EPITOME

ANTIVIRAL LLC

The Opportunity: Inhaled Green Tea for Lung Disease

This is a brief summary of the full presentation, which also has the bibliographic references.

Respiratory failure requiring ventilation affects 455 per 100,000 people a year in the US. The death rate is 23% and survivors have many morbidities; treatment cost was $181 billion in 2017. There are many manifestations of respiratory failure, called ARDS, ALI, ARF, and SARS, but they share commonalities. The COVID-18 pandemic gave new impetus to research in this field. A striking finding of Rouhani *et al* at, 2021, at University of Chicago was that the cytokines IL-6 and CCL2 of the cytokine storm were being generated by the lung type II pneumocytes, not the circulating immune cells. Their Figure 4 shows these infected TTF+ lung cells lighting up with yellow IL-6 mRNA and the light-blue SARS-CoV-2 mRNA.

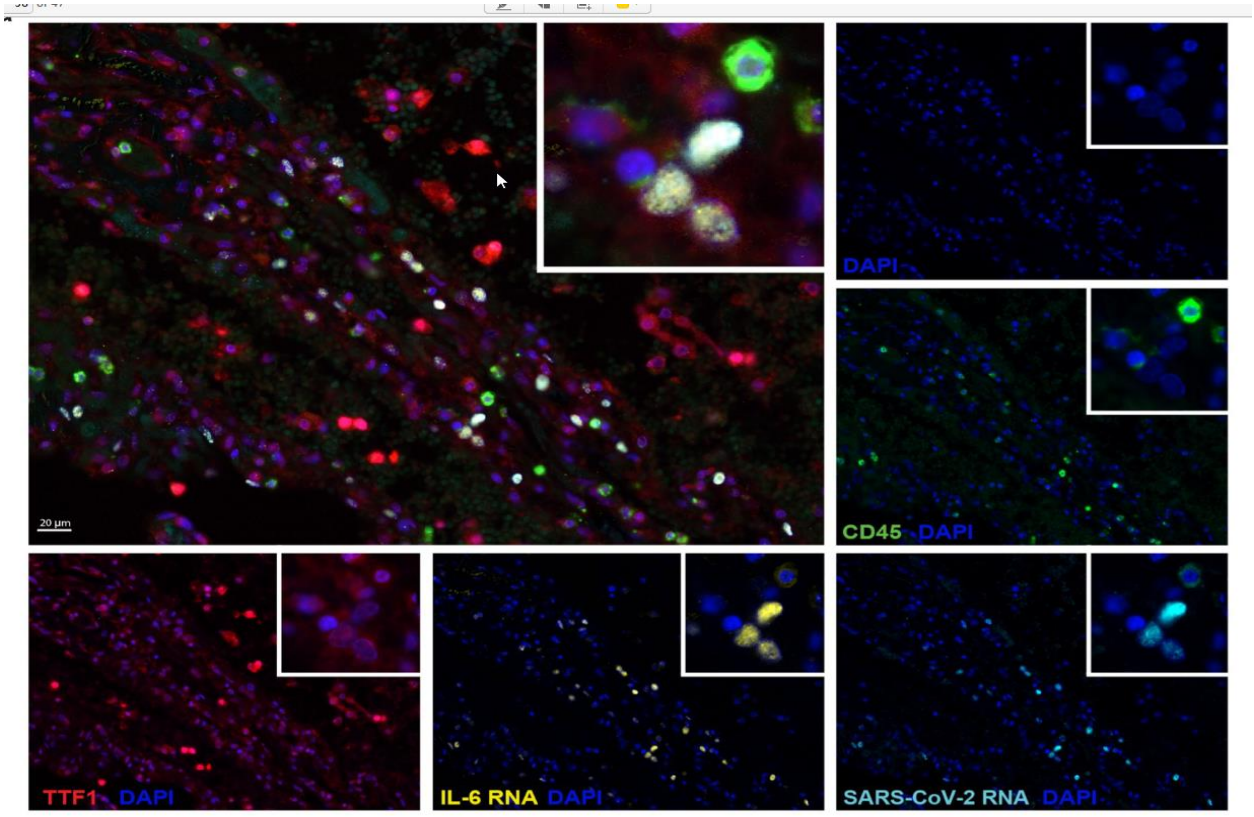

Figure 4: Lung epithelial cells predominantly express IL-6 in lung autopsy tissue in fatal COVID-19. Autopsy lung sections from 10 fatal COVID-19 cases were simultaneously stained for SARS-CoV-2 RNA, IL-6 mRNA, TTF1+ pneumocytes, and CD45+ leukocytes using RNA-ISH combined with multispectral immunofluorescence staining for protein. (a) Representative staining for TTF1 (red), CD45 (green), IL-6 RNA (yellow), SARS-CoV-2 RNA (light blue), and nuclear DAPI counterstain (blue); each stain shown separately and merged. Multispectral images were acquired at 40x magnification. Overlaying high-power images showing SARS-CoV-2 infected TTF1+ pneumocytes expressing high levels of IL-6. (b) Bar plots showing the phenotype composition of cell populations in each

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The cytokine response is triggered by activation of NF-κB, which induces transcription of a host of inflammatory mediators. NF-κB is an ancient molecule which acts as the fire alarm. It is triggered by a variety of danger signals and its effects are seen in many diseases. There is no lack of interest in NF-κB; 750 inhibitors have been developed, but failed in clinical trials due to toxicity.

During the COVID pandemic, which was very intense in northern Italy in 2019 – 2020, Dr. Saverio Bettuzzi and colleagues tested the green tea extract Theaphenon E, delivered orally and by inhalation through a nebulizer, in 10 patients who tested positive for the virus. All 10 recovered in a median of 9 days, range 7 – 15 days, with 7 of 10 testing free of virus, with a range of 6–13 days. Notably, 3 patients received a CT scan; the two oldest patients had 10% lung involvement and an already hospitalized patient had 40% involvement, yet all three recovered in the same range. Muncusco *et al* followed 4,480 patients who tested positive in the neighboring province and found a median time to first negative test of 31 days (IQR 24–41). Comparison by the Fisher-Yates test showed the probability that the Bettuzzi results would happen by chance after 10 days was $p < 0.0023$ and $p < 0.005$ at 20 days. (Bettuzzi *et al* 2021)

