

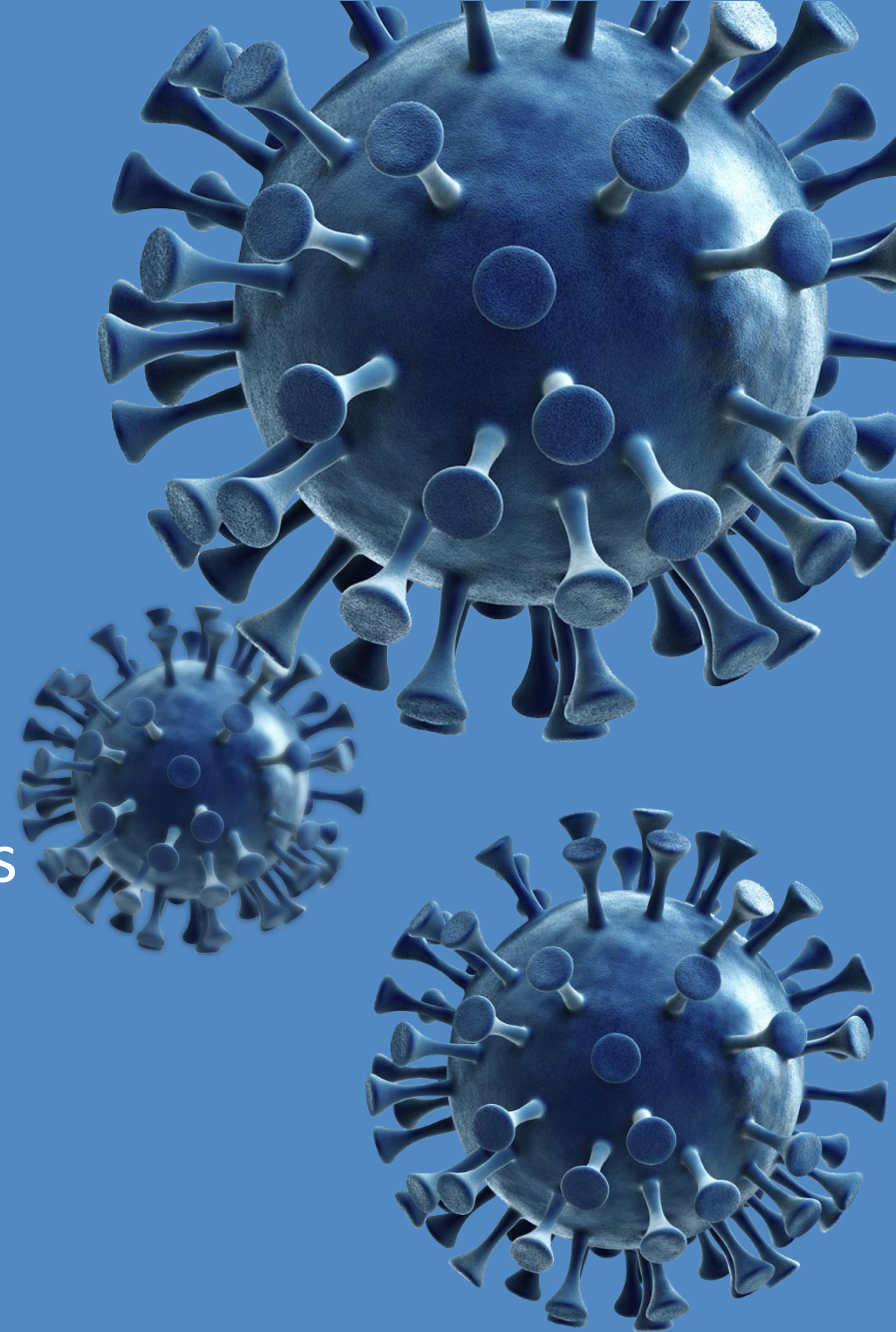
Synairgen

Developing inhaled IFN- β
(SNG001) – a broad spectrum
antiviral initially for COVID-19

