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Liquid Foam Therapy (LIFT) for Acute COVID-19 Patients

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Within three months, the operational prototype of a **liquid foam therapy (LIFT)** drug delivery device will be available. Our technology will be used in preclinical trials as a rescue therapy for **compassionate use in acute COVID-19 patients suffering from acute respiratory distress syndrome (ARDS)**.

Background

The infectious coronavirus disease 2019 (COVID-19) has become a global pandemic. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), entering primarily through the respiratory tract. Once inside the lungs, it penetrates epithelial cells and begins to replicate, killing the cells in the process. In the most severe cases, the disease will deteriorate to acute respiratory distress syndrome (ARDS), a deadly inflammatory lung condition accountable for most deaths from COVID-19. This syndrome, first described 50 years ago[1], still has no effective pharmacological treatment in adults[2–4]**.**

COVID-19 and ARDS: One of the hallmarks of ARDS is damage to pulmonary surfactant, the inner liquid lining of the lungs. Surfactant regulates inflammation and reduces surface tension in the alveoli, thus enabling the act of breathing[3,4]. Although COVID-19 pathophysiology is not yet thoroughly understood, it was shown that the virus kills surfactant secreting type II alveolar cells after it binds to a receptor called ACE2 on their surface[5,6]. **We hypothesize that surfactant depletion may be particularly severe in COVID-19-related ARDS**.

Surfactant replacement therapy (SRT) exists and is a lifesaving clinical procedure in treating ARDS in preterm newborn children (neonates), whose immature lungs lack pulmonary surfactant. In neonates, SRT is based on endotracheal administration of liquid surfactant instillations[7]. Due to differences in lung size, this clinical strategy is ineffective in adults[2]. Liquid instillations are strongly affected by gravity and quickly drain into pools (see the green stains in **Fig. 2a below**), drowning some lung regions while leaving others untreated. Administering surfactant via inhalation aerosols has been explored, but the doses inhalation devices deliver remain too low, <<1 ml for inhalers and <1 ml/hour for nebulizers[8], compared to the required ~100–200 ml of surfactant. Altogether, current administration methods for ARDS in adults remain sorely inadequate, leaving the disease untreatable. ARDS patients stay in intensive care units ventilated for a median of 10 days, with mortality rates[9] around 40%.

Breakthrough with patent pending liquid foam therapy[10] (LIFT): We propose using liquid foam as a carrier for surfactant delivery to the lungs and **repurposing existing neonatal drugs for acute COVID-19 patients on a short development timescale**. Unlike liquid instillations, foam is "gravity defiant": LIFT distributes homogeneously throughout the lungs (see **Fig. 2b** below) and is capable of delivering doses of >100 ml to each lung. **LIFT has the potential to become one of the biggest breakthroughs in pulmonary drug delivery** in the last several decades, increasing deliverable doses 100-fold (e.g., pulmonary surfactant) and the size of the deliverable particles over 10-fold (e.g., enabling for the first time delivery of stem cell therapy directly to the lungs).

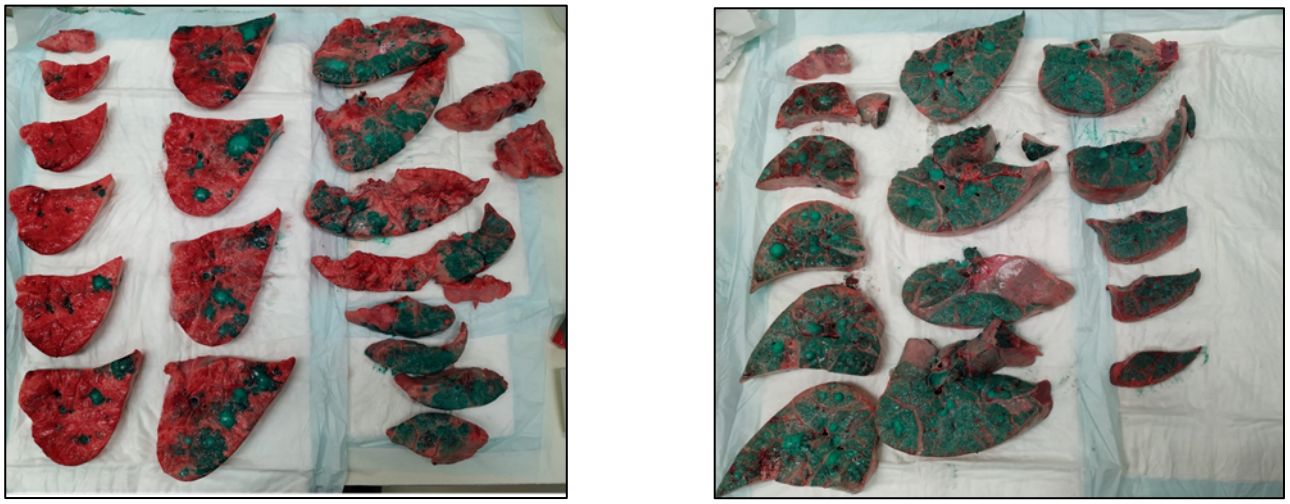
Mechanism of Action and Results to Date

To deliver LIFT, the device (under construction, see **Fig. 1** below) is intended for clinical use under the supervision of a physician, and can be deployed in either intubated or ventilated patients, through bronchoscopy, laryngeal mask or voluntary inhalation (after local anesthesia, suppressing cough reflex).

