays a catalytic role in the biosynthesis and the remodelling of growing filaments. So, it could represent a new therapeutic target for anti-*Aspergillus* antibodies.

Several Single-Chain Fragments Variables (scFvs) directed towards this target have been generated by phage display. They are able to bind to the antigen with a high affinity. Thereafter, they have been conjugated to an Fc domain of IgG_1 (scFv-Fc).

Thus, the main purposes of this work will are:

1. describing the immunological response during aspergillosis, in order to explain the mechanisms of action of the antibodies-based constructions;
2. assessing the *in vitro* activity of the antibodies-based constructions against *A. fumigatus* conidia and hyphae by microbiological tests;
3. evaluating the pharmacological activity of the most interesting antibodies-based constructions in animals. A rat model of invasive pulmonary aspergillosis, already available within the research team, will be used in this purpose. Regarding the delivery route, the airways appear as a relevant non-invasive alternative to the conventional intravenous route, enabling a massive, rapid and sustainable delivery of the biologics directly to the site of pulmonary aspergillosis. Their efficacy will be appreciated upon clinical criteria (survival rate) and biological findings (serological biomarkers, histology, PCR …) which are objective outcomes. The pharmacokinetics and biodistribution of antibodies-based constructions will also be investigated by the means of *in vivo* imaging.

This preclinical study should support a proof of concept of the efficacy of antibody-based therapeutics to treat *Aspergillus fumigatus*. If the results are interesting enough, a patent will be deposited.