Progress update and
interim results for the 6 months
ended 30 June 2021

Richard Marsden CEO

Sep 2021



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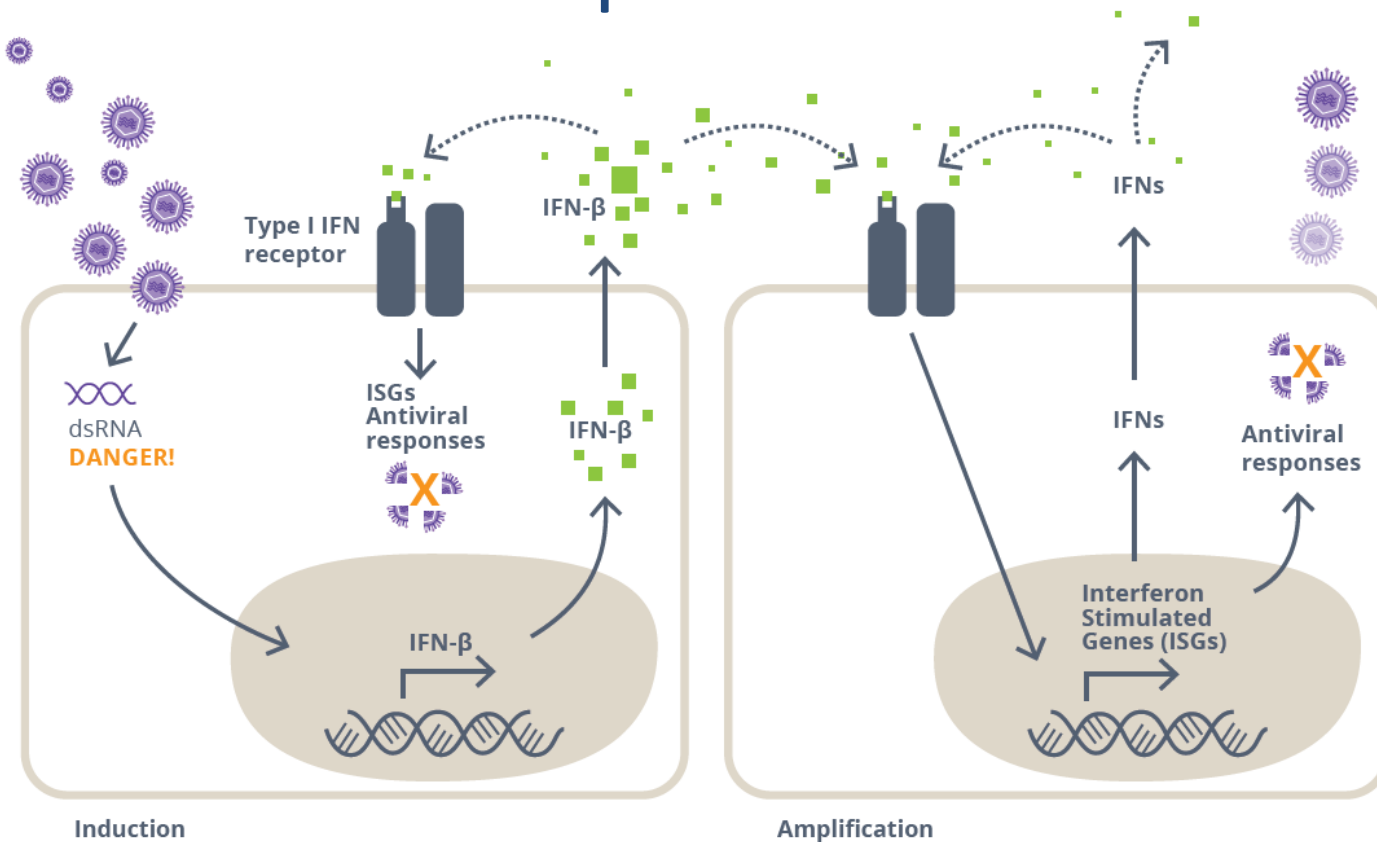
SNG001 being progressed rapidly as a potential treatment for COVID-19 patients

