PRESS RELEASE by APEPTICO

Vienna, Austria, December 1st 2014

Vienna, Austria, 1st December 2014: APEPTICO, a privately-held biotechnology company developing peptide drugs, today announced that it will present major scientific break-through results for its AP301-peptide based inhalation medicine at leading international conferences in December this year.

Scientists of APEPTICO, in close collaboration with the Department of Pharmacology and Toxicology of the University Vienna, have discovered essential details of the molecular interactions of APEPTICO's AP301-peptide drug compound and its pulmonary tissue target, the amiloride-sensitive epithelial sodium ion channel (ENaC). APEPTICO's AP301-peptide, also known as the 'lectin-like domain', is highly specific for its binding to glycan structures. Based on site-directed mutagenesis of ENaC subunits, individual glycosylation sites of an outer-loop structure of ENaC were removed by mutations, followed by heterologous expression of mutated ENaC in HEK-293 cells and electrophysiological analysis of sodium-ion movement through mutated ion channels. The 'glycosylation-dependent activation of ENaC by AP301-peptide' will be presented during the European Peptide Society conference in Salzburg (4th December 2014).

Since 2009 APEPTICO has successfully developed the AP301-peptide inhalation medicine for treatment of pulmonary permeability oedema and for treatment of primary graft dysfunction of the lung of mechanically ventilated patients. Since it was founded, APEPTICO has become a champion in pulmonary delivery of biologic macromolecules to patients with life-threatening lung diseases. In recognition of this major achievement, APEPTICO has been invited to present the AP301-peptide drug development story at this years' annual conference 'Drug Delivery to the Lung' of The Aerosol Society held in Edinburgh from 10th to 12th December 2014.

Bernhard Fischer, CEO of APEPTICO commented: "I am very proud that our research consortium has further elucidated at molecular level the interaction between the AP301-peptide drug and the pulmonary ENaC receptor, that brings about alveolar liquid clearance in patients with lung oedema." "Having been selected to present the AP301 story at this year's 'Drug Delivery to the Lung' international conference, marks a highlight in our efforts to develop better therapeutic treatment option for intensive care patients" he added.

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About APEPTICO GmbH (www.apeptico.com)

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 general risks associated with gene- and cell-technologies. APEPTICO makes use of its technology platforms PEPBASE$^{(TM)}$ and PEPSCREEN$^{(TM)}$ to significantly reduce cost and to shorten time to market.

About the AP301-peptide / TIP-peptide

The AP301-peptide (synonym to TNF-derived TIP-peptide) is a synthetic molecule whose structure bases on the lectin-like domain of the human Tumour Necrosis Factor α. The AP301 peptide is 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. APEPTICO's most recent clinical phase II proof-of-concept study (ClinicalTrials.gov ID NCT01627613) demonstrated that orally inhaled AP301-peptide activates alveolar liquid clearance in mechanically ventilated patients with pulmonary permeability oedema and ARDS.

Comprehensive research and development studies conducted by the APEPTICO research consortium demonstrated that AP301-peptides are effective therapeutic molecules in various forms of pulmonary oedema, such as pulmonary permeability and hydrostatic oedema, high altitude pulmonary oedema (HAPE), pulmonary oedema associated with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), pulmonary oedema resulting from pneumonia and sepsis, and primary graft dysfunction following lung transplantation.

APEPTICO's AP301 has been granted orphan drug status (i) for treatment of pulmonary permeability oedema in ALI/ARDS, (iii) for treatment of primary graft dysfunction following lung, and (iii) for treatment of high altitude pulmonary oedema by the European Commission and European Medicines Agency (EMA) and by the Food and Drug Agency (FDA).

About 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 heart failure (cardiac/hydrostatic lung oedema); inhaling high concentrations of smoke, toxins, or oxygen; severe burns; blood infections / sepsis; infection of the lung / pneumonia; aspirations, cerebral damage or trauma to other parts of the body and lung transplantation. 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 35% to 45% within two to four weeks.

Currently, no specific drug treatment exists for patients suffering from pulmonary permeability oedema and ARDS, patients developing primary graft dysfunction following lung transplantation and patients having acute high altitude pulmonary oedema.

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PRESS RELEASE by APEPTICO

Vienna, Austria, September 16th 2014

Most recently, in a scientific collaboration effort between APEPTICO, the Vascular Biology Center of the Georgia Regents University (Prof. Dr. Rudolf Lucas, USA), and the Institute of Pharmacology and Toxicology of the University of Vienna (Prof. Dr. Rosa Lemmens-Gruber, Austria), the detailed mechanism has been discovered how APEPTICO's clinically stage "AP301-peptide" (identical to the lectin-like domain of native TNF-alpha) activates the specific pulmonary ion channel "ENaC" to result in "Activation of Lung Oedema Clearance".

