Petraitis Lab

Pre-clinical models

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The primary objective of Dr. Petraitis lab is to advance, explore, and apply state-of-the-art technologies in the development of novel immunotherapeutics, antimicrobial agents, and molecular detection systems. The focus is on diagnosing, treating, and preventing life-threatening infections through translational research that bridges the gap between experimental findings and practical application.

1. Preclinical models:

Pre-clinical animal models, including rabbit models, play a significant role in the research and development (R&D) of new medications. Rabbits are commonly used in pre-clinical studies due to their physiological and anatomical similarities to humans in certain aspects. Here are some key reasons why pre-clinical rabbit models are important in the R&D of new medications:

- Pharmacokinetics and bioavailability: Rabbit models help researchers understand how drugs are processed in the body, including absorption and distribution.
- Safety evaluation: Rabbits are used to assess the safety and potential adverse effects of medications on various organ systems.
- Infectious disease research: Rabbits mimic human infections, enabling the evaluation of antimicrobial agents or vaccines.
- Wound healing and tissue regeneration: Rabbits help assess the effects of medications on wound closure and tissue repair.
- Drug-device interaction: Rabbits are employed to study the interaction between medications and medical devices, optimizing drug delivery systems.

Advantages of using rabbit preclinical models:

The use of rabbit preclinical models offers several benefits in biomedical research and drug development. Here are some key advantages of utilizing rabbit models:

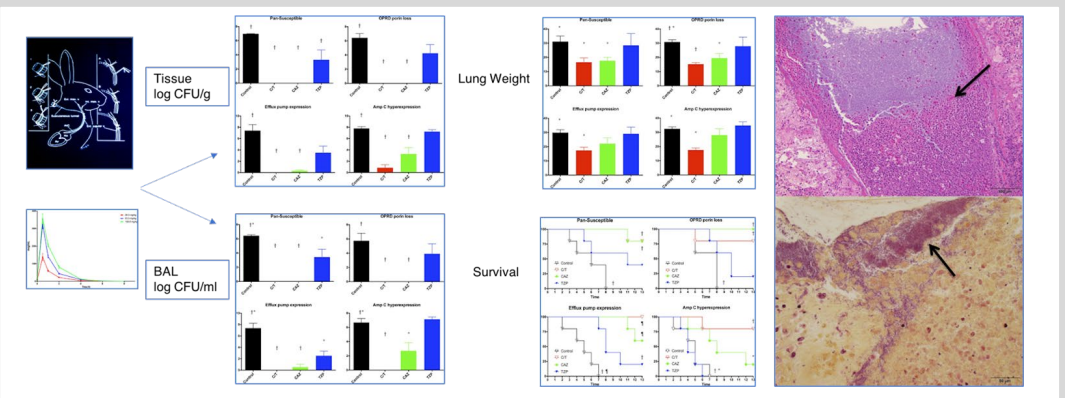
- Anatomical and physiological similarity: Rabbits resemble humans in their cardiovascular, respiratory, digestive, and immune systems, aiding in studying diseases and drug responses.
- Size and ease of handling.
- Similarities in anatomical features and physiological features between humans making studies preclinically relevant. E.g.
- Surgical and interventional studies
- Allergy and hypersensitivity testing
- Skin-related studies
- Immunogenicity and immunological studies
- Metabolism and pharmacokinetics
- Ophthalmic and regenerative studies
- Toxicology and safety testing: Larger size enables comprehensive safety assessments, including acute and chronic toxicity.
- Easy regulatory acceptance.

2. Available models:

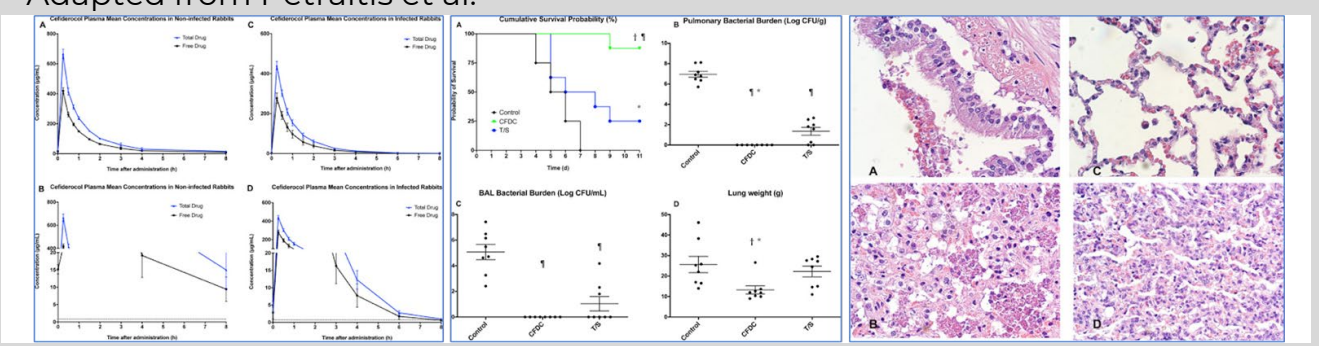
Over the course of the past three decades, our research laboratory at the National Institutes of Health (NIH), Weill Cornell Medicine, and the Center for Discovery Innovation (CDI) have made substantial advancements in the realm of scientific inquiry by successfully creating and refining approximately 30 pre-clinical animal models. Below we would like to demonstrate a select assortment of these models, delineating their notable features and elucidating their pivotal role in the domain of biomedical research.