- SNG001 is an inhaled, broad-spectrum antiviral IFN- β 1a formulation which is delivered directly to the lower respiratory tract, stimulating the lungs' immune defences
- Stage of development:
 - Phase III (SPRINTER) being conducted by Synairgen
 - Approaching 80% enrolled
 - Topline data expected in early 2022
 - Phase II (ACTIV-2) in the home setting being conducted by the US NIH
- Potential availability in 2022 conditional upon:
 - Positive data from SPRINTER
 - COVID-19 hospitalisation rate remaining a concern
 - Regulatory approval, potentially under an EUA in the US, BLA and MAAs to follow
- Synairgen scaling up manufacturing capability and 'in-market' infrastructure

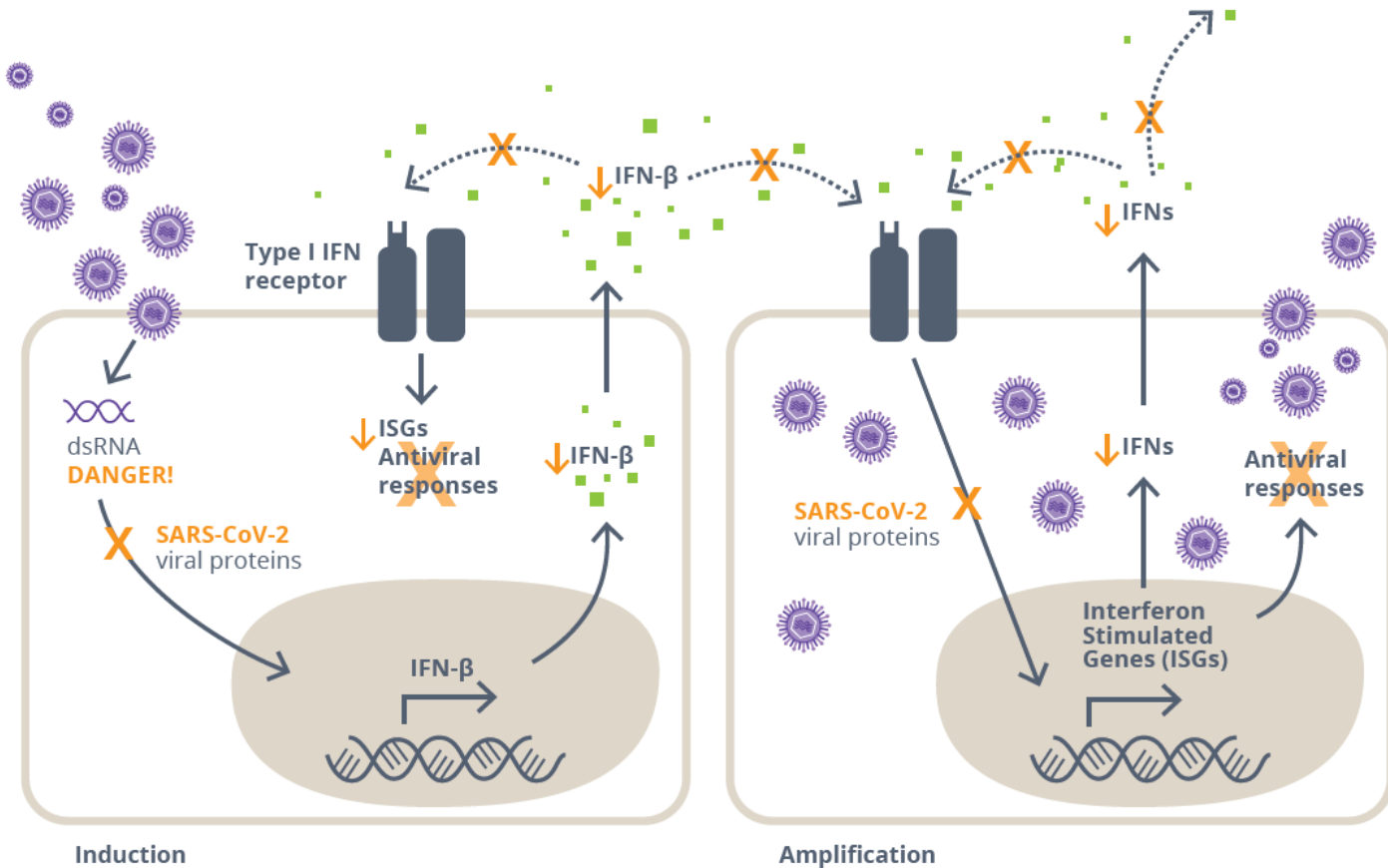
Multiple potential applications for SNG001

