

# Leveraging the Immune System to Defeat COVID-19

## Agentus iNKT Cell Therapy in Patients as Hospitalizations Surge

The COVID-19 pandemic has had a devastating impact worldwide. More than 62 million people have been infected with this life-threatening virus, with over 1.45 million deaths.<sup>1</sup> This global health crisis continues to persist; indeed, it is currently experiencing a significant resurgence in the United States (see figure 1). As of November 29, the 7-day average for number of daily cases in the United States is exceeding 150K, with a record ~93K patients hospitalized and ~18K patients currently in ICU.<sup>2</sup> **While preventative vaccines have much promise, there is a critical need for effective therapies.**

### Cell Therapy As a Promising Treatment for COVID-19 Patients

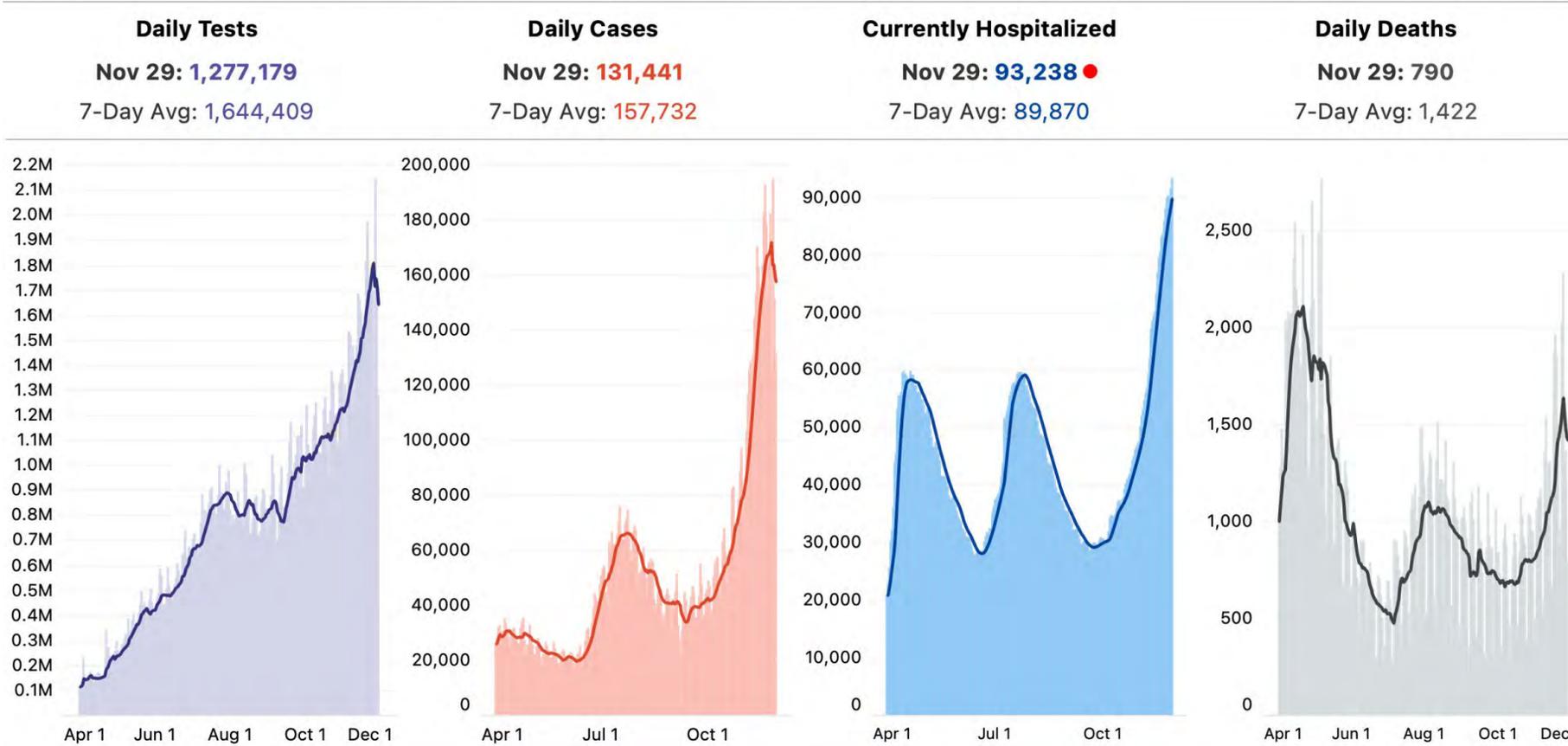
Nearly 15% of patients diagnosed with COVID-19 experience serious conditions including pneumonia and difficulty breathing.<sup>3</sup> Approximately 5% of patients with more severe disease experience acute respiratory distress syndrome (ARDS), which can lead to respiratory failure, and death.<sup>3</sup> This severe condition is linked to