In the most recent EDITORIAL in "American Journal of Respiratory Critical Care" (Am J Respir Crit Care Med Vol 190(6), pp 595–605, Sep 15, 2014; http://www.atsjournals.org/doi/abs/10.1164/rccm.201407-1364ED#.VBfyMha7ZbI) by Gary C. Sieck and Mark E. Wylam from the Mayo Clinic, Rochester, both the ground-braking scientific discoveries and the clinical-therapeutically potential of AP301 peptide have been highlighted.

In the EDITORIAL the authors summarise as follow "Previously, the lectin-like domain of TNF-alpha was shown to activate ENaC in type 2 alveolar epithelial cells (Ref. 1). Importantly, this effect has been mimicked by a small 17-amino acid circular peptide known as TNF inhibitory peptide (TIP; APEPTICO code "AP301"). A recent European study compared placebo treatment with TIP inhalation in patients with ALI/ARDS and found that TIP elicited earlier and more pronounced clearance of pulmonary edema (Ref. 2, Ref. 3). The molecular mechanism underlying TIP-induced ENaC activation remained uncertain until the study by Czikora and colleagues, published in the September 1, 2014, issue of the Journal (Ref. 4)."

The EDITORIAL makes explicate reference to APEPTICO's most recently completed phase IIa clinical study in patients with ARDS and pulmonary oedema. During the European Respiratory Society International Conference (Munich, 6-9 September 2014), Dr. Krenn from the Department of Intensive Care Medicine, Medical University of Vienna, reported key findings of the AP301-trial in mechanically ventilated patients with pulmonary permeability oedema.

The EDITORIAL concludes, "Taken together, these basic science results provide new physiological insight into the potential role of the lectin-like domain of TNF-a (AP301 peptide) and support the novel therapeutic use of AP301 aerosols in patients with ALI/ARDS and ischemia reperfusion lung injury."

In addition, Dr. Krenn's presentation of the AP301 clinical trial at the ERS International Conference was immediately reflected as "Top story of the week" in Pulmonary/Respiratory Medicine (http://dgnews.docguide.com/novel-peptide-activates-pulmonary-oedema-clearance-mechanically-ventilated-patients). MUNICH, Germany -- September 10, 2014: Jenny Power reported "Novel Peptide Activates Pulmonary Oedema Clearance in Mechanically Ventilated Patients. -- Acute lung injury (ALI) mediated by acute pulmonary permeability oedema can be reduced by a novel synthetic peptide that promotes pulmonary oedema clearance by decreasing extra-vascular lung water (EVLW) among mechanically ventilated patients in the intensive care unit (ICU)." (PDF copy attached).

Dr. Bernhard Fischer, CEO of APEPTICO added: "We are very proud that Prof. Rudolf Lucas' scientific discoveries and APEPTICO's therapeutic approach have been rewarded an Editorial in the American Journal of Respiratory Critical Care". "APEPTICO develops the "AP301-peptide", a synthetic version of the lectin-like domain of TNF, as a new life-saving medicine for patients with pulmonary permeability

oedema. Most recently we could demonstrate in a clinical phase II proof-of-concept study (ClinicalTrials.gov ID NCT01627613) that orally inhaled "AP301-peptide" activates alveolar liquid clearance in mechanically ventilated patients having lung oedema and ARDS," he added.

Reference

Ref. 1: Tzotzos S, Fischer B, Fischer H, Pietschmann H, Lucas R, Dupre´ G, Lemmens-Gruber R, Hazemi P, Prymaka V, Shabbir W. AP301, a synthetic peptide mimicking the lectin-like domain of TNF, enhances amiloride-sensitive Na(1) current in primary dog, pig and rat alveolar type II cells. Pulm Pharmacol Ther 2013;26:356–363.

Ref. 2: Hartmann EK, Thomas R, Liu T, Stefaniak J, Ziebart A, Duenges B, Eckle D, Markstaller K, David M. TIP peptide inhalation in experimental acute lung injury: effect of repetitive dosage and different synthetic variants. BMC Anesthesiol 2014;14:42.