- COVID-19 patients recently admitted to hospital
 - >10,000 patients/day being hospitalised per day due to COVID-19 in the US alone
- Pandemic preparedness
- As a broad-spectrum antiviral for any patient admitted to hospital due to a severe viral lung infection
 - Year round usage (mostly winters)
 - Multiple patient types
 - Multiple causative viruses

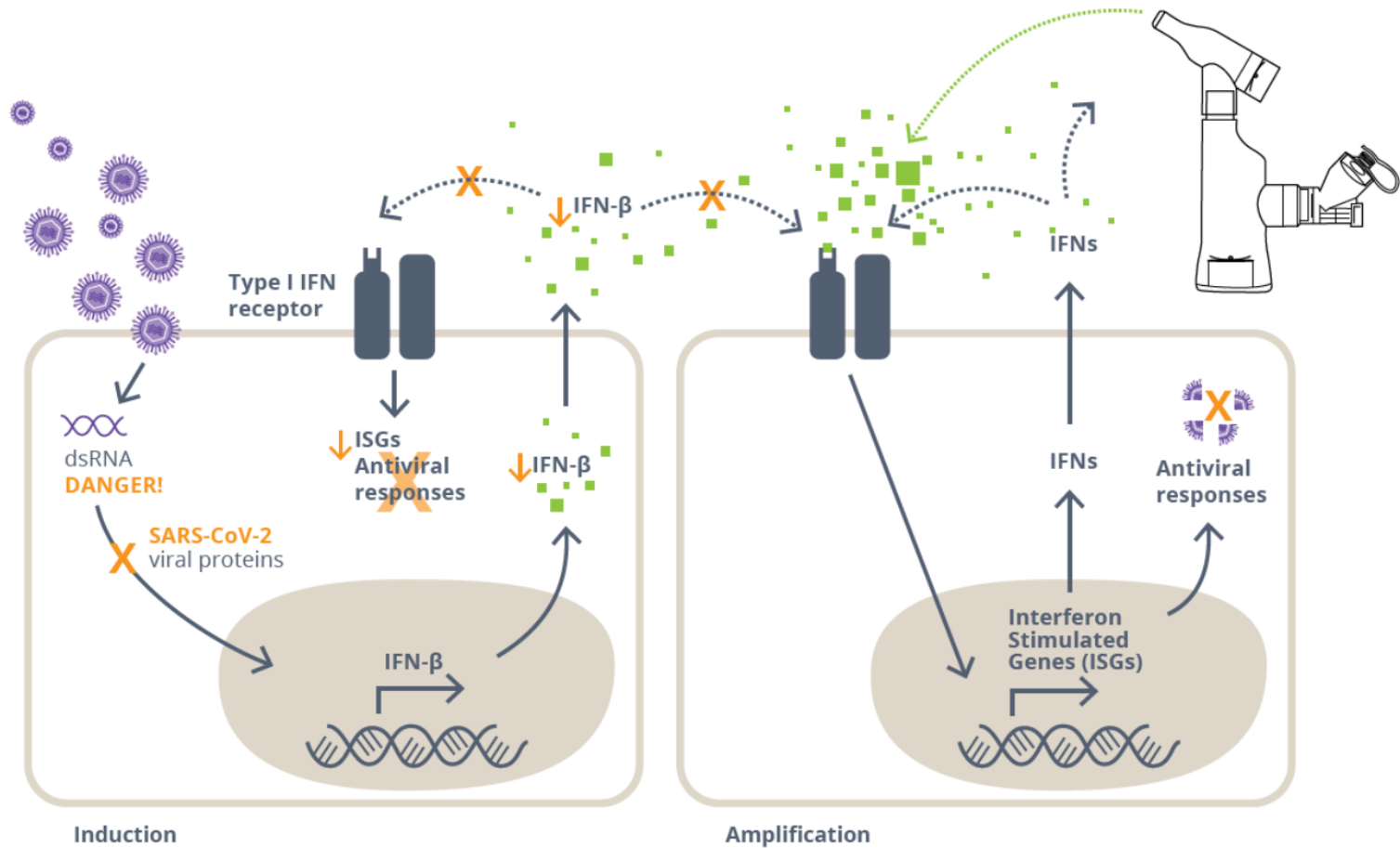
Production of IFN- β by cells drives antiviral activity, preventing infection and virus replication



