1. PHD PROJECT DESCRIPTION (4000 characters max., including the aims and work plan)

Project title: Pharmacokinetic-pharmacodynamic modeling of cefuroxime in foal sepsis

1.1. Project goals

The main project goal is to propose guidelines for the treatment of foal sepsis. This will be achieved thanks to the realization of specific research goals:

- characterization of the etiological factors of foal sepsis in Poland;

- establishing pharmacokinetic parameters for cefuroxime in foals after i.v. administration;

- PK/PD modeling using the obtained data;

- verification of the utility of procalcitonin as the marker for termination of antimicrobial treatment.

1.2. Outline

Foal sepsis is a relatively common life-threatening disease. Its etiological factors have never been described in the Polish population. Because of that, empirical treatment may not be effective enough. The intravenous administration of wide-spectrum antimicrobials, e.g. cephalosporines is necessary but for some of them, efficiency has not been proven with PK/PD approach. There are no validated biomarkers warranting the end of treatment, in contrast to human sepsis, where procalcitonin is such a biomarker.

1.3. Work plan

- Characterization of the etiological factors of foal sepsis in Poland

Blood samples will be collected from clinical cases of foal sepsis. After the culturing, antimicrobial sensitivity testing (AST) will be performed using disc diffusion/ microdilution approach. MIC values will be determined whnever possible (at least for cefuroxime). The local antibiogram will be developed.

- Establishing pharmacokinetic parameters for cefuroxime in foals after i.v. administration

The animal experiment will be performed on both healthy and septic foals to study the pharmacokinetics of cefuroxime after its i.v. administration. The drug concentration in plasma will be determined using HPLC. PK parameters will be set, including volume of distribution, clearance, plasma protein binding, half-life of elimination, etc.

- PK/PD modeling using the obtained data

Using data from previous tasks, PK/PD modeling will be performed to establish PK/PD cut-offs and clinical breakpoints for cefuroxime against different bacteria in foals.

- Verification of time of termination of antimicrobial treatment using biomarkers

Procalcitonin and other potential protein biomarkers will be measured throughout the treatment to verify how their concentrations correlate with clinical condition.

1.4. Literature *(max. 10 listed, as a suggestion for a PhD candidate)*

- Bonelli F, Meucci V, Divers T, Radcliffe R, Jose-Cunilleras E, Corazza M, Guidi G, Tognetti R, Castagnetti C, Intorre L, Sgorbini M: Evaluation of Plasma Procalcitonin Concentrations in Healthy Foals and Foals Affected by Septic Systemic Inflammatory Response Syndrome. Journal of Equine Veterinary Science 2015, 35, 645-649. https://doi.org/10.1016/j.jevs.2015.06.007
- Lee DH, Birhanu BT, Lee EB, Lee SJ, Boby N, Park YS, Park SC: Pharmacokinetic and pharmacodynamic integration for optimal dosage of cefquinome against Streptococcus equi subsp. equi in foals. Veterinary Research 2020, 51,131. https://doi.org/10.1186/s13567-020-00853-2
- McNeal CD, Ryan CA, Berghaus LJ, Credille BC, Lo C-P, Fajt VR: Plasma disposition of ceftazidime in healthy neonatal foals following intravenous and intramuscular administration. Journal of Veterinary Pharmacology and Therapeutics 2021, 44, 560-567. https://doi.org/10.1111/jvp.12947
- Schuetz P, Bretscher C, Bernasconi L, Mueller B: Overview of procalcitonin assays and procalcitonin-guided protocols for the management of patients with infections and sepsis. Expert Review of Molecular Diagnostics 2017, 17, 593-601. https://doi.org/10.1080/14737159.2017.1324299
- Theelen MJP, Wilson WD, Byrne BA, Edman JM, Kass PH, Magdesian KG: Initial antimicrobial treatment of foals with sepsis: Do our choices make a difference? The Veterinary Journal 2019, 243, 74-76. https://doi.org/10.1016/j.tvjl.2018.11.012
- Theelen MJP, Wilson WD, Edman JM, Magdesian KG, Kass PH: Temporal trends in in vitro antimicrobial susceptibility patterns of bacteria isolated from foals with sepsis: 1979–2010. Equine Veterinary Journal 2014, 46, 161-168. https://doi.org/10.1111/evj.12130
- Toutain P-L, Bousquet-Mélou A, Damborg P, Ferran AA, Mevius D, Pelligand L, Veldman KT, Lees P: En Route towards European Clinical Breakpoints for Veterinary Antimicrobial Susceptibility Testing: A Position Paper Explaining the VetCAST Approach. Frontiers in Microbiology 2017, 8, 2344. https://doi.org/10.3389/fmicb.2017.02344

1.5. Required initial knowledge and skills of the PhD candidate

- Basic laboratory skills
- Background in veterinary, pharmacy, or related field
- Critical thinking
- English, at least B2
- Experience in research
- Interest in clinical microbiology and pharmacology

1.6. Expected development of the PhD candidate's knowledge and skills

- Veterinary clinical microbiology (bacterial culturing, antimicrobial sensitivity testing,

interpretation of results in regard to patient's clinical condition)

- Analytical chemistry, including LC-MS/MS and its application in PK studies
- Pharmacokinetic data analyses, including specialistic software
- PK/PD modeling
- Design of animal experiments
- Presentation of results in written (scientific journals) and oral form (scientific congresses)