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Development of novel radiopharmaceuticals to combat invasive fungal infections

In Canada, there were over half-a-million cases of serious fungal infections diagnosed in 2017. However, there is a low number of medications available for mycoses. Therefore, the need for a low toxicity, high efficient and low resistibility therapy is highly apparent. Radioimmunotherapy (RIT) utilizes antigen-antibody interaction to deliver lethal doses of ionizing radiation to cells. FDA, Health Canada and European regulatory authorities have approved this therapeutic modality for treatment of different cancer types. Our laboratory is interested in targeting invasive fungal infections, such as Blastomyces dermatitidis which affects both human and companion dogs using RIT. To achieve this, we initially compared the binding ability of radiolabeled antibodies to fungal beta-glucan and to fungal heat shock protein 60 (HSP60) antibody to the less invasive Cryptococcus neoformans. Our results show that antibodies that targeted beta-glucan had significantly higher binding capability. Therefore, the antibody to beta-glucan was chosen for further development into the RIT reagent against B. dermatitidis. For this purpose, we have set forward two objectives. Our first objective was the in vitro evaluation of the efficacy of the antibody to beta-glucans armed with alpha-particles emitting radionuclide 213Bismuth in killing B. dermatitidis cells. For this, B. dermatitidis cells were cultured, then exposed to alpha-RIT. The percentage of cell death was calculated by determining the colony forming units (CFU). Our second objective is the in vivo evaluation of the efficacy and long term toxicity of the RIT in mice infected with B. dermatitidis. Our in vivo experiments will be conducted by infecting the lungs of the mice with B. dermatitidis by intranasal intubation. The infected mice will be treated with 213Bi-labeled antibody to beta-glucans and the residual infections load in their lungs will be analyzed after 1 week. If the treatment is successful and safe, our next step in the project will be a clinical trial in companion dogs infected with B. dermatitidis.

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