Infectious diseases models

A. Persistently neutropenic rabbit models of bacterial pneumonia caused by multidrug resistant organisms including:
Carbapenemase producing *Klebsiella pneumoniae* (KPC-1; blakpc)
ESBL (CTX-M)-producing *Klebsiella pneumoniae*
Amp-producing *Enterobacter cloacae*
Multidrug resistant *Acinetobeacter baumannii*
Multidrug resistant and Pan-susceptible *Pseudomonas aeruginosa*
Stenotrophomonas maltophilia



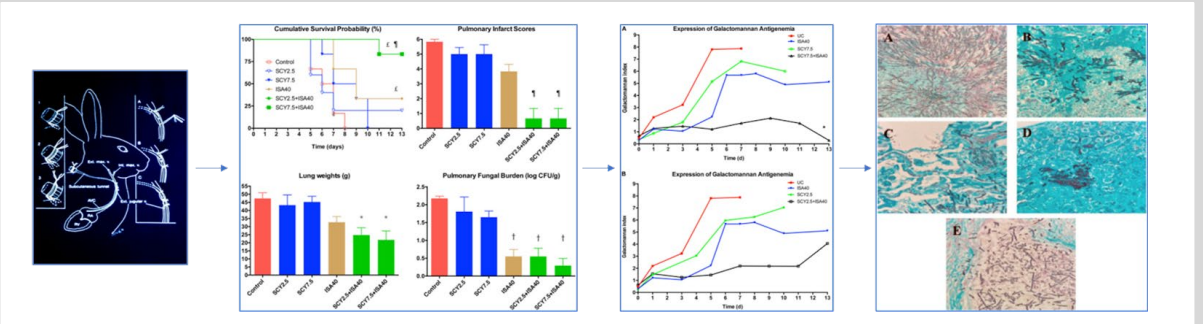
Schematic shows experimental bacterial pneumonia caused by MDR *Pseudomonas aeruginosa* with genetically defined mechanisms of resistance treated with ceftolozane-tazobactam (C/T), ceftazidime (CAZ), or piperacillin-tazobactam (TZP). Adapted from Petraitis et al.



Schematic shows response of *Stenotrophomonas maltophilia* pneumonia in persistently neutropenic rabbits to treatment with cefiderocol (CFDC) and trimethoprim-sulfamethoxazole (T/S). Adapted from Petraitis et al.

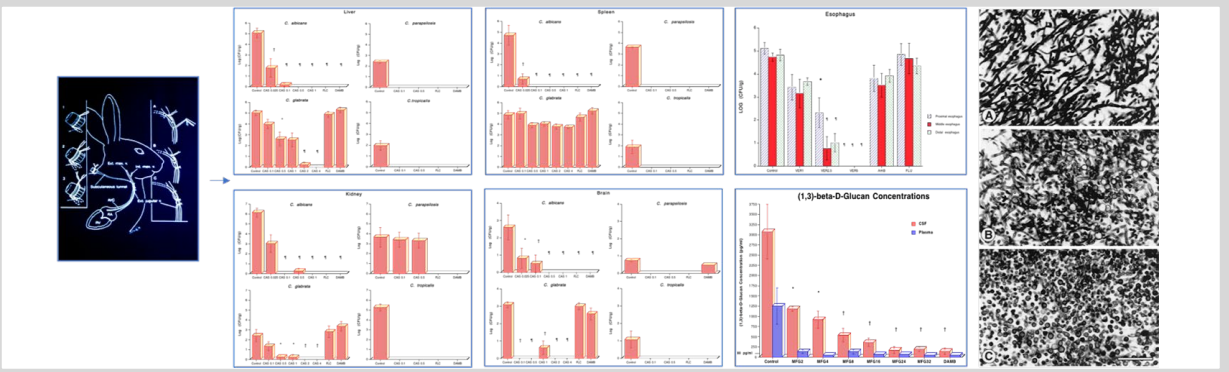
B. Animal models of Invasive Fungal Infections:

B1. Persitently neutropenic rabbit models of pulmonary Aspergillosis, Mucormycosis, Fusariosis, Scedosporiosis.



