SPECIFIC AIMS

Introduction: CMTx Biotech is a drug development company working to rescue and repurpose a proprietary *clinical-stage* drug candidate, incyclinide (CMT-3 / COL-3), for the treatment of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and suffering from Coronavirus disease 2019 (COVID-19). Our drug repurposing strategy is supported by the identification of incyclinide as a potential treatment for COVID-19 in two publicly available computational analyses [1, 2], as well as a comprehensive repository of research and peer-reviewed publications demonstrating the efficacy of the compound in multiple animal models of acute respiratory distress syndrome (ARDS) across four species, including mice, rats, pigs and sheep [3-17]. With this compelling scientific rationale, the primary goal of this application is to request financial support to pursue clinical trial planning activities meant to advance incyclinide into a Phase II human clinical study to evaluate its safety and efficacy in COVID-19 patients.

Significance: *Problem to be solved:* Since late December 2019, an outbreak of a novel zoonotic coronavirus (SARS-CoV-2 / COVID-19) with clinical presentations greatly resembling viral pneumonia has claimed the lives of over 418,000 worldwide, including over 117,000 in the U.S. alone (as of 6/13/2020). COVID-19 is highly contagious, infecting over 7.4 million patients globally so far, with an estimated mean R_0 of 3.28 [18] and an average incubation period of 4 days. According to the Centers for Disease Control (CDC), frequently reported COVID-19 symptoms include fever, cough, myalgia or fatigue, and shortness of breath. Approximately 20-30% of hospitalized COVID-19 patients have required intensive care for respiratory support [19, 20]. COVID-19 can lead to acute lung injury, ARDS, multiple organ failure and death [19, 21, 22]. Studies have shown that COVID-19 has a mortality rate of up to 4.2% [23]. Predictors of fatal outcomes include age, the presence of underlying diseases or secondary infection, as well as elevated inflammatory indicators in the blood, and mortality may be due to virus-activated "cytokine storm syndrome" or fulminant myocarditis [24, 25].

Gap in Knowledge: There is currently no vaccine for COVID-19, and only Remdesivir (Gilead Sciences) has shown efficacy in a randomized, double-blind, placebo-controlled clinical trial, along with Emergency Use Authorization from the FDA [26]. Clinical management of COVID-19 patients includes prompt implementation of recommended infection prevention and control measures, as well as supportive management of complications, including mechanical ventilation and advanced organ support. There remains a critical unmet medical need for safe and effective therapeutic interventions that mitigate the host hyper-inflammatory response to COVID-19 in order to prevent lung injury, ARDS, multiple organ failure and death.

Preliminary Studies: Two recent independent studies performed *in silico* have suggested that incyclinide may have significant therapeutic benefit in patients with COVID-19 [1, 2]. Importantly, the safety of incyclinide has already been demonstrated in Investigational New Drug (IND)-enabling studies, and incyclinide has been evaluated in a number of human clinical trials for the treatment of diseases as disparate as AIDS-related Kaposi's sarcoma, recurrent high-grade gliomas, refractory metastatic cancer, acne, rosacea and periodontitis [27-38]. Moreover, published pre-clinical efficacy studies have shown that systemic administration of incyclinide prevents the development of ARDS and septic shock, and improves survival in several chronic insidious onset animal models of ARDS across several species, including mice, rats, pigs and sheep [3-17]. Taken together, CMTx Biotech is well-positioned to demonstrate the safety and efficacy of incyclinide as a treatment of COVID-19 patients in a Phase II human clinical trial.

Product: Incyclinide is a *clinical-stage*, non-antibiotic, chemically-modified tetracycline that belongs to a class of pleiotropic matrix metalloproteinase (MMP) modulators which inhibit pathologically-excessive collagenolysis and resolve systemic inflammation, including predecessor drugs Periostat® and Oracea® [39, 40]. CMTx Biotech is working to repurpose and commercialize incyclinide as a once-daily, orally-administered treatment for hospitalized COVID-19 patients. We strongly anticipate that incyclinide will inhibit COVID-19 disease progression, mitigate acute lung injury and respiratory distress, reduce the need for intensive care and intubation, and improve clinical outcomes for COVID-19 patients, including overall survival.

Specific Aim I: To design a Phase II clinical study to evaluate the safety and efficacy of incyclinide for the treatment of hospitalized COVID-19 patients, develop a pre-IND briefing document inclusive of a clinical study synopsis, and engage the FDA in a pre-IND meeting.

Specific Aim II: To prepare key clinical study documents, including a full clinical study protocol, investigator brochure and informed consent form, along with detailed plans for statistical analysis, recruitment and retention, and data management, in support of an Investigational New Drug (IND) submission to the FDA.

Long-Term Goal: Our goal is to obtain Emergency Use Authorization (EUA) and regulatory approval from the FDA to market incyclinide for the safe and effective treatment of COVID-19 patients, as well as to establish a partnership with a pharmaceutical company in the form of a license or acquisition.

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