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1 **Could IL-17 represent a new therapeutic target for the treatment and/or**
2 **management of COVID-19-related respiratory syndrome?**

3

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21

22 **Keywords:** COVID-19, IL-6, IL-17, respiratory diseases, virus.

23

24 **PubChem:** Fedratinib (PubChem CID: 16722836); IL-1 β (PubChem CID: 123872); IL-8
25 (PubChem CID: 44357137); PGE₂ (PubChem CID: 5280360); Plaquenil (PubChem CID: 3652).

26

27 This paper is dedicated to Sofia Maione born during COVID-19 outbreak.

28

29 **Abbreviations:** BALF, bronchoalveolar lavage fluid; COVID-19, Coronavirus disease-19; **FDA,**
30 **Food and Drug Administration;** G-CSF, granulocyte-colony stimulating factor; GM-CSF,
31 granulocyte-macrophage colony stimulating factor; Gro- α , growth-regulated oncogene- α ; IL-
32 interleukin-; **IP-10, interferon γ -induced protein 10; JEK2, Janus kinase 2; MCP-1, monocyte**
33 **chemoattractant protein-1; MERS, Middle East respiratory syndrome; MIPs, macrophage**
34 **inflammatory proteins; mRNA, messenger RNA; PGE₂, Prostaglandin E₂; SARS, severe acute**
35 **severe syndrome; STAT3, signal transducer and activator of transcription 3; TLRs, toll-like**

36 receptors; TNF- α , tumor necrosis factor- α ; TREM-1, triggering receptor expressed on myeloid
37 cells-1; WHO, World Health Organization.

38

39 Letter to the Editor

40 Since 2003, outbreaks of Coronavirus have caused multiple public health epidemics including
41 severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). **The**
42 **first case of infection in response to a new strain of Coronaviridae, designated Coronavirus disease-**
43 **19 (COVID-19) was recorded in Wuhan, China [1].** This virus appears to be weaker than SARS, in
44 terms of pathogenesis but more sustained in its transmission behavior [2]. COVID-19 is transmitted
45 through droplet inhalation, saliva, nasal and mucous membranes of **eyes**. Symptoms include fever,
46 continuous coughing and shortness of breath. This has been **shown to lead** to a mild or severe
47 respiratory **illness and, in a number of cases, death. However,** this is largely dependent upon the
48 health status of the patient, with highest risk associated with those who have pre-existing respiratory
49 tract pathologies [3]. **As of April 2, 2020, the World Health Organization (WHO) reported 896,450**
50 **cases of COVID-19 and 45,525 deaths worldwide.** The number is growing, and urgent clinical
51 strategies are needed [supplementary materials 1].

52 The pathological presentation following COVID-19 infection in severe cases [supplementary
53 materials 2] includes specific modulation and release, mainly by lung epithelial cells, of pro-
54 inflammatory cytokines, such as interleukin-(IL)-6, IL-1 β and tumor necrosis factor- α (TNF- α)
55 which contribute to lung damage by further aggravating clinical features, such as pneumonia
56 **severity in** patients affected by this virus [4].

57 **From a cellular viewpoint, lung epithelial cells play a crucial role locally in the release of several**
58 **pro-inflammatory cytokines such as IL-8 and IL-6. Recent studies have shown that the production**
59 **of these mediators is regulated at the transcriptional level. Indeed, human lung epithelial cells turn**
60 **from normo-responsive to hyper-responsive IL-8 and IL-6-producing** cells when related messenger
61 RNA (mRNA) degradation is reduced. Recent findings demonstrate the involvement of pro-
62 inflammatory cytokines in several respiratory system diseases including asthma and chronic
63 obstructive pulmonary **disease. In particular, IL-6** has been shown to play a critical role in
64 increasing airway resistance, thus increasing the risk of respiratory crisis [5].

65 Considering **the role that** IL-6 plays in airway disease, preliminary studies targeting this cytokine
66 therapeutically in response to COVID-19 infection through the use of humanized monoclonal
67 antibodies against the IL-6 Receptor (Tocilizumab), have demonstrated encouraging results as
68 reported in "TOCIDVID-19 Protocols" but further validation is still required. Interestingly,
69 hydroxychloroquine (Plaquenil), an antimalarial drug, has also been reported to downregulate the
70 expression of toll-like receptors (TLRs) and IL-6 production, and therefore may have potential anti-
71 COVID-19 activity [supplementary materials 3].

72 **However, other inflammatory cytokines** require attention in this disease, and this has prompted
73 investigators and clinicians around the world to set new mechanistical hypothesis/approaches. In
74 this context, we would like to propose a potential interplay between IL-6 and IL-17 in COVID-19-
75 related respiratory pathological events.