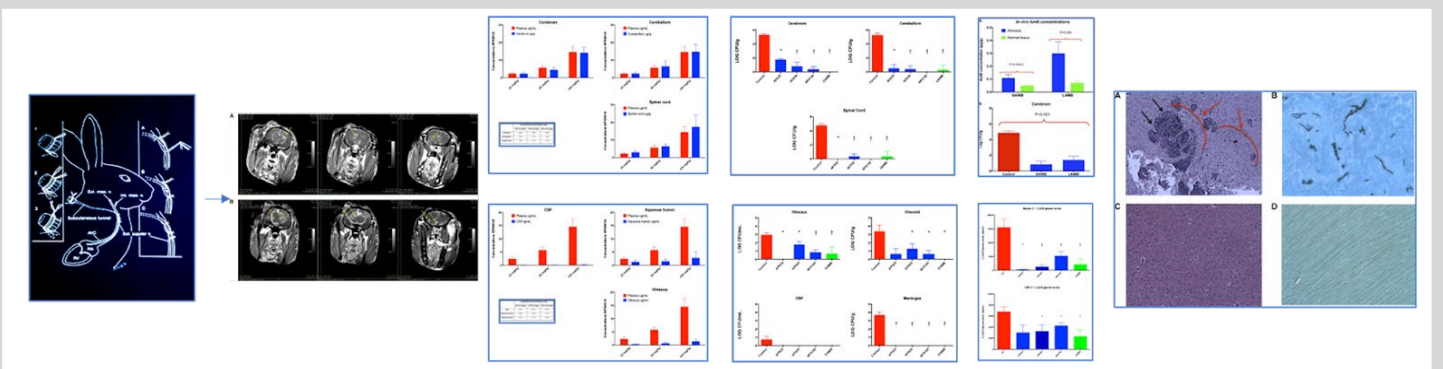
Demonstration of response of primary pulmonary aspergillosis in persistently neutropenic rabbits to antifungal therapy receiving ibrexafungerp alone or in combination with oral isavuconazole. Adapted from Petraitis et al.

B2. Persistently neutropenic rabbit models of disseminated *Candida* and *Fusarium* infections.



Schematic shows disseminated candidiasis model in persistently neutropenic rabbits including caused by: *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*. Adapted from Petraitiene et al.

B3. Hematogenous Candida meningoencephalitis



Demonstration of efficacy and pharmacokinetics in the treatment of *Candida* endophthalmitis and hematogenous meningoencephalitis in nonneutropenic rabbit model. Adapted from Petraitiene et al and Petraitis et al.

3. Outcomes and endpoints measured

We use comprehensive approach to assess, evaluate, analyze, and understand *in vivo* outcome variables.

3a. Pharmacokinetics

- Central silastic venous catheter permits multiple serum or plasma samples from same animal to generate concentration time curves at first infusion, steady, and last dose with wash out
- Robust PK can be established in infected and non-infected animals
- Variation of dosing regimen can establish full PK/PD profiles in murine and rabbit models
- Intrapulmonary PK of distribution of study drug in following compartments: ELF, Pulmonary alveolar macrophages, PMNs, whole lung and other tissues.
- Applying state-of-the-art advanced techniques by integrating laser capture microdissection (LCM) with liquid chromatography/mass spectrometry (LC/MS) analysis, we can achieve precise measurement of drug levels in specific cells or tissues, providing valuable insights into the drug's distribution, metabolism, and pharmacokinetics within the animal model.
- For more details refer to the link.

3b. *In vivo* Therapeutic endpoints

- Residual organism burden (Quantitative cultures of tissue)
- Quantitative cultures of BAL fluid
- Serial quantitative blood cultures
- Time to resolution of bacteremia
- Histology
- Survival
- Vascular catheter-related mycological studies
    - Quantitative cultures
    - Confocal microscopy
    - Scanning electron microscopy
    - Gene expression profiles

3c. Fungal and bacterial Biomarkers

- Time to resolution of qPCR signal for circulating genomic DNA of organism
- Serial quantitative qPCR signals for circulating genomic DNA of organism
- Galactomannan: serum and BAL fluid
- (l-»3)-b-D-glucan: serum, CSF