excessive immune activation that causes a condition called “cytokine storm,” in which the inflammatory immune protein in the lungs increases to dangerously high levels. While hyper-reaction of the immune system has also been observed with other coronaviruses, like SARS and MERS, the dramatic increase in infectivity of COVID-19 has elevated its threat to the levels of the current global pandemic.<sup>4</sup>

Cell therapy has shown promise for treating respiratory distress syndrome.<sup>3</sup> In today’s newsletter, we highlight the scientific rationale for advancing iNKTs for the treatment of COVID-19.

### NATIONWIDE COVID-19 METRICS. 7-DAY AVERAGE LINES

Apr 1 - Nov 29



Agentus, a subsidiary of Agenus, has commenced a [clinical trial](#) evaluating Agent-797, our allogeneic iNKT cell therapy, in patients with moderate to severe symptoms of COVID-19. The trial started enrolling patients recently with Koen van Besien, M.D., Ph.D., Professor of Medicine and Director of the Stem Cell Transplant Program at Weill Cornell Medical Center and New York Presbyterian Hospital.

### Rationale for iNKT Cell Therapy to Treat COVID-19

Invariant natural killer T cells (iNKT cells) are a unique cell type that combine features of two critical arms of the immune system, T cells (adaptive immunity) and NK cells (innate immunity). Such a strategy is invaluable in combating diseases such as COVID-19. It has been observed that the number of iNKT cells are reduced in people with cancer and infectious diseases like COVID-19, resulting in an inadequate immune response against the invading pathogen.<sup>3</sup> Administration of Agent-797 is expected to increase the number of iNKTs in the body, which in turn has the potential to enhance an appropriate immune response against the infection.

Source: The COVID Tracking Project

Figure 1. US COVID statistics<sup>2</sup>

**Forward-Looking Statements:** This Agenus Newsletter includes forward-looking statements that are made pursuant to the safe harbor provisions of the federal securities laws, including statements regarding the therapeutic potential of Agent-797 and iNKT cell therapy generally, as well as clinical trial plans and timelines. These statements are subject to risks and uncertainties, including those described in our SEC filings.

Both scientific literature and AgenTus in-house data have demonstrated the potential of iNKT cells to effectively treat COVID-19 patients. Further, clinical trials have shown that iNKTs with a natural lipid ligand (alpha-galactoceramide) are safe and effective in patients with infections and cancer.<sup>5-10</sup>

**Activated iNKTs elicit a rapid anti-viral response via multiple mechanisms.** Activated iNKTs are designed to combat virally induced diseases such as influenza, HIV, hepatitis B, and hepatitis C.<sup>11</sup> In preclinical influenza models, activated iNKTs were shown to decrease the levels of the virus.<sup>12</sup> These cells promote an anti-viral response and enhance immunity through various mechanisms. These include the activation and regulation of other essential immune cells such as NK cells, T cells, and B cells. Generally, such an army of cells is crucial for an effective response against viral infections. Importantly, iNKT cells reduce the immune suppressive activity of myeloid-derived suppressor cells (MDSCs).<sup>13</sup> Recent studies have demonstrated that COVID-19 patients have increased expansion of myeloid derived suppressor cells (MDSCs), which dampen the body's immune response against the virus.<sup>14</sup> Thus, iNKT therapy could potentially benefit COVID-19 patients by reversing MDSC-mediated immune suppression.

