

## **Preclinical Study Showing Beneficial Effects of Cymerus™ MSCs in Acute Respiratory Distress Syndrome Accepted for Publication in Leading Peer-Reviewed Journal**

**Melbourne, Australia; 17 April 2020:** Cynata Therapeutics Limited (ASX: CYP), a clinical-stage biotechnology company specialising in cell therapeutics, is pleased to announce that a scientific paper describing the use of Cymerus™ mesenchymal stem cells (MSCs) in a model of Acute Respiratory Distress Syndrome (ARDS) has been accepted for publication in the *American Journal of Respiratory and Critical Care Medicine (AJRCCM)*.<sup>1</sup> The AJRCCM, commonly known as “*The Blue Journal*”, is widely regarded as the foremost peer-reviewed journal in the field of respiratory and critical care medicine.

### **Background**

The study was conducted in 14 sheep with severe ARDS supported by extracorporeal membrane oxygenation (ECMO), which were given an endobronchial infusion of either Cymerus MSCs (n=7) or placebo (n=7). Animals were monitored and supported for 24 hours, at which time the study concluded.

ARDS is an inflammatory process leading to build-up of fluid in the lungs and respiratory failure. It can occur due to a range of insults, including infection, trauma and inhalation of noxious substances. It has received significant global attention in recent times, as it is one of the most serious complications experienced by patients suffering from COVID-19. ARDS accounts for approximately 10% of all ICU admissions and almost 25% of patients requiring mechanical ventilation, and results in hospital mortality of up to 46%.<sup>2</sup> In addition, survivors of ARDS are often left with severe long-term illness and disability.<sup>3</sup>

ECMO is a last-line intervention used in patients whose lungs are unable to provide an adequate amount of oxygen to the blood, despite the use of ventilators and other interventions. ECMO circulates blood through an artificial lung, oxygenating the blood before returning it to the patient’s circulation. ECMO can help support the vital organs in patients with severe ARDS, but it is not in itself a treatment for ARDS and the mortality among patients supported by it remains high.

This study was conducted independently of Cynata by a group of leading academics known as the *Combining Extracorporeal Life Support and Cell Therapy in Critical Illness (CELTIC) Investigators*, led by Professor John Fraser of the Critical Care Research Group, The Prince Charles Hospital, Brisbane. The study was funded by the Queensland Government, the National Health and Medical Research Council (NHMRC), the Intensive Care Society UK, and the Prince Charles Hospital Foundation.

### **Key Results**

Cymerus MSC treatment was shown to exert a number of important beneficial effects in this study:

- The severity of lung injury was significantly reduced, as shown by histological lung injury score (p=0.04)
- Inflammation was significantly reduced, as shown by levels of the inflammatory cytokine IL-8 in the lungs at 3, 13 and 23 hours after treatment (p=0.013, 0.016, and 0.028 respectively)
- There was a reduction in the depth and severity of circulatory shock, as shown by a highly significant increase in arterial blood pressure after 4 hours (p=0.001), and a significant reduction in the requirement for noradrenaline (a drug used to maintain blood pressure) over the entire study period (p=0.01). Circulatory shock is a life-threatening condition that often occurs in patients with ARDS, which can result in low blood pressure, increased heart rate, and impaired function of multiple organs.

There were no statistically significant differences in oxygenation index between groups. The authors of the paper suggested that this may have been due to the severity of the lung injury induced; the fact that the

observation period may have been too short to observe all beneficial effects of the treatment; and practical challenges performing these assessments during ECMO.

The authors also observed that a different dose regimen and/or route of administration could lead to further improved outcomes.

The study also found that MSCs adhere to the membranes in the ECMO device, resulting in a significant increase in pressure, and there was a higher incidence of thrombosis in the lungs observed post-mortem. While this did not lead to failure of the ECMO device or other observed adverse events, the study team considered that it could potentially do so, and therefore concluded that they cannot currently recommend the use of MSCs in combination with ECMO. It is important to note that this finding is relevant to MSCs in general (regardless of source), as it is related to the propensity of MSCs to adhere to plastic, but it does not have implications for the treatment of patients with ARDS who are NOT receiving ECMO.

Dr Kilian Kelly, Cynata's Chief Operating Officer, commented:

*"We are very encouraged by the beneficial effects of Cymerus MSCs on a number of important, clinically-relevant endpoints in this model of ARDS. These results provide valuable guidance on the potential clinical utility of Cymerus MSCs in the treatment of ARDS. It is also very useful to learn more about the practical mechanical challenges associated with administering MSCs at the same time as ECMO, but it is important to note that most patients with ARDS do not receive ECMO. Furthermore, in humans with ARDS who are not receiving ECMO, we expect to be able to administer repeated intravenous infusions of MSCs, which may have advantages compared to the approach that was taken in this preclinical study. We are currently in discussions with leading key opinion leaders about a possible clinical trial in human patients with ARDS, including those who have developed ARDS as a result of the devastating COVID-19 pandemic."*

**-ENDS-**

**Authorised for release by Dr Ross Macdonald, Managing Director & CEO**

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### **About Cynata Therapeutics (ASX: CYP)**

Cynata Therapeutics Limited (ASX: CYP) is an Australian clinical-stage stem cell and regenerative medicine company focused on the development of therapies based on Cymerus, a proprietary therapeutic stem cell platform technology. Cymerus overcomes the challenges of other production methods by using induced pluripotent stem cells (iPSCs) and a precursor cell known as mesenchymoangioblast (MCA) to achieve economic manufacture of cell therapy products, including mesenchymal stem cells (MSCs), at commercial scale without the limitation of multiple donors.

Cynata's lead product candidate CYP-001 met all clinical endpoints and demonstrated positive safety and efficacy data for the treatment of steroid-resistant acute graft-versus-host disease (GvHD) in a Phase 1 trial. Cynata plans to advance its Cymerus MSCs into Phase 2 trials for GvHD, critical limb ischemia and osteoarthritis. In addition, Cynata has demonstrated utility of its Cymerus MSC technology in preclinical models of asthma, diabetic wounds, sepsis, heart attack and cytokine release syndrome, a life-threatening condition stemming from cancer immunotherapy.

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<sup>1</sup> Millar JE, Bartnikowski N, Passmore MR, et al. Combined Mesenchymal Stromal Cell Therapy and ECMO in ARDS: A Controlled Experimental Study in Sheep. *Am J Crit Care Med*, 2020.

<sup>2</sup> Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *Jama*. 2016;315(8):788.

<sup>3</sup> Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-304.