
PRESS RELEASE

The 2011 Annual Conference of the European Respiratory Society has been a major success for APEPTICO Forschung und Entwicklung GmbH

29th September, 2011, Vienna, Austria: APEPTICO Forschung und Entwicklung GmbH, a biotechnology company developing novel peptide-based drugs for the treatment of life threatening lung diseases today announced that the 2011 Annual Conference of the European Respiratory Society has been a major success for the company.

At the 2011 Annual Congress of the European Respiratory Society (ERS) in Amsterdam (The Netherlands, September 24th to 28th 2011), APEPTICO has presented significant research results of its clinical stage development compound AP301. The beneficial effects of APEPTICO's development compound AP301, also known as "TIP-peptide", have been subject of three presentations at this prestigious congress.

Professor Dr. Rudolf Lucas (Georgia Health Sciences University, Augusta, USA) reported that the AP301 TIP-peptide reduces lung dysfunction in experimental influenza A virus infection *in vitro* and *in vivo*. Dr. Susan Tzotzos reported on characterisation of TNF-alpha lectin-like domain derived AP301 TIP-peptides associated with improved alveolar fluid clearance in pulmonary oedema. The potential synergism of AP301 and anti-viral drugs, such as oseltamivir and zanamivir, was reported in by Dr. Hendrik Fischer.

The AP301 peptide is being developed by APEPTICO for inhalation therapy for prevention and treatment of Oedematous Respiratory Failure. AP301 activates the pulmonary epithelial sodium ion channel (ENaC) and prevents Protein Kinase C activation in lung tissues. It thus accelerates pulmonary oedema reabsorption and stabilises endothelial-epithelial barrier function in life-threatening conditions resulting from hyper-permeability of lung micro-capillaries. Currently, AP301 is subject to a Phase I clinical study in the Vienna General Hospital.

Extracts from presentations

Prof. Dr. R. Lucas: "The AP301 "TIP-peptide" which reduces PLY-induced oedema, can blunt influenza A virus (IAV) induced Alveolar Liquid Clearance dysfunction and combined IAV/PLY-induced barrier dysfunction. The TIP peptide represents a therapeutic candidate for the treatment of IAV-associated lung dysfunction, since it interferes with both IAV infection-associated ALC and barrier dysfunction, upon reducing PKC- α activation."

Dr. S. Tzotzos: "Our data suggest that TIP-peptides with charge distribution and interatomic distances most closely resembling the 3D structure of the native lectin-like domain of TNF-alpha, are those with greater ability to enhance activation of sodium current through ENaC. No standard therapy exists for pulmonary oedema, thus these TIP-peptides represent promising therapeutic agents for activating sodium uptake from the alveolar fluid through ENaC and improving clinical outcome in this condition."

Dr. H. Fischer: "Influenza A is a serious public health problem that causes severe illnesses and deaths for higher risk populations. Antiviral drugs like oseltamivir and zanamivir block increase and spreading of the virus in the body, however already existing virus particles will not be affected. 2/3 of patients show pulmonary oedema that can deteriorate to ALI/ARDS. Current experiments suggest a benefit of combining anti-viral drugs (neuraminidase inhibitors) and AP301 a substance with alveolar liquid clearing activity."

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Notes to Editors:

About APEPTICO GmbH

APEPTICO is a privately-held biotechnology company based in Austria, developing peptide-based products targeting chronic and life-threatening diseases. The peptide molecules correspond to validated, pharmacodynamic active structures and domains of well-known proteins and biopharmaceuticals. By concentrating on synthetically produced protein structures APEPTICO avoids any risk of transmitting microbial and viral infections. Development cost and time to market are significantly reduced if compared to the recombinant development process of biomolecules. APEPTICO's development platform PEPBASE™ combines structural, functional and clinical data from relevant biopharmaceuticals and well-characterised proteins. Based on preclinical and clinical data, including adverse reactions, risk factors and contraindications to be circumvented and supported by structural, biochemical and physicochemical data, for each relevant protein a specific profile is established that links biological & functional properties with discrete structural elements.

About the AP301 peptide family

AP301 and derived peptides are synthetic molecules whose structures are based on the lectin-like domain of human Tumour Necrosis Factor alpha. AP301 peptides are water soluble and can be administered into the lung by oral inhalation. Formulated AP301 is easily nebulised and the resulting aerosol is composed of peptide/water droplets of diameter 4 µm or less. AP301 and derived peptides are designed for activation of the pulmonary epithelial sodium channel (ENaC). Activation of ENaC by AP301 peptides results an accelerated oedema clearance in the airspace. Comprehensive research and development conducted by APEPTICO has demonstrated that AP301 peptides are effective in animal models of pulmonary permeability oedema, pneumonia, influenza virus lung infection, Acute Lung Injury / Acute Respiratory Distress Syndrome and lung transplantation. AP301 has received Orphan Drug Designation by the EMA and by the FDA for various indications.

Currently, AP301 is subject to a Phase I clinical study in the General Hospital in Vienna.

About Oedematous Respiratory Failure

Respiratory failure occurs when the respiratory system fails in oxygenation and/or carbon dioxide elimination. Oedematous Respiratory Failure is caused by a massive and life-threatening pulmonary oedema. Pulmonary oedema occurs when fluid leaks from the pulmonary capillary network into the lung interstitium and alveoli. There are many possible causes of lung oedema, such as inhaling high concentrations of smoke, toxins, or oxygen; severe burns; blood infections; lung infections; or trauma to other parts of the body. Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) are catastrophic forms of lung oedema.

