

STRIDE



STRATEGIC RSV INTERVENTION DEVELOPMENT ENTITY

HRSV BACKGROUND – UNMET CLINICAL NEEDS

HRSV is the most common cause of lower respiratory tract infections among young children worldwide with also a major impact on elderly and immunocompromised individuals. HRSV infections occur mostly in yearly winter epidemic outbreaks. It is highly contagious and spreads through droplets upon coughing or sneezing. Approximately 33.8 million episodes of HRSV-associated acute lower respiratory infections occur in children worldwide every year. HRSV infection causes a worldwide burden of morbidity and mortality and has been presented as the second main cause of death during infancy.

It is estimated that 53.000 to 199.000 HRSV-related deaths happen per year, of which 99% occur in developing countries. In Europe and the US, on average 1% of children in their 1st year of life are hospitalized with a severe infection. In Europe, HRSV accounts for 42-45% of hospital admissions for lower respiratory tract infections in children under 2. Besides being a severe acute disease, HRSV infection has been linked to increased risk of the development of asthma in later life.

HRSV is a complex public health problem. The level of clinical, industrial and public interest is only becoming proportionate to the magnitude of the problem. There are currently no vaccine approaches and prophylaxis is largely limited to passive immunisation with palivizumab^(1,2). An unmet need exists for more effective intervention strategies for HRSV infections, including long-term development strategies for candidate HRSV (i) vaccines, (ii) immunoprophylactic, compounds, including biosimilars for palivizumab, and (iii) antivirals.

1. Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. Mazur NI, et al., *Respiratory Syncytial Virus Network (ReSViNET)*. *Lancet Respir Med*. 2015 Nov;3(11)
2. Challenges and opportunities in RSV vaccine development: Meeting report from FDA/NIH workshop. Roberts JN, et al., *Vaccine*. 2016 Sep 22;34(41):4843-9
3. Ferrets as a Novel Animal Model for Studying Human Respiratory Syncytial Virus Infections in Immunocompetent and Immunocompromised Hosts. Stittelaar KJ, et al., *Viruses*. 2016 Jun 14;8(6).

DEVELOPMENT OF AN ENTITY FOR HRSV INTERVENTION STRATEGIES

It is time to challenge the current dogma of how biopharmaceutical companies are engaging CRO's and consultants. Ad hoc vendor selection to address important questions during the product development lifecycle may lead to an unnecessarily fragmented and disconnected approach to R&D. There is an opportunity to offer more **value** to clients by combining expertise into integrated project teams, dedicated to realizing **accelerated** preclinical and clinical development of drugs, biologicals, vaccines and diagnostics targeting viral infectious diseases. To this end the following groups have decided to create **STRIDE**, a highly interactive and collaborating entity, that covers **all R&D** activities that will bring **novel** ideas for HRSV intervention strategies in an **integrated** way from basic scientific discoveries, via preclinical and clinical studies to clinical use.

1

University of Veterinary Medicine Hannover/Research Center for Emerging Infections and Zoonoses (TiHo/RIZ)

is a recently established cutting-edge research institute, at the University of Veterinary Medicine Hannover, that undertakes fundamental and applied multi-disciplinary research on infectious diseases to improve human, animal and ecosystem health, thereby promoting the 'One Health approach'. Researchers of several disciplines like; Virology, Immunology, Microbiology, Parasitology and Food science collaborate in TiHo-RIZ to create a unique symbiosis



Prof. A.D.M.E. Osterhaus
PhD, DVM

Director

albert.osterhaus@tiho-hannover.de



www.tiho-hannover.de

2

Viroclinics Biosciences (VCB)

operates at a global level and is the preferred virology testing laboratory for several of the top 10 biopharmaceutical companies. Viroclinics' mission is to improve human and animal health by serving the biopharmaceutical community with state-of-the-art diagnostics, custom-made models in (pre)clinical drug testing and expert advice on development of antivirals and vaccines.



Koert Stittelaar
PhD

Director Preclinical Services

stittelaar@viroclinics.com



www.viroclinics.com

3

Clinical Research Rotterdam (CR²O)

is a full service CRO focusing on managing and operating clinical early stage clinical trials for vaccine-, drug-, and diagnostics development by industry and public organizations. CR²O maintains trusted partnerships with leading clinics and research centers in Europe. The unique synergy between CR²O's early stage clinical trial services and Viroclinics' operational virology capability, combined with access to an extensive network of external key advisors creates a powerful, all-inclusive early stage service platform.



Hadil Es-Sbai
MSc.

Chief Executive Officer

hadil.es-sbai@cr2o.nl



www.cr2o.nl

4

Julius Clinical

is a unique Scientific Clinical research organization (Science CRO) that combines strong scientific leadership and operational excellence to conduct innovative national and global clinical trials. The Julius Clinical approach fosters a working relationship where Investigators possess a deep commitment to reviewing operational issues raised by their academic peers versus the site interaction approach employed by conventional CROs. For this reason, Julius Clinical gains entry to high performing sites and access hospital staff adept at managing clinical studies involving high complexity and large volumes of subjects.