Proteins made by viruses can lead to a suppression of IFN- β production



Inhaled IFN-β designed to restore or boost antiviral activity in the lungs



Growing body of evidence supporting rationale to assess SNG001 in COVID-19 patients

RESEARCH

RESEARCH ARTICLE SUMMARY

CORONAVIRUS

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

Qian Zhang et al.

INTRODUCTION: Clinical outcomes of human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection range from silent infection to lethal coronavirus disease 2019 (COVID-19). Epidemiological studies have identified three risk factors for severe disease: being male, being elderly, and having other medical conditions. However, interindividual clinical variability remains huge in each demographic category. Discovering the root cause and detailed molecular, cellular, and tissue- and body-level mechanisms underlying life-threatening COVID-19 is of the utmost biological and medical importance.

RATIONALE: We established the COVID Human Genetic Effort (www.covidhge.com) to test

the general hypothesis that life-threatening COVID-19 in some or most patients may be caused by monogenic inborn errors of immunity to SARS-CoV-2 with incomplete or complete penetrance. We sequenced the exome or genome of 659 patients of various ancestries with life-threatening COVID-19 pneumonia and 534 subjects with asymptomatic or benign infection. We tested the specific hypothesis that inborn errors of Toll-like receptor 3 (TLR3)- and interferon regulatory factor 7 (IRF7)-dependent type I interferon (IFN) immunity that underlie life-threatening influenza pneumonia also underlie life-threatening COVID-19 pneumonia. We considered three loci identified as mutated in patients with life-threatening influenza: *TLR3*, *IRF7*, and *IRF9*. We also con-

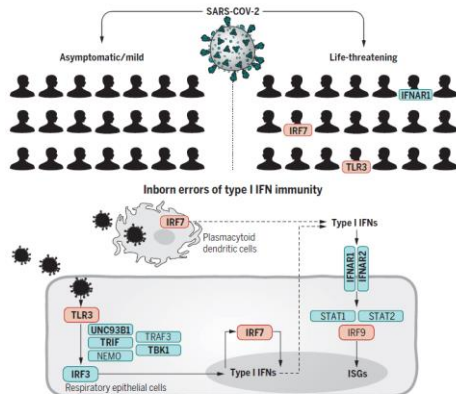
sidered 10 loci mutated in patients with other viral illnesses but directly connected to the three core genes conferring influenza susceptibility: *TICAM1/TRIF*, *UNC93B1*, *TRAF3*, *TBK1*, *IRF3*, and *NEMO/IKBK* from the TLR3-dependent type I IFN induction pathway, and *IFNAR1*, *IFNAR2*, *STAT1*, and *STAT2* from the IRF7- and IRF9-dependent type I IFN amplification pathway. Finally, we considered various modes of inheritance at these 13 loci.