Lungs contain alveoli, which are tiny air sacs where the oxygen is passed into the blood. During lung oedema, blood and fluid begin to leak into the alveoli. When this happens, oxygen cannot enter the alveoli, which means oxygen no longer passes into the blood. Because the lungs are inflamed and filled with fluid, the patient finds it increasingly difficult to breathe. The mortality rate of patients with pulmonary oedema in ALI/ARDS is 30% to 60% within 2 to 4 weeks.

Currently, no specific drug treatment exists for patients suffering from hyper-permeability-caused lung oedema.

About ERS Conference

The ERS Conference is the largest international conference specialising in pulmonary medicine. It provides a unique forum where scientists and medical professionals from around the world have the opportunity to meet and exchange ideas and information in the field of respiratory medicine. The scientific programme of the ERS Congress aims to provide a perfect balance between clinical education and the latest scientific developments. The ERS Congress highlights key issues in the diagnosis, management and treatment of respiratory diseases, giving clinicians and research scientists the opportunity to report the latest findings in basic, clinical and population research.

Contact

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Monday , 26 September 2011

ERS EUROPEAN
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Room 3.1 Session 216 08:30-10:30

09:00

OP Oral Presentation : Molecular pathology and functional genomics of lung disease

1702

The TNF-derived TIP peptide reduces lung dysfunction in experimental influenza A virus infection

R. Lucas, G. Yang, S. Sridhar, Z. Traylor, H. Hossain, B. Fischer, T. Chakraborty, I. Davis (Augusta, Columbus, United States Of America; Giessen, Germany; Vienna, Austria)

Background. Permeability edema during Influenza A virus (IAV) infection is characterized by reduced alveolar liquid clearance (ALC) and pulmonary endothelial hyperpermeability. Mortality after IAV infection is mainly due to secondary pneumococcal infections and occurs after antibiotic therapy, which can release the toxin pneumolysin (PLY) in the lungs. **Aims.** To investigate whether the TNF-derived TIP peptide, which reduces PLY-induced edema, can blunt IAV-induced ALC dysfunction and combined IAV/PLY-induced barrier dysfunction. **Methods.** ALC is assessed in BALB/c mice infected i.n. for 2d with 10,000 FFU/mouse (strain H1N1-A/WSN/33), using the BSA dilution method. We measure IAV/PLY-induced changes in transendothelial resistance (TER) in monolayers of human lung microvascular endothelial cells (HL-MVEC; ECIS). **Results.** IAV infection reduces basal ALC by 50±5%, which is prevented by co-instillation of the TIP peptide (2.5 mg/kg; n=11). The combination of PLY (7.5 ng/ml) and UV-inactivated IAV (1 virus/cell) causes a significant drop in normalized TER in HL-MVEC monolayers from 100 to 40±3% of baseline. The TIP peptide (50 µg/ml), as well as Ro32-4032 (10 nM), a specific inhibitor of PKC-α, implicated in both ALC dysfunction and hyperpermeability, restore TER to 86±4 and 80±6% of ctrl, respectively (n=4). IAV-treatment increases PKC-α activation by 110±7% over basal in HL-MVEC, an effect significantly blunted by the TIP peptide (23±1% over basal, n=4). **Conclusions.** The TIP peptide represents a therapeutic candidate for the treatment of IAV-associated lung dysfunction, since it interferes with both IAV infection-associated ALC and barrier dysfunction, upon reducing PKC-α activation.



Wednesday, 28 September 2011

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Room 5.2 Session 484 08:30-10:30

09:45

OP Oral Presentation : Translational models of airway disease

4688

Characterisation of TNF-alpha lectin-like domain derived peptides associated with improved alveolar fluid clearance in pulmonary oedemaS. Tzotzos, B. Fischer, H. Pietschmann, H. Fischer, R. Lucas, W. Shabbir, R. Lemmens-Gruber
(Vienna, Austria; Augusta, United States Of America)

The beneficial effect of the lectin-like domain of TNF-alpha, including the TIP peptide which mimics this domain, on activation of oedema resorption, improved alveolar clearance and protection of lung function after transplantation, is well documented from several independent *in vitro* and *in vivo* studies using animal models. The effect is mediated by activation of sodium uptake through the amiloride-sensitive epithelial sodium ion channel (ENaC), which plays a major role in alveolar fluid clearance in normal and diseased lungs. Several peptides mimicking the lectin-like domain of human TNF-alpha, and differing from the human TIP peptide by mutation or substitution of amino acid residues with non-natural derivatives, were synthesised and tested for their ability to enhance sodium current through ENaC in A549 cells with the patch clamp technique.

For all ENaC-activating TIP peptides a maximum effect was observed at 120 nM. Compared to TNF-alpha (EC_{50} 8.2 nM) and the original human TIP peptide (EC_{50} 54.3 nM), several of the newly-designed peptides were more effective at enhancing amiloride-sensitive current than the latter: the most active peptide had an EC_{50} of 19.9 nM. Our data suggest that TIP peptides with charge distribution and interatomic distances most closely resembling the 3D structure of the native lectin-like domain of TNF-alpha, are those with greater ability to enhance activation of sodium current through ENaC. No standard therapy exists for pulmonary oedema, thus these TIP peptides represent promising therapeutic agents for activating sodium uptake from the alveolar fluid through ENaC and improving clinical outcome in this condition.



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