Combatting the long-term spectre of COVID-19: LAMELLASOME as a therapeutic approach to complement antivirals and immunisation.

- Even with the development of antivirals and vaccination, coronaviruses will be with humanity for the indefinite future, in the form of epidemic waves, new strains, and seasonal recurrence.
- As a result, acute coronavirus pneumonitis, and possibly consequential fibrotic lung disease, will remain a major long-term burden for patients, health systems and society. To impact this burden, specific treatments are needed to tackle pneumonitis and long-term fibrotic lung disease.
- Recent research suggests that naturally occurring lipid constructs found within the lung, known as lamellar bodies, have evolved to regulate the inflammatory processes involved in pneumonitis and fibrosis.
- Synthetic lamellar bodies ("LAMELLASOME") have been developed, and these have been shown to reduce or possibly even prevent pneumonitis after lung injury and to prevent or mitigate the degree of consequential lung fibrosis.
- LAMELLASOME represents a critical opportunity to complement antivirals and immunisation in our global efforts to tackle the long-term spectre of coronavirus.

Severe COVID-19 causes widespread inflammation of the lung, known as pneumonitis. Pneumonitis causes shortness of breath, impairs lung function and can result in acute respiratory distress syndrome and death. It is the most common reason for hospitalisation of COVID-19 patients; for intensive care admission and for ventilatory support.

At present, there are no specific treatments to prevent pneumonitis or to prevent it worsening in patients with COVID 19.

Pneumonitis & severe COVID-19

Pneumonitis is a common feature of many types of lung injury, including infection (including COVID-19 infection), burns, radiation, mechanical damage and trauma (for example road traffic accidents and as an adverse effect of mechanical ventilation).

In some people, pneumonitis can deteriorate rapidly because of an immune hyper-reaction. In these individuals, instead of initiating a healing response that mitigates the initial damage, their immune response spirals out of control, damaging the lung further. This in turn further stimulates their immune system, initiating a vicious cycle that further damages the lung and can go on to damage other organs. At a molecular level, this progression is marked by a rapid increase in inflammatory mediators (a "cytokine storm") and widescale up-regulation of genes associated with inflammation and the immune response.

Lung fibrosis after pneumonitis

In the longer term, even if patients recover from pneumonitis, the damaged lung tissue can undergo a process of remodelling, after which it does not go back to normal but is replaced by scar tissue. The scar tissue cannot contribute to respiratory function and, because the scarring increases the rigidity of the lungs, breathing can become more difficult. Like scar tissue anywhere in the body, scarring in the lungs is permanent.

This scarring process can continue to develop in the longer term, even after the effects of the initial injury have subsided (a process known as progressive lung fibrosis). This results in the lungs gradually becoming stiffer over time, causing increasing shortness of breath and diminishing quality of life, and in some cases proving fatal.

There is a legitimate concern in the emerging literature that after COVID-19 pneumonitis, a proportion of patients may develop permanent lung fibrosis and experience lung impairment. It is not yet clear whether such fibrosis will progress over time.

Vaccines and antivirals are not enough

Vaccine and antiviral development are critical in the ongoing fight against COVID-19. However, they should not constitute the be-all and end-all of our approach.

Antivirals aim to hinder the SARS-CoV2 virus' ability to enter cells in the body and to replicate. But even if they do perform these functions, the extent to which they can prevent hyper-immune responses, life-threatening pneumonitis and subsequent fibrosis in susceptible individuals remains to be seen.

Vaccines may be only partially effective. It is also possible that vaccines – which work by stimulating the immune system - may be least effective in the very people who are most at risk from COVID-19: those with underlying comorbidities and the elderly. These people are more likely to have an impaired immune system that may render them poorly responsive to vaccines.

Herd immunity, whether achieved through immunisation or infection will also, in the longer term, provide some mitigation against future epidemics of SARS-CoV2. Unfortunately, in the absence of vaccination, this would require some 60% of the population to have been infected, with all the attendant clinical, economic and societal consequences both during periods of acute infection and in the long term. Widespread natural infection is also no guarantee against localised outbreaks, future epidemics or seasonal recurrences. Studies on previous coronaviruses have shown immunity from natural infection to be short lived (around 1 year), with reinfection likely.

The bottom line is that:

- Coronaviruses will be with humanity for the indefinite future, in the form of epidemic waves, new strains and seasonal recurrence
- Acute coronavirus pneumonitis, and possibly consequential long-term fibrotic lung disease, will remain a major global burden for patients, health systems and society

The message is clear: We need a wider array of specific strategies, beyond antivirals, vaccination and public health measures.

Harnessed natural lung mechanisms

One key avenue of opportunity is to effectively prevent, halt or limit pneumonitis and fibrotic damage in the lung. However, the level of biological complexity involved is a big challenge. The standard biological research approach is to focus on a specific pathway and to target a protein or gene that might dampen the immune response. Unfortunately, intervening in this way in such a complex, multifactorial, hyper-responsive immune cascade looks unlikely to be effective any time soon.

Just as vaccines leverage the complexity of our bodies' immune system to protect against specific infections, there may be ways of harnessing the lungs' intrinsic ability to regulate inflammation – to exploit the complex mechanisms that evolution has already installed to maintain healthy lung function. Over the last 20 years, a new class of naturally occurring constructs have been researched, which seem to provide an opportunity to do exactly this. These "lamellar bodies" are small lipid vesicles, located in a variety of organs including the lung. One of their functions appears to be to preserve and protect the lung from damage, including immunological damage, following injury.

Artificially synthesised versions (so-called "mimetics") of lamellar bodies, LAMELLASOME™, have demonstrated the ability to prevent or at least reduce the severity of pneumonitis after lung injury and to prevent or mitigate the degree of consequential fibrosis of the lung tissue. This capability has obvious significant beneficial implications for COVID-19. Recently the potential role of synthetic lamellar bodies in the treatment of COVID-19 has been postulated, including the possibility that it may prevent downstream fibrosis in those recovering from COVID-19.

Synthetic lamellar body mimetics are therefore potentially of great value as an additional line of attack against COVID-19, as well as other lung diseases with a pneumonitis component. They offer a strategy that complements vaccines and anti-virals and which could be a critical pillar in our fight against this new and long-term threat to human health and wellbeing.