RESULTS: We found an enrichment in variants predicted to be loss-of-function (pLOF), with a minor allele frequency <0.001, at the 13 candidate loci in the 659 patients with life-threatening COVID-19 pneumonia relative to the 534 subjects with asymptomatic or benign infection ($P = 0.01$). Experimental tests for all 118 rare nonsynonymous variants (including both pLOF and other variants) of these 13 genes found in patients with critical disease identified 23 patients (3.5%), aged 17 to 77 years, carrying 24 deleterious variants of eight genes. These variants underlie autosomal-recessive (AR) deficiencies (*IRF7* and *IFNAR1*) and autosomal-dominant (AD) deficiencies (*TLR3*, *UNC93B1*, *TICAM1*, *TBK1*, *IRF3*, *IRF7*, *IFNAR1*, and *IFNAR2*) in four and 19 patients, respectively. These patients had never been hospitalized for other life-threatening viral illness. Plasmacytoid dendritic cells from IRF7-deficient patients produced no type I IFN on infection with SARS-CoV-2, and *TLR3*^{-/-}, *TLR3*^{+/+}, *IRF7*^{-/-}, and *IFNAR1*^{-/-} fibroblasts were susceptible to SARS-CoV-2 infection in vitro.

CONCLUSION: At least 3.5% of patients with life-threatening COVID-19 pneumonia had known (AR *IRF7* and *IFNAR1* deficiencies or AD *TLR3*, *TICAM1*, *TBK1*, and *IRF3* deficiencies) or new (AD *UNC93B1*, *IRF7*, *IFNAR1*, and *IFNAR2* deficiencies) genetic defects at eight of the 13 candidate loci involved in the TLR3- and IRF7-dependent induction and amplification of type I IFNs. This discovery reveals essential roles for both the double-stranded RNA sensor TLR3 and type I IFN cell-intrinsic immunity in the control of SARS-CoV-2 infection. Type I IFN administration may be of therapeutic benefit in selected patients, at least early in the course of SARS-CoV-2 infection. ■

The full author list and the list of affiliations is available in the full article online.
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Inborn errors of TLR3- and IRF7-dependent type I IFN production and amplification underlie life-threatening COVID-19 pneumonia. Molecules in red are encoded by core genes, deleterious variants of which underlie critical influenza pneumonia with incomplete penetrance, and deleterious variants of genes encoding biochemically related molecules in blue underlie other viral illnesses. Molecules represented in bold are encoded by genes with variants that also underlie critical COVID-19 pneumonia.

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Growing body of evidence supporting rationale to assess SNG001 in COVID-19 patients

RESEARCH

RESEARCH

RESEARCH ARTICLE SUMMARY

RESEARCH ARTICLE CORONAVIRUS

Inborn errors with life-threatening COVID-19

Paul Bastard[†] and Lindsey B. Rosen[†] et al.

Qian Zhang et al.

INTRODUCTION: Clinical severe acute respiratory virus 2 (SARS-CoV-2) is silent infection to lethal 2019 (COVID-19). Epidemic identified three risk factors: being male, being older, and having certain medical conditions. How clinical variability remains graphic category. Discov and detailed molecular, or body-level mechanisms and COVID-19 is of the utmost importance.

RATIONALE: We establish Genetic Effort (www.ge

INTRODUCTION: Interindividual clinical variability is vast in humans infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ranging from silent infection to rapid death. Three risk factors for life-threatening coronavirus disease 2019 (COVID-19) pneumonia have been identified—being male, being elderly, or having other medical conditions—but these risk factors cannot explain why critical disease remains relatively rare in any given epidemiological group. Given the rising toll of the COVID-19 pandemic in terms of morbidity and mortality, understanding the causes and mechanisms of life-threatening COVID-19 is crucial.