Hiroshi Yamada conducted inhalation trials of another GTE in bed-ridden patients to treat MRSA infection, with some success and no adverse events. Patients with respiratory failure often develop fibrosis, scar tissue in the healing lung, and several animal studies and one human study support suppression of fibrosis by GTE. Both inhaled and oral Polyphenon E may be effective.

Dr. Yukihiko Hara is the father of green tea, as we know it. As Director of the Mitsui Norin Food Research Lab, he led development of the green tea extract Polyphenon E©, which was used by the US National Cancer Institute (NCI) in many trials of cancer prevention. NCI sponsored pre-clinical toxicology tests of Polyphenon E and EGCG before submitting their IND in the late 1990s. Dr. Hara and his colleague Dr. Shu Jun Cheng of the Chinese Academy of Medical Science tested and patented (1996) the use of Polyphenon E in a topical formulation to treat genital warts. Epitome Pharmaceuticals licensed this patent, submitted the IND and conducted the first clinical trial in 2000. The patent was licensed by MediGene AG and they completed development, receiving an NDA in 2006 for Veregen. We have a long-standing relationship with Dr. Hara and Mitsui Norin Co. Ltd.

Epitome Antiviral LLC submitted an IND and the subsequent dialog with the FDA in 2021. The FDA requires pre-clinical inhalation toxicology testing in rodents, as expected. We have mapped out a plan to reach market in less time than a typical new chemical entity.

The potential market for Polyphenon E inhalation therapy in respiratory distress is at least one billion USD in the US alone, with a million people per year receiving ventilation in hospitals. Oral use to prevent fibrosis is not counted in this total, not the more speculative use for influenza at home. Worldwide use is also not counted due to the uncertainties of the price in countries that regulate price.

Aside from the three years of exclusivity granted to a botanical product like Polyphenon E used in a new indication, there is no easy way for a competitor to enter the market. Generics are not allowed for botanical medications in the US. The definition of the product is the process that produced it, not the final composition; competitors have to have their green tea extract tested with the full pre-clinical toxicology program before the FDA will allow an IND.

The safety profile of inhaled Polyphenon E is excellent. A total of 109 patients received inhalation therapy at roughly the same dose for two weeks. There were no adverse effects.

I look forward to discussing this opportunity with you.

Respectfully submitted, Paul T. Wegener