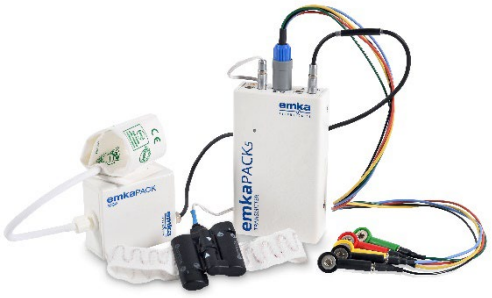
ENHANCING PRECLINICAL COVID-19 SAFETY AND EFFICACY STUDIES WITH THE emkaPACK

The COVID-19 pandemic has emphasized the critical need for rapid development and validation of effective treatments and vaccines.

Advanced monitoring technologies, such as emkaPACK, play a crucial role in preclinical safety pharmacology and toxicology studies, ensuring the safety and efficacy of new therapeutics.

This application note reviews the significant contributions of emkaPACK in the research and development of Olgotrelvir, the ZF2001 vaccine, and nebulized SARS-CoV-2 neutralizing antibodies.



1. CASE STUDY 1: OLGOTRELVIR IN COVID-19 TREATMENT

Background

This study by Mao *et al* (2024) investigates Olgotrelvir (STI-1558), a promising oral antiviral candidate for COVID-19. Olgotrelvir was designed to address challenges such as viral rebound, drug-drug interactions, and emerging resistance. It inhibits SARS-CoV-2 main protease (Mpro) and human cathepsin L (CTSL), essential for viral replication and entry into host cells, respectively.

Efficacy

- ***In Vitro* and *In Vivo* Studies:** Olgotrelvir's active form, AC1115, demonstrated potent inhibition of viral replication across various SARS-CoV-2 variants. Animal models, particularly the K18-hACE2 transgenic mouse model, showed significant reductions in lung viral loads and prevention of weight loss and lung pathology.

- **Human Studies:** Phase I clinical trials highlighted olgotrelvir's favorable safety profile, effective antiviral activity, and high oral bioavailability without the need for ritonavir, enhancing its potential as a standalone treatment.

Safety Pharmacology

- **Cardiovascular Studies in Beagle Dogs:** emkaPACK telemetry was employed to monitor cardiovascular parameters in a study involving eight beagle dogs. The dogs received single oral doses of olgotrelvir in a 4x4 Latin Square design, with thorough monitoring of clinical signs, body weight, and cardiovascular metrics such as MBP, SBP, DBP, PR, QRS, RR, QT, HR, and QTcv.

- **Findings:** The telemetry data collected via emkaPACK revealed that olgotrelvir was well-tolerated, with no significant adverse cardiovascular effects. This underscores the importance of advanced telemetry systems in ensuring drug safety in preclinical studies.

General Toxicology Studies

Systematic studies indicated that olgotrelvir is tolerable at high doses in rats and beagle dogs. Minimal and reversible changes in organs were observed, deemed non-adverse and with low human risk.

Conclusion

Olgotrelvir's dual inhibitory action and high efficacy against SARS-CoV-2 variants position it as a significant advancement in COVID-19 treatment.

2. CASE STUDY 2: ZF2001 COVID-19 VACCINE IN CYNOMOLGUS MONKEYS

Background

ZF2001, a recombinant protein vaccine, targets the SARS-CoV-2 receptor-binding domain (RBD) and includes an aluminum adjuvant. It has shown strong potential in preclinical studies. This study by Yang *et al* (2022) evaluated the general toxicity and immunogenicity of ZF2001 in cynomolgus monkeys, involving four intramuscular injections. emkaPACK monitored cardiovascular, respiratory, and body temperature parameters, providing continuous and accurate data collection.

Safety Pharmacology Study with emkaPACK

- **Methodology:** emkaPACK's non-invasive physiological signal telemetry system enabled the collection and transmission of telemetry physiological signals, allowing the monkeys to remain unrestrained and freely mobile. This reduced stress and provided accurate physiological data.

- **Findings:** The study found no significant systemic toxicities or abnormal cardiovascular and respiratory events following ZF2001 vaccinations. Importantly, no toxic target organs were identified, and there were no signs of immunotoxicity or systemic toxicity, even with repeated dosing.

Immunogenicity

ZF2001 demonstrated strong immunogenicity, producing specific binding and neutralizing antibodies in the monkeys. The vaccine activated cellular immune responses, indicated by increased levels of IL-12, IFN-γ, and IL-4 in splenic lymphocytes, evidencing a balanced Th1/Th2 immune response.

Antibody-Dependent Enhancement (ADE) and Vaccine-Enhanced Disease (VED)

The study addressed concerns about ADE and VED, which have been problematic with other coronavirus vaccines. ZF2001 did not induce Th2 cell hypersensitivity or imbalance, reducing the risk of ADE and VED. This was corroborated by clinical trials showing low ADE and VED risk in humans.

Conclusion

The preclinical evaluation of ZF2001 in cynomolgus monkeys demonstrated its safety and strong immunogenicity, supporting its progression to large-scale clinical trials.

3. CASE STUDY 3: NEBULIZED SARS-COV-2 NEUTRALIZING ANTIBODY

Background

The study by Jia *et al* (2022) investigated the feasibility of delivering SARS-CoV-2 neutralizing antibodies directly to the respiratory tract through nebulization to enhance antiviral efficacy. The research focused on HB27, a potent receptor-binding domain (RBD)-specific humanized monoclonal antibody. emkaPACK monitored respiratory minute volume (RMV) and other physiological responses, ensuring accurate and non-invasive data collection during inhalation studies.

Safety Pharmacology and Toxicology

- **Mice Studies:** At a single 5 mg/kg dose, the peak concentration of HB27 in mice pulmonary epithelial lining fluid (ELF) reached 857.8 µg/mL, maintaining levels above the PRNT90 value for over 240 hours. Intravenous administration at the same dose resulted in ELF antibody concentrations below the PRNT90 value.
- **Cynomolgus Monkey Studies:** Inhalation of a single 10 mg/kg dose resulted in high ELF antibody concentrations that remained elevated for three days. No drug-related safety concerns were observed, indicating a favorable safety profile for the inhalation method.

Conclusion

The feasibility study of nebulized SARS-CoV-2 neutralizing antibody delivery in mice and cynomolgus monkeys demonstrated significant advantages over traditional intravenous methods. The findings advocate for further preclinical development and clinical trials to validate this approach.

4. SUMMARY

emkaPACK has significantly contributed to advancing COVID-19 research by providing precise and reliable data in safety pharmacology and toxicology studies. Its application in monitoring Olgotrelvir, ZF2001 vaccine, and nebulized antibodies underscores its versatility and critical role in preclinical testing. As research progresses, emkaPACK will continue to be an invaluable tool in developing safe and effective treatments for global health crises.

REFERENCES

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