RATIONALE: B cell autoimmune infectious phenotypes of three inborn errors of cyto

kine immunity exist, in which neutralizing autoantibodies (auto-Abs) against interferon- γ (IFN- γ) (mycobacterial disease), interleukin-6 (IL-6) (staphylococcal disease), and IL-17A and IL-17F (mucocutaneous candidiasis) mimic the clinical phenotypes of germline mutations of the genes that encode the corresponding cytokines or receptors. Human inborn errors of type I IFNs underlie severe viral respiratory diseases. Neutralizing auto-Abs against type I IFNs, which have been found in patients with a few underlying noninfectious conditions, have not been unequivocally shown to underlie severe viral infections. While searching for inborn errors of type I IFN immunity in patients with life-threatening COVID-19 pneumonia, we also tested the hypothesis that neutralizing auto-Abs against type I IFNs

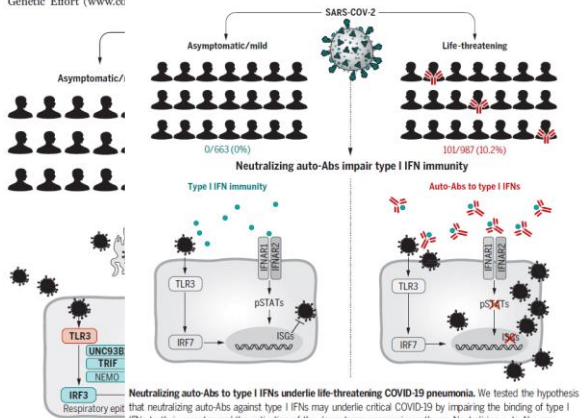
may underlie critical COVID-19. We searched for auto-Abs against type I IFNs in 987 patients hospitalized for life-threatening COVID-19 pneumonia, 663 asymptomatic or mildly affected individuals infected with SARS-CoV-2, and 1227 healthy controls from whom samples were collected before the COVID-19 pandemic.

RESULTS: At least 101 of 987 patients (10.2%) with life-threatening COVID-19 pneumonia had neutralizing immunoglobulin G (IgG) auto-Abs against IFN- α (13 patients), against the 13 types of IFN- α (36), or against both (52) at the onset of critical disease; a few also had auto-Abs against the other three individual type I IFNs. These auto-Abs neutralize high concentrations of the corresponding type I IFNs, including their ability to block SARS-CoV-2 infection in vitro. Moreover, all of the patients tested had low or undetectable serum IFN- α levels during acute disease. These auto-Abs were present before infection in the patients tested and were absent from 663 individuals with asymptomatic or mild SARS-CoV-2 infection ($P < 10^{-16}$). They were present in only 4 of 1227 (0.33%) healthy individuals ($P < 10^{-16}$) before the pandemic. The patients with auto-Abs were 23 to 87 years old (half were over 65) and of various ancestries. Notably, 95 of the 101 patients with auto-Abs were men (94%).

CONCLUSION: A B cell autoimmune phenocopy of inborn errors of type I IFN immunity accounts for life-threatening COVID-19 pneumonia in at least 2.6% of women and 12.5% of men. In these patients, adaptive autoimmunity impairs innate and intrinsic antiviral immunity. These findings provide a first explanation for the excess of men among patients with life-threatening COVID-19 and the increase in risk with age. They also provide a means of identifying individuals at risk of developing life-threatening COVID-19 and ensuring their enrolment in vaccine trials. Finally, they pave the way for prevention and treatment, including plasmapheresis, plasmablast depletion, and recombinant type I IFNs not targeted by the auto-Abs (e.g., IFN- β).

The full author list and the list of author affiliations is available in the full article online.
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Inborn errors of TLR3- and threatening COVID-19 pneumonia which underlie critical influenza encoding biochemically related are encoded by genes with

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Growing body of evidence supporting rationale to assess SNG001 in COVID-19 patients

RESEARCH

RESEARCH