**A very critical additional role of iNKT cells includes their ability to reduce the life-threatening complications of cytokine storm**

**implicated in respiratory distress.** COVID-19 can cause severe damage to the lungs leading to difficulty in breathing, pneumonia, or acute respiratory distress syndrome (ARDS), which can be fatal.<sup>3</sup> Patients with this condition accumulate extremely high levels of pro-inflammatory cytokines (like IL-6 and IL-1) that overwhelm the body causing injury, including to the lungs.<sup>15</sup> In preclinical models representative of COVID-19, activated iNKT cells have been shown to specifically migrate to areas of infection such as the lungs.<sup>11</sup> They result in a decrease in viral titers and prevent lung injury by reducing the number of inflammatory cells.<sup>16</sup> These unique abilities of iNKT cells support the rationale for developing AgenT-797 to treat harmful respiratory complications associated with infectious diseases such as COVID-19.

## Phase 1 Study of AgenT-797 is Underway for the Treatment of Moderate to Severe ARDS in COVID-19 Patients

Based on the scientific rationale described in this newsletter, we have initiated a [Phase 1 study](#) evaluating AgenT-797 in moderate to severe ARDS patients who require mechanical ventilation. Patients are administered a single infusion of iNKT cells in this dose escalation study. Besides evaluating safety, we will assess: i) time to

improvement in pulmonary function (number of ventilator free days and oxygenation improvement), ii) decline in viral burden from the respiratory tract and iii) persistence of iNKT cells. Data readouts from this trial are anticipated in 2021.

At Agenus / AgenTus, we are committed to contributing to the global efforts to combat the COVID-19 pandemic. In addition to our iNKT cell therapy, we are developing a sustainable source for the production of QS-21 Stimulon™, our best-in-class adjuvant system, for potential use in pandemic-related vaccines. [QS-21 has demonstrated](#) enhanced antibody responses in preclinical SARS-CoV-2 models. We are developing a proprietary manufacturing process that could yield high quantities of QS-21, potentially for billions of doses of vaccines. As described in a previous [newsletter](#), this pure, lower-cost product would enable much broader use of the QS-21 Stimulon™ adjuvant than allowed by the current source of QS-21, including its use in vaccines to prevent future pandemics.

### References:

1. <https://coronavirus.jhu.edu/map.html/>; as of November 29, 2020
2. <https://covidtracking.com/data>
3. <https://newyork.cbslocal.com/2020/11/02/covid-19-agentus-immune-cell-therapy-sponsored/>
4. [Hu T et al. Peer J. \(2020\)](#)
5. [Motohashi S et al. Clin Cancer Res. \(2006\)](#)
6. [Yamasaki K et al. Clin Immunol. \(2011\)](#)
7. [Exley MA et al. Clin Cancer Res. \(2017\)](#)
8. [Crowe NY et al. J Exp Med. \(2005\)](#)
9. [Schneiders FL et al. Clin Immunol. \(2011\)](#)
10. [Field JJ et al. PLoS One. \(2017\)](#)
11. [Ho L et al. Euro J Immunol. \(2008\)](#)
12. [Artiaga B et al. Nature. \(2016\)](#)
13. [Juno J et al. PLoS Pathog. \(2012\)](#)
14. [Agrati C et al. Cell Death Differ. \(2020\)](#)
15. [Cauchois R et al. PNAS. \(2020\)](#)
16. [Kok WL et al. J Leukoc Biol. \(2012\)](#)