76 IL-17A is a pro-inflammatory cytokine mainly **produced by Th17 cells, but** also by innate and other
77 adaptive immune cell components such as natural killer T cells, macrophages, **neutrophils, CD8⁺ T**

78 cells, $\gamma\delta$ T cells and innate lymphoid cells [supplementary materials 4]. The biological functions of
79 this cytokine include i) the production of chemokines such as IL-8, monocyte chemoattractant
80 protein-1 (MCP-1) and growth-regulated oncogene- α (Gro- α) which increase the recruitment of
81 neutrophils and monocytes, ii) the production of IL-6, a cytokine produced by macrophages,
82 epithelial cells and T cells in response to extracellular microorganisms, iii) the production of the
83 hematopoietic cytokines such as granulocyte-colony stimulating factor (G-CSF) and granulocyte-
84 macrophage (GM)-CSF, that stimulate the expansion of myeloid lineages and the production of
85 other mediators such as IL-1, TNF- α and Prostaglandin E₂ (PGE₂) [6]. Moreover, it has been
86 reported that IL-17 is associated with several inflammatory respiratory diseases. Laan and
87 colleagues reported that the autocrine action of IL-17 encourages the production of chemokines
88 such as IL-8 in human bronchial epithelial and venous endothelial cells, thereby promoting the
89 influx of neutrophils and exacerbating airway inflammation [supplementary materials 5].

90 Paradoxically, IL-17 plays a key role in defence from both extracellular bacteria and viruses that
91 infect airway mucous membranes. In fact, this cytokine, in combination with IL-22, regulates
92 homeostasis and contributes to the repair of epithelial cells, damaged previously by extracellular
93 inflammatory stimulus. However, an exacerbation of this type of stimuli, **can induce** an
94 overproduction of IL-17, which may tip the balance towards a more pro-inflammatory pathological
95 activity, contributing to increased risk of airway diseases [supplementary materials 6].

96 Several studies, including those from our research group, have shown that IL-17 sustains rather than
97 induces inflammation and promotes the recruitment of inflammatory monocytes which results in the
98 release of a range of mediators including IL-16, triggering receptor expressed on myeloid cells-1
99 (TREM-1) and different cyto-chemokines which collectively are involved in lung-related
100 inflammatory diseases [supplementary materials 7 and 8]. **Interestingly, a recent study from Yuan**
101 **and colleagues demonstrated that deletion of TREM-1 significantly reduced IL-1 β , TNF- α , and IL-6**
102 **production and improved lung injury damage [supplementary materials 9].**

103 **As reported in** the representative figure [supplementary materials 10], we would like to speculate
104 that IL-17 could potentially enhance IL-8 and (more specifically) IL-6 production in both human
105 lung epithelial cells and fibroblasts. This poses an interesting paradigm whereby IL-17 released
106 from innate cellular components, may direct lung structural cells to respond more vigorously. **Our**
107 **hypothesis is also in accordance to a recent article from Wu & Yang [7] which reviewed Th17**
108 **responses in patients with SARS-CoV-2. They found that peripheral blood cells from patients with**
109 **severe COVID-19 infection had strikingly high numbers of circulating Th17 cells which were**
110 **associated with a “cytokine storm” including IL-1 β , IL-2, IL-7, IL-10, IL-17, G-CSF, interferon γ -**
111 **induced protein 10 (IP-10), MCP-1, macrophage inflammatory proteins (MIPs) and TNF- α . As a**
112 **result of this hyper-inflammatory state, the authors suggested the use of Fedratinib, a Janus kinase**
113 **2 (JAK2) small molecule inhibitor which is involved in the suppression of signal transducer and**
114 **activator of transcription 3 (STAT3), as a potential therapeutic agent for patients with elevated**
115 **Th17 (but also Th1) type immune profiles [8,9].**

116 **It would therefore be of** great interest to **further strengthen** this hypothesis by accessing
117 bronchoalveolar lavage fluid (BALF) **and plasma/serum** samples from mild- and severe-infected
118 COVID-19 patients to measure IL-17 levels. This would potentially provide a rationale for testing
119 neutralizing antibodies targeting IL-17. **Could targeting IL-17 alone or in combination with IL-6**
120 **supersede other therapeutic approaches? A global effort by the research community will certainly**
121 **help to tackle such questions and we hope to be part of this.**

122 **Conflict of interest**

123 This article has been conducted and written in the absence of any commercial or financial
124 relationships that could be construed as a potential conflict of interest.

125

126 **Author contributions**

127 GMC, AAM, FR and AS drafted the manuscript. NM, AJI and FM wrote and revised the
128 manuscript. All Authors gave final approval to the publication.

129

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197 [supplementary materials 10] Schematic representation of inflammatory pathways involved in the
198 COVID-19-related respiratory syndrome. The left part shows the inflammatory scenario induced by
199 COVID-19 and potentially amplified by the presence of IL-17. The right part could represent the
200 future therapeutic approach for COVID-19-related syndrome using a combined IL-6 and IL-17
201 neutralizing antibodies.