Ref. 3: Krenn K, Croize A, Klein KU, Bo¨ hme S, Markstaller K, Ullrich R, Hermann R, Lucas R, Fischer B. Oral inhalation of AP301 peptide activates pulmonary oedema clearance: initial results from a phase IIa clinical trial in mechanically ventilated ICU patients. Presented at the ERS International Congress 2014. September 6–10, Munich, Germany.

Ref. 4: Czikora I, Alli A, Bao H-F, Kaftan D, Sridhar S, Apell H-J, Gorshkov B, White R, Zimmermann A, Wendel A, et al. A novel tumor necrosis factor–mediated mechanism of direct epithelial sodium channel activation. Am J Respir Crit Care Med 2014;190:522–532.

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Comprehensive research and development studies conducted by Dr. Rudolf Lucas and the APEPTICO research consortium demonstrated, that AP301-peptides are effective therapeutic molecules in various forms of pulmonary oedema, such as pulmonary permeability and hydrostatic oedema, high altitude pulmonary oedema (HAPE), pulmonary oedema associated with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), pulmonary oedema resulting from pneumonia, sepsis and lung transplantation (primary graft dysfunction).

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interstitium and alveoli. There are many possible causes of lung oedema, such as heart failure (cardiac/hydrostatic lung oedema); inhaling high concentrations of smoke, toxins, or oxygen; severe burns; blood infections / sepsis; infection of the lung / pneumonia; aspirations, cerebral damage or trauma to other parts of the body and lung transplantation. 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 35% to 45% within two to four weeks. Currently, no specific drug treatment exists for patients suffering from pulmonary permeability oedema and patients having ARDS. ARDS is also a major economic burden to hospitals and health care budgets. It is estimated that due to a long ICU and hospital stay the cost of every saved live from ARDS is approximately $70,000 USD.

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PRESS RELEASE

APEPTICO announces break-through results in scientific understanding of alveolar liquid clearance regulation by the pulmonary epithelial sodium channel (ENaC)

Vienna, Austria, 16th July, 2014: APEPTICO, a privately held biotechnology company developing peptide drugs, today announced that Dr. Rudolf Lucas, co-founder of APEPTICO and Professor of Pharmacology and Toxicology at the Vascular Biology Center, Medical College of Georgia, Georgia Regents University, has produced breakthrough results in the scientific understanding of alveolar liquid clearance regulation by the apically expressed pulmonary epithelial sodium channel (ENaC).

APEPTICO announces breakthrough results in scientific understanding of alveolar liquid clearance regulation by the pulmonary epithelial sodium channel (ENaC)

Alveolar liquid clearance is regulated by Na+ uptake through the apically expressed epithelial sodium channel (ENaC) and the basolaterally localised Na+-K+-ATPase in type II alveolar epithelial cells. Dysfunction of these Na+ transporters during pulmonary inflammation and bacterial infection can contribute to formation of life-threatening pulmonary permeability oedema.

Using a combined biochemical, electrophysiological and molecular biological approach in vitro and by performing in vivo studies in transgenic mice, Dr. Lucas' team from the Medical College of Georgia, Georgia Regents University, in collaboration with APEPTICO and researchers from the Institute of Pharmacology and Toxicology of Vienna University and from Emory University, demonstrated that the "TIP-peptide", which mimics the lectin-like (TIP) domain of TNF, direcly activates ENaC, but not the Na+-K+-ATPase, upon binding to the carboxy-terminal domain of the ion channel's alpha subunit. Binding of the "TIP-peptide" to ENaC increases open probability of the channel and preserves ENaC alpha protein expression in the presence of bacterial toxins, by means of blunting the protein kinase C alpha pathway. Transgenic mice lacking the TNF-derived lectin-like domain are more prone to develop oedema in the presence of bacterial toxins than wild type mice. All data have been published in the American Journal of Respiratory and Critical Care Medicine of 16th July, 2014.

Professor Lucas commented: "These results demonstrate a novel TNF-mediated mechanism of direct ENaC activation and indicate a physiological role for the TIP-domain of TNF in the resolution of alveolar oedema during lung inflammation".

Pulmonary oedema and lung inflammation resulting from pneumonia, aspiration of gastric content, inhalation trauma, near drowning, sepsis, multiple trauma, multiple blood transfusion, burns, acute pancreatitis, drug overdose and other causes, may lead to acute respiratory distress syndrome (ARDS), a life-threatening condition having a mortality rate of around 35-45% despite modern day hospital care. Currently, there is no effective pharmacotherapy available for treatment of pulmonary oedema and patients suffering from ARDS.

