White Paper

Preclinical Animal Models of COVID-ARDs

CBI is offering customized preclinical animal models to address acute respiratory failure in COVID-19 pulmonary infections.

COVID LUNG-COVID ARDS

ARDS-Shock lung-Smoke lung-Danang Lung-SIRS -Sepsis

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ARDS, shock lung, smoke lung, Danang lung, SIRS, sepsis. These are terms for acute pulmonary failure where the lung is acting as a shock organ. It has been demonstrated that patients dying of respiratory failure due to COVID have histopathologic lesions consistent with ARDS. There is a cytokine storm. There are signs of septic shock and multi-system organ failure. There are no successful therapies.

Acute respiratory distress syndrome (ARDS) is often fatal and very difficult to treat. Ventilation, fluids, anti-inflammatories, diuretics, antibiotics are used as supportive care for decades. In the case of COVID-19, WHO reports that severely affected patients demonstrate clinical signs and histopathology compatible with ARDs. It follows that developing novel or refining existing treatments for ARDS should be effective in treating COVID-19 patients with respiratory distress.

The Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) (Report) is a comprehensive document presenting what is known at this point about the disease in China. The Report makes a number of recommendations about the disease and how to further characterize it. The Report recommends initiation of monitoring of pro-inflammatory mediators, via multiplex assays, to characterize and predict cytokine storm development. The Report also recommends development of animal models as well as the investigation of corticosteroids and other mediators for treatment and further suggests pulmonary biopsies of patients to characterize the histopathologic changes.

Preclinical infection studies have been recently conducted in rodents and primates in China. In transgenic ACE2 mice and primates infected with the virus by the pulmonary route, lung lesions are characterized by multifocal pneumonia with interstitial hyperplasia. In patients, cellular and

fibromyxoid exudation, pneumocytic desquamation of pneumocytes, pulmonary edema, interstitial monocytic and lymphoid infiltrations were bilaterally present. Further, multinucleated syncytial cells, enlarged atypical pneumocytes showing viral cytopathic-like changes, but no viral inclusions, were common. Mediator data was not presented in the Report, but hopefully will be published soon.

Now is the time to review the literature and look for older drug candidates that have been explored for treating ARDS or sepsis in the past. Now is the time to revisit PAF antagonists, TNF, IL-6, IL 17 and other interleukins, cytokine antagonists, stem cells and other agents to determine if these agents have a meaningful role in reducing the severity of COVID ARDS. Certainly, pharma and biotech have new drugs in development or on the shelf that could be evaluated for activity in experimental ARDS as a model for COVID-19 induced ARDS.

We at CBI has decades of experience in infectious, sepsis, and inflammatory models, including pulmonary and systemic inflammation. Our CEO, Dr. Carol Meschter, worked for a number of years at Hoffmann LaRoche and then in biotech in Silicon Valley on Sepsis teams, with various inhibitors such as humanized anti-TAC, anti-TNF fusion proteins, interleukins, PAF antagonists, stem cells and anti-infectives.

At CBI, we offer a number of ARDS type models including oleic acid-induced ARDS, LPS-induced pulmonary inflammation, albumin-induced immune mediated pulmonary inflammation, murine sarcoidiosis- *Propionibacterium acne*-induced hypersensitivity or granulomatous pneumonia, pulmonary hyperoxygenation, aspergillus pneumonia, murine Farmer's Lung- Saccharopolyspora rectivirgula-induced hypersensitivity pneumonitis, cecal ligation and puncture and oxygen-induced pulmonary bronchodysplasia. All of these models offer good correlation with the lesions in COVID ARDs including inflammation, edema, hemorrhage, fibrin, thrombosis, hyaline membrane formation. We offer customized and innovative pulmonary models. With our models, assessments include respiratory signs, oxygenation, cytokine assays, BAL assessment, histopathology and immunohistochemistry as part of a plan to assess the potential activity of test articles for treatment of COVID-19 ARDS.

Our established ARDS models are summarized:

Summary of ARDS Pulmonary Preclinical Models			
LPS-induced and oleic acid induced	Albumin-induced	RSV in cotton rats	Customized and innovative models
Pulmonary hyperoxygenation	Saccharopolyspora rectivirgula-induced hypersensitivity	Pulmonary bronchodysplasia	Cecal ligation and puncture
Aspergillus pneumonia	Propionibacterium acnes-induced pneumonitis	RSV infection in cotton rats	Bacterial pneumonia

Parameters assessed			
Cytokine assays	BAL assessment	Cytokine panels – blood and lung tissue	Pharmacokinetics of test article
Hemoglobin saturation	Fibrin products	Histopathology	Target toxicity of test article
Hematology, clinical chemistry, coagulation	Bacterial culture	Immunohistochemistry	Others upon request

References

Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19).

Menachery VD, YountBL, DebbinkK, AgnihothramS, GralinskiLE, et al. SARS-like cluster of circulating bat coronavirus pose threat for human emergence. Nat Med. 2015 December ; 21(12): 1508–1513.

Meschter, CL, VanZee K, Moldawer, L, Lowry, S, Lesslauer, W. Tumor necrosis factor receptor fusion protein protects against E. Coli-induced septic shock pathology in baboons. Advances in Sepsis and Endotoxemia, June 17, 18, 1993, Philadelphia, Pa. Poster.

Van Zee K, Moldawer LL, Stackpole SA, Montegu WJ, Rogy MA, Meschter CL, Loetscher H, Brockhaus M, Wurm F, Calvano SE, Lowry SF, Lesslauer W: Protection against lethal E. coli septic shock in baboons by pretreatment with novel TNF immunoadhesions. J Exp Med, 179:1185-1191, 1994

Thomas, TK, Meschter, CL, Nwachuku, UA, Descarfino, J, Will, PC: Attenuation of platelet activating factor induced inflammation and E-selectin expression in rabbit skin by a PAF antagonist. 7th Int Conf, IRA, Sept 25-29, 1994

Kelly KJ, Tolkoff-Rubin NE, Rubin RH, Williams, WW, Meehan SM, Meschter CL, Christenson JG, Bonventre JV: An oral platelet activating factor Ro 24-4736 protects the rat kidney from ischemic injury. AmJPhysiol: 271:(5Pt2) F1061-7, 1996.

Haberberger TC, Meschter CL, Murphy JE: Ectopic expression of connective tissue growth factor causes fibrosis in mouse lung. Accepted for publication, AmJRespCellMolBio. 2001.

Quantification of lung injury with phase contrast analysis in a rodent model of postnatal hyperoxia-induced pulmonary dysplasia. OoiL, ZhangQ, EbrahimnejadA, PaniaguaF, SukhuR, MeschterC, WarrenD: Society of Toxicologic Pathology, Poster Presentation, March 2017

Poster presented at: Society of Toxicology Annual Meeting; March 12-15, 2017; Quantification of lung injury with phase contrast analysis in a rodent model of postnatal hyperoxia-induced pulmonary dysplasia. Baltimore, MD. Ooi L, Zhang Q, Ebrahimnejad A, Paniagua F, Sukhu R, Meschter C, Warren D