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**Development of a CF, IL-8/NF-KB transgenic mouse model for the in vivo long-term monitoring of the inflammatory response induced by bacteria treated or not with azithromycin**

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**Background.** The possibility of monitoring the inflammatory response in a IL-8 transgenic WT and CF non invasive animal model has been demonstrated in this project. Experimental support has been provided for the proposal that azithromycin (AZM) acts by inhibiting the synthesis of bacterial metalloproteases (MPs) thus causing a mitigation of the lung inflammation. The possibility of further take advantage of the CF mouse model to analyze the possible anti-inflammatory activity of other antibiotics with mechanism of action similar to that of AZM and that of inhibitors of human metallo-proteases appears of high interest.

**Objectives and Methods.** The objectives of this new part of the project are i) to use the IL-8 transgenic CF mouse model to monitoring the expected significant reduction of the pro-inflammatory response induced by Pseudomonas MPs by using protease inhibitors such as Galardin and other approved drugs for human use, namely Marimastat and the antibiotic Doxycycline and ii) to analyze the possible anti-inflammatory activity of other antibiotics with mechanism of action similar to that of AZM and used in CF such as claritromycin (CLAR) and tobramycin (TOB).

To this end, our main action will be 1) to perform preliminary tests to evaluate the activity of inhibitors of human proteases ((Galardin, Marimastat, doxycycline) on bacterial metallo-proteases and to calculate sub-lethal doses of tobramycin and claritromycin to treat P. aeruginosa; 2) to prepare culture supernatants from Pseudomonas grown with and without the selected drugs and 3) to instillate the prepared Sns in WT and CF transgenic mice and monitoring the inflammatory response by measuring BIL in mouse lungs.

**Expected results and their significance** 1) Further knowledge on the mechanism of action of a number of drugs and on the role of bacterial products in the inflammatory response in CF: antibiotic treatment personalized for the specific patients, design of new therapeutic molecules against targeted bacterial products; 2) The transgenized IL-8, CF mouse model will be further validated. This might reveals an interesting tool to the monitoring of the inflammatory process in CF induced by infective and non-infective causes and to test in vivo the antibacterial/anti-inflammatory effect of candidate molecules to be used in cystic fibrosis.

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