Figure 1: Computer-aided design of LIFT pulmonary drug delivery device.

Our device incorporates proprietary capsules containing chemically inert foaming material, which is capable of carrying various drugs. Alternatively, the drug itself is foamed. Briefly, after loading the capsule, the device foams its content and pushes the foam out of the device through an outlet tube. In parallel, the device pushes an interchangeable therapeutic liquid solution through the same outlet tube. The foam and therapeutic solution mix in the outlet tube and enter the patient's respiratory system as a homogeneous medicinal foam. The patient is ventilated throughout the treatment, and the ventilator's action pushes the foam deep into the patient's alveoli. The foam doesn't flow back or obstruct the patient's airways, and the entire treatment lasts from less than one minute to up to two minutes.

Homogenous distribution of LIFT was demonstrated **in vitro in anatomically realistic 3D-printed airway models** on the macroscale, as well as **ex vivo in excised porcine lungs** (**Fig. 2**). The ability of LIFT to transport live cells for future applications (e.g., stem cells for treatment of COVID-19) was also demonstrated in vitro.



(a) **(b)**

Figure 2: (a) Liquid vs. (b) LIFT administration of identical dye doses to excised 90 kg porcine lungs.

Furthermore, we **successfully completed the first preclinical in vivo experiments in rats to examine the safety of the carrier foam**. No adverse events were observed during the trials (e.g., blood oxygen levels and lung compliance were monitored). The carrier foam formulation is based solely on materials that have been in use for decades in pulmonary drugs, with well-established safety profiles.

Additionally, specifically in the case of surfactant, the process may be further simplified by foaming the commercially available surfactant as-is with no carrier. To examine this alternative method, a severe-ARDS model was induced in rats (repeated whole-lung lavage model). The trials were successful. **Rats treated with surfactant-laden LIFT recovered to a healthy state within 15–30 minutes with no adverse effects.**

Lifeline Workplan

Following our successful preclinical in vivo experiments in models of ARDS in rats, and, in parallel, the successful ex vivo experiments in excised pig lungs, we need financial support for a “lifeline” for the next three months (see **Fig. 3** below). This support will guarantee the development of a functional full-scale prototype of the delivery device and conduct a small (~5 pigs) proof-of-concept in vivo study for the treatment of LIFT in models of ARDS in pigs. Successful in vivo results in pigs will fast-track the chances of deploying LIFT immediately as a compassionate treatment in severe COVID-19 patients suffering from ARDS.

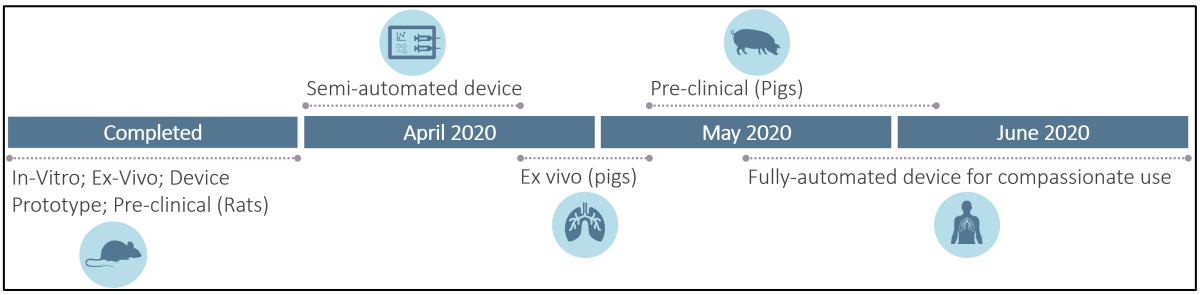


Figure 3: Estimated accelerated LIFT delivery device development timeline.

Funding

Implementing the Lifeline Workplan requires funding of $150,000 to cover research staff salaries, research and prototyping equipment, device parts and consumables, drug purchasing (i.e., surfactant) and preclinical experiments.

Bibliography

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet*. 1967 Aug 12;2(7511):319–323.
2. Grotberg JB, Filoche M, Willson DF, Raghavendran K, Notter RH. Did reduced alveolar delivery of surfactant contribute to negative results in adults with acute respiratory distress syndrome? *Am J Respir Crit Care Med*. 2017 Feb 15;195(4):538–540 .
3. Matthay MA, McAuley DF, Ware LB. Clinical trials in acute respiratory distress syndrome: challenges and opportunities. *Lancet Respir Med.* 2017 Jun;5(6):524–534.
4. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. *N Engl J Med.* 2017 Nov 9;377(19):1904–1905.
5. del Rio C, Malani PN. COVID-19—New insights on a rapidly changing epidemic. *JAMA* [online]. 2020 Feb 28. doi:10.1001/jama.2020.3072
6. Penninger J. World leading geneticist and immunologist Josef Penninger on potential COVID-19 treatment. 2020 Mar 13. Available at: https://youtu.be/jAW6VBWTiAA?t=1156
7. Polin RA, Carlo WA. Surfactant replacement therapy for preterm and term neonates with respiratory distress. *Pediatrics*. 2014 Jan;133(1):156–163.
8. Claus S, Weiler C, Schiewe J, Friess W. How can we bring high drug doses to the lung? *Eur J Pharm Biopharm.* 2014 Jan;86(1):1–6.
9. 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 Feb 23;315(8):788–800.
10. Ostrovski Y, Sznitman J. Foam for pulmonary drug delivery. 2017 Nov. PCT/IL2017/051208. Available at: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018083703