Dr. Bernhard Fischer, CEO of APEPTICO added: "We are very proud of Dr. Lucas' scientific achievements. His new discovery comes only weeks after scientists in the same consortium published work demonstrating that "TIP-peptide" binding to ENaC increases the open probability of this ion channel". "APEPTICO is developing the "AP301-peptide", a synthetic version of the lectin-like domain of TNF, as a new life-saving medicine. Most recently we demonstrated in a clinical phase II proof-of-concept study (ClinicalTrials.gov ID NCT01627613) that orally-inhaled "AP301-peptide" (synonym "TIP-peptide") activates alveolar liquid clearance in mechanically ventilated patients having lung oedema and ARDS," he added.

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Comprehensive research and development studies conducted by Dr. Rudolf Lucas and the APEPTICO research consortium demonstrated, that AP301-peptides are effective therapeutic molecules in various forms of pulmonary oedema, such as pulmonary permeability and hydrostatic oedema, high altitude pulmonary oedema (HAPE), pulmonary oedema associated with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), pulmonary oedema resulting from pneumonia, sepsis and lung transplantation (primary graft dysfunction).

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About pulmonary oedema

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PRESS RELEASE

APEPTICO announces top-line results in phase IIa clinical study of AP301 in treatment of pulmonary permeability oedema in mechanically ventilated patients

Vienna, Austria, April 9th, 2014: APEPTICO, a privately held biotechnology company developing peptide drugs, today announced that the phase IIa clinical study of AP301 delivered top-line results in the treatment of pulmonary permeability oedema in mechanically ventilated patients suffering from Acute Respiratory Distress Syndrome.

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 sepsis, trauma, pneumonia, aspiration, cardiac failure, and other. Massive pulmonary permeability oedema is a major characteristic of Acute Respiratory Distress Syndrome (ARDS) too, a life-threatening condition having a mortality rate of around 35-45%, despite modern day care. Currently, there is no effective pharmacotherapy available for treatment of pulmonary permeability oedema and patients having ARDS.

AP301 is a small peptide designed to activate pulmonary oedema clearance in a variety of patients, including mechanically ventilated patients. AP301 opens up the pulmonary epithelial sodium ion channel (ENaC), blunts protein kinase C-α activation and MLC phosphorylation, and reduces reactive oxygen species generation in lung tissue. All this leads to lung tissue repair and pulmonary oedema clearance.

The proof-of-concept phase IIa clinical study was conducted at the Division of General Anaesthesia and Intensive Care Medicine of the Medical University of Vienna. It was an interventional, randomized, double blind, placebo-controlled, parallel-group study. Patients were randomized in a 1:1 ratio. The primary objective of this study was to assess the treatment-associated changes of extra-vascular lung water (EVLW) upon oral inhalation of AP301 in comparison to placebo. Patients were evaluated every 12 hours for 7 days.

Results from this study showed that oral inhalation of AP301 led to an earlier onset and more pronounced activation of pulmonary oedema clearance compared to placebo. Subgroup analysis revealed that oral inhalation of AP301 was statistically significant and more effective in pulmonary oedema clearance in patients with elevated Sequential Organ Failure Assessment (SOFA) score compared to placebo. AP301 was equally effective in patients with direct and indirect lung injury and patients with initial very low P/F-ratio. In addition to oedema clearance, upon AP301 inhalation, critical patient's parameters, such as oxygenation index and Murray Lung Injury score, improved.

Dr. Bernhard Fischer, CEO of APEPTICO, stated: "We are very proud to have achieved this significant clinical goal. I am convinced that AP301 will have the potential to play a key role in the management of various forms of pulmonary oedema. This major success would not have happened without the steady support by Professor Rudolf Lucas from the Medical College of Georgia, Professor Rosa Lemmens-Gruber from the Institute of Pharmacology and Toxicology of the University of Vienna, and the clinical teams of Professor Roman Ullrich and Professor Klaus Markstaller from the Division of General Anaesthesia and Intensive Care Medicine of the Medical University Vienna". "Our excellent scientific results will establish partnering process with interested global and specialised pharmaceutical and biotech companies," Dr. Fischer added.

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About the AP301 peptide family

AP301 and derived peptides are synthetic molecules whose structures are based on structural elements of human proteins. AP301 peptide is 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 results an accelerated lung oedema clearance in the airspace.

