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Press release

Synovo announces entry into development of its Covid-19 viral pneumonia therapy candidate.

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Synovo GmbH announced that it will accelerate development of SYD015, a compound designed to treat acute viral and bacterial pneumonia and acute respiratory distress syndrome (ARDS). Although generally active in pneumonia, the compounds have properties that make them particularly relevant to use for acute Covid-19 pneumonia and respiratory distress.

The compounds have demonstrated proof of concept in models of pneumonia and have now demonstrated key safety properties.

"Therapies like CSY015" are important because they are not viral strain specific, or indeed virus or bacteria specific. Thus, they could also be used also in other SARS-like diseases, should new variants emerge in the future. They are developed for the seriously ill and can be used to treat many different viral and bacterial pneumonias outside of epidemics. Measures that are pandemic specific are difficult to finance and stockpile. In the current Covid-19 emergency, the immediate response has largely been through compound re-purposing from existing therapies used in other diseases.

Unlike existing supporting therapies for acute pneumonia that are immune suppressive, SYD015 supports active immune response while limiting destructive effects. It also has broad spectrum effects limiting secondary infections by multi-resistant pathogens.

Synovo's founder and managing Director, Dr. Michael Burnet said:

"In late 2019, we received confirmation from specialist European laboratories that our candidate compounds fulfill the key requirements for treatment of acute pneumonia and acute respiratory distress syndrome. This pattern of activity fits very well with the profile needed to deal with acute phases of Covid-19 infection and we are now taking the steps necessary to accelerate development for this use."

He added: "After encouraging discussions with US-based colleagues, and expressions of interest from Chinese pharmaceutical companies, we are initiating development steps including the those required for entry into human trials."

SYD015 is an immune modulator that promotes immune reactions against pathogens while reducing the destructive reaction against host tissues. It does this through a form of "fore warning" of the immune system enabling a more effective response when it encounters the pathogen. This reduces excess inflammatory reactions without compromising intrinsic immune processes. It also

supports the immune response to bacterial secondary infections that are reported to worsen the lung symptoms induced by Covid-19.

Amongst other advantages, SYD015 requires very low doses. The human oral dose is likely to be in the range of 0.1 to 0.5 mg. This means that a kilogram of material will be sufficient to make 1-20 million doses. Because the substance is easy to make and inexpensive, it is particularly well suited to uses in less developed settings where access to ventilators may not be feasible. The potential impact of Covid-19 in less developed countries is currently not receiving significant attention, but in the absence of intensive care facilities with ventilators, the few patients with severe signs will be vulnerable. Cost-effective therapies that are also useful in this setting will be needed.

Background

About Covid-19 and SARS-CoV-2

One of the large Corona virus family, SARS-CoV-2 causes the disease called Covid-19. Corona viruses cause a range of diseases in humans and animals although thus far, the 3 variants endemic to the human population were associated with "common colds" rather than lethal viral pneumonias. SARS and MERS were similar phenomena to Covid-19, with related viral sequences, but higher mortality.

SARS-CoV-2 is an RNA virus that infects the upper airways and progressively the lower airways, heart and major blood vessels. It enters cells via the Angiotensin Converting Enzyme (ACE2) which is up-regulated in certain forms of cardiovascular disease, and this is proposed as one reason why it is particularly severe in patients with heart disease.

Although apparently mild in children, it appears to be progressively more severe with the increasing age of patients. This is common in some viral diseases where adult immune systems either over-react to the virus, worsening signs, or are unable to raise an effective anti-viral response. The age effects may also reflect cumulative weakening of the lungs and heart with age. Patients with severe disease appear to have a limited lymphocyte response, slowing the immune reaction that would ordinarily neutralise the virus.

Where severe, it also causes inflammation of both the lungs and the heart and major coronary vessels. This inflammation is both a reaction to the damage that the virus does to cells, but also a form of "over-reaction" in which more immune cells than needed arrive at the tissue and amplify signals of distress. This leads to further edema (accumulation of fluid) which fills airways and prevents air reaching the alveoli.

Another form of symptoms are muscular aches and fever which are a consequence of the production of inflammation signals called interferons which are part of the anti-viral immune response. In severe cases, Covid-19 causes production of very high levels of these signals and these in turn can reach excessive levels causing what is known as "cytokine storm" in which the body's own inflammatory signals induce their own production in a futile cycle. The adaptive

response to the virus takes time and during this time, these acute excessive responses can generate more damage than the virus itself.

Excess accumulation of immune cells in the lung is particularly dangerous due to edema restricting breathing efficiency. Existing, treatments to manage or reduce edema are, however, suppressive of adaptive immunity and can potentially delay the immune response. Thus, better supportive therapies are needed to help patients survive acute effects.

So far, several therapies appear to be effective in severe cases. These include "host modifiers" chloroquin, hydroxy chloroquin and azithromycin in combinations, and the more broad-spectrum anti-virals that interfere with viral replication favipiravir and remdesivir.

About SYD015

SYD015 is in development for the treatment of infections of the airway and chronic lung disease. It is an "immune normalizer" – that is to say that it supports immune reactions towards pathogens, but prevents excess immune reaction to host tissue.

SYD015 is a small molecule drug that is suitable for oral (pill/tablet/capsule) or inhaled delivery. It is active in various models of pneumonia between 0.01 to 1 mg/kg via the oral route.

SYD015 reduces production of cytokines like IL-6 while at the same time stimulating the activity of immune cells towards pathogens. This means that fewer immune cells are required to neutralize the pathogen.

All pathogens including viruses employ means to suppress the immune system while the pathogen multiplies. When it has multiplied, the pathogen then induces inflammation and secretion of fluids to ensure its distribution. Thus, the cough and runny nose of a cold or flu are the over-reaction induced by the virus to ensure that it will be further distributed by the release of excess fluids via the airway.

In certain instances, inflammation and fluid accumulation is excessive or bacteria take advantage of the situation, and pneumonia is the result. Severe pneumonia of this type is common in a range of viral diseases and amongst sufferers of chronic obstructive pulmonary disease (COPD) and other chronic lung disease. It is a major cause of loss of life every year.

About Synovo GmbH

Synovo is a drug discovery company based in Tübingen Germany. It was founded in 2004 and is focused on immune and inflammation-related diseases. It has 54 employees on two sites. It has extensive collaborations with European and international pharmaceutical and biotechnology companies and universities and public sector organisations. Synovo is lead by its founder and managing director Michael Burnet. Prior to founding Synovo, Dr. Burnet was a project manager for Zeneca in the United Kingdom.