Leyla Kragten-Tabatabaie
PhD

Scientific Network Manager

leyla.kragten@juliusclinical.com



www.juliusclinical.com



One of the basic research programs TiHo-RIZ focuses on contributions to the development of intervention strategies for HRSV infections, by conducting state-of-the-art molecular, *in vitro*, and *ex vivo* studies. This basic research is performed in close collaboration with consortium partner VCB, that is closely involved in their *in vivo* ferret studies and in laboratory evaluation studies of clinical trials.

TiHo-RIZ research activities in this field have resulted in a large collection of HRSV related assays and reagents, including:

- Deep sequencing and analysis of patient samples (and virus isolates)
- Virus isolation from clinical specimens
- Complete minigenome systems for HRSV A and B
- Reverse genetics system for wild-type HRSV B
- recombinant HRSV B expressing EGFP
- recombinant HRSV B expressing dTOM
- Next generation reverse genetics system under development for HRSV A
- Virus titration and qPCR on human/animal model samples
- Novel *ex vivo* model systems
- Novel *in vivo* model systems⁽³⁾

These HRSV related assays and reagents form the basis for the evaluation of intervention strategies that are under pre-clinical and clinical evaluation.

Animal models are indispensable for evaluating novel intervention strategies in complex patient population that is affected seriously by HRSV infection. Available models at VCB are shown in the Table. To complement existing models in rodents and non-human primates, we have evaluated the potential benefits of an HRSV infection model in ferrets (*Mustela putorius furo*). Ferrets can be productively infected with HRSV. In addition, immunocompromised ferrets are more susceptible and show, like immunocompromised patients, increased viral loads and prolonged virus shedding⁽³⁾. These animal models can contribute to the assessment of the efficacy and safety of novel HRSV intervention strategies. Although HRSV is unstable, it can maintain its infectivity for several hours and can be transmitted through droplets and direct contact. Factors that contribute to spread of the virus remain elusive. None of the existing animal models are suitable for studying transmission of HRSV. The HRSV ferret model can be used to study the contribution of host and viral factors to the transmission of HRSV and to evaluate strategies for prevention and control of nosocomial transmission.

Species	Immunogenicity	Efficacy	Pros.
Cynomolgus macaques	✓	✓	Read-out atypical dis.
Ferrets: - Immunocompr. - New borns	✓	✓✓*	Practical transmission
Guinea pigs	✓	✓	Maternal immunization
Cotton rats	✓	✓	Atypical dis. sensitive
Mice	✓	✓	Read-out

* Antivirals

Table: Animal models operational at VCB in collaboration with TiHo-RIZ .

3. Ferrets as a Novel Animal Model for Studying Human Respiratory Syncytial Virus Infections in Immunocompetent and Immunocompromised Hosts. Stittelaar KJ, et al., Viruses. 2016 Jun 14;8(6).

VCB operates at a global level and is the preferred virology testing laboratory for several of the top 10 biopharmaceutical companies as an expert virology CRO for clinical virology sample analysis and operational services.

VCB provides clinical virology diagnostics, for example high throughput RSV primary assays such as:

- qPCR
- Virus titration and qPCR on human samples
- VNA's.
- antiviral resistance monitoring
- RSV phenotyping to determine EC50/EC90 and identify resistant minority variants
- genotypic assays (Sanger sequencing / NGS for minority variants)
- stability and cold chain solutions for HRSV

To achieve the most optimal virology results, we offer all the operational and logistical services involved in RSV virology sample handling. This includes manufacture and supply of customized RSV sampling kits, optimal cold chain and courier logistics, and an on line help desk for all virology operational and logistical sample reconciliations.



CR²O specializes in managing and operating phase I and II clinical trials, while Julius Clinical has a long and esteemed track record with conduct of innovative national and global phase II and III clinical trials. Together, we combine scientific leadership with industrial efficiency, while ensuring regulatory requirements are incorporated at the trial design stage.

Julius Clinical provides academic leadership through its RSV network (ReSViNET) using its extensive RSV expertise and the Peer-to-Peer Leadership model. The Peer-to-Peer Leadership model will offer constructive support for the (ReSViNET) sites to complement the routine operational management of sponsors team and CRO and will support sponsor to enhance the successful realization of the trials focusing mainly on boosting patient recruitment and retention. ReSViNET is a global network of experts in the field of RSV infections and is the first and the only international, integrated, multidisciplinary and translational research network focused on HRSV infections.

ReSViNET's mission is to decrease the global burden of HRSV infection by integrating expertise and capacity required to enhance development of novel HRSV therapeutics. This network endeavors to increase knowledge for trial design and to provide partnership in performing clinical trials.

STRIDE



STRATEGIC RSV INTERVENTION DEVELOPMENT ENTITY