Comprehensive research and development conducted by APEPTICO has demonstrated that AP301 peptides are effective in various forms of pulmonary oedema, such as pulmonary permeability oedema, hydrostatic oedema, high altitude pulmonary oedema (HAPE), pulmonary oedema associated with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), pulmonary oedema resulting from pneumonia, sepsis and lung transplantation (primary graft dysfunction).

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PRESS RELEASE

Top-line research results highlighted as key scientific contribution in biomedical research

Vienna, Austria, March 13th, 2014: APEPTICO, a privately-held biotechnology company developing peptide drugs, today announced that the target selection team at Global Medical Discovery has identified our publication "Mechanism of Action of Novel Lung Edema Therapeutic AP301 by Activation of the Epithelial Sodium Channel" as a key scientific article contributing to excellence in biomedical research. (http://globalmedicaldiscovery.com/key-drug-discovery-articles/mechanism-action-novel-lung-edema-therapeutic-ap301-activation-epithelial-sodium-channel/)

In a combined research effort between the Department of Pharmacology and Toxicology of the University of Vienna and APEPTICO Research & Development, Vienna, a unique ENaC-dependent mechanism was unveiled that mimics fluid transport in the lung, which is not only relevant to pathological mechanism of lung oedema but might also present physiological means of acutely activating ENaC in the lung and other organs.

Consequently, this study was undertaken to determine whether the Epithelial Sodium-ion Channel "ENaC" is the specific target of APEPTICO's synthetic peptide AP301. The effect of AP301 in pulmonary A549 cells as well as in human embryonic kidney cells and Chinese hamster ovary cells heterologously expressing human ENaC subunits ({Alpha}, {Beta}, {Gamma}, and {Delta}) was measured in patch clamp experiments. AP301 increased current in proteolytically activated (cleaved) but not near-silent (uncleaved) ENaC in a reversible manner. {Alpha}{Beta}{Gamma}- or {Delta}{Beta}{Gamma}-ENaC co-expression was required for maximal activity. No increase in current was observed after deglycosylation of extracellular domains of ENaC. Thus, our data suggest that the specific interaction of AP301 with both endogenously and heterologously expressed ENaC requires precedent binding to glycosylated extracellular loop(s).

APEPTICO develops the AP301 peptide compound for the activation of pulmonary oedema clearance in various forms of life-threatening oedematous respiratory failure. In 2011, APEPTICO conducted a Phase I clinical study for safety and tolerability of orally inhaled AP301. From mid-2012 to February 2014 APEPTICO assessed the effect of orally inhaled AP301 on alveolar liquid clearance in ICU patients in an interventional, randomized, double-blind, placebo-controlled, parallel-group, Phase IIa clinical study in collaboration with the Medical University Vienna. This proof-of-concept study delivered top-line results for AP301 treatment associated changes of extra-vascular lung water (EVLW) within 7 days of treatment of mechanically ventilated patients with various forms acute lung injury.

Dr. Bernhard Fischer, CEO of APEPTICO, commented: "Together with the researchers from the Department of Pharmacology and Toxicology of the University Vienna we are very happy to have our scientific results highlighted as key scientific contribution in the biomedical research. These cell-based results confirm was we have discovered very recently in our Phase IIa "proof-of-concept" clinical study in mechanically ventilated patients: AP301 activates pulmonary oedema clearance in patients with life-threatening respiratory failure." "AP301 will be the one-and-only orally inhaled drug compound that activates oedema clearance making use of the sodium-ion transport mechanism in pulmonary tissue" Dr. Fischer added.

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Notes to Editors:

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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 heart failure (cardiac/hydrostatic lung oedema); inhaling high concentrations of smoke, toxins, or oxygen; severe burns; blood infections (sepsis); lung infections (pneumonia); cerebral damage or trauma to other parts of the body. 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 two to four weeks. Currently, no specific drug treatment exists for patients suffering from hyper-permeability-caused lung oedema.

About Primary Graft Dysfunction

Primary Graft Dysfunction (PGD) (Ischemia Reperfusion Injury, IRI) is characterized by poor oxygenation as the main criterion for the condition and is also characterized by low pulmonary compliance, interstitial/alveolar oedema, pulmonary infiltrates on chest radiographs, increased pulmonary vascular resistance, intrapulmonary shunt and acute alveolar injury, as revealed by diffuse alveolar damage (DAD) on pathology. PGD occurs in approximately 20% of lung transplant recipients and patients face prolonged ventilation, prolonged stays in the ICU and the hospital overall, increased medical costs, and increased risk of morbidity and mortality. Currently, no specific drug treatment exists for patients suffering primary graft dysfunction following lung transplantation.

Contact

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