New bioluminescent preclinical infection mouse models using recently isolated strain of multi drug resistant KAPE bacteria.

Authors: Marc VANDAMME[1], Christian KEMMER[2], Vincent TREBOSC[2], Birgit SCHELLHORN[2], Julia MATONTI[3], Emmanuel CHEREUL[1]

[1] VOXCAN, 1305 route de Lozanne, 69380 DOMMARTIN, France
[2] BIOVERSYS Technologiepark, Hochbergerstrasse 60c, 4057 BASEL, Switzerland
[3] ERBC, Chemin de Montifault, 18800 BAUGY, France

Antimicrobial resistance is of increasing concern, with the rise in drug resistant pathogens causing life-threatening infections that are difficult to treat. Screening of molecules on predictive animal models using recently isolated bacteria provide a tool for the development of new antimicrobials.

Main objective of this project was to develop bioluminescent mouse models of various pathology with drug-resistant KAPE bacteria strains (*Acinetobacter baumannii – ABA; Escherichia coli - EC; Pseudomonas aeruginosa - PAO; Klebsiella pneumoniae - KP*) to allow *in vivo* drug candidate evaluation.

Partnerships were established with various Hospitals to obtain patient isolates of KAPE bacteria. These bacteria were characterized to assess their antibiotic resistance profile and kinetic growth curves. Strain virulence was assessed *in vivo* at the biological niche relevant for the infection model and a suitable strain was selected for model development.

The selected bacterial strains were genetically engineered to constitutively express luciferase, allowing monitoring of infection progression via bioluminescence in animals. Engineered pathogenic bacteria were characterized *in vitro* and no fitness costs of the stable luciferase expression or reduction of bioluminescent expression was observed after serial passages.

Theses bioluminescent strains were evaluated in mice to obtain the most relevant model by testing different administration routes and mouse strains. Neutropenic mouse models presented the best infection rate and growth kinetics as compared to infection in immunocompromised mice (nude mice). A significant increase of ~2-log of bioluminescence signal with respect to the background was obtained for all models with an increase of the luminescence in the infected area in correlation with the clinical signs. To validate the models, the infection response to a reference antibiotic was monitored by bioluminescence and demonstrated that reduction of bioluminescence correlated with diminished bacterial loads determined by CFU counts.

Finally, 6 different bioluminescent infection mouse models (sepsis models with ABA, EC and PAO; lung models with ABA, KP and PAO) were developed and characterize. Such models enable us to perform screening campaigns for new antibacterial drug by real-time monitoring of infection development using bacterial bioluminescence.

The research project “IMAPCT2 AMR” has received funding from European Union through Eurostar program under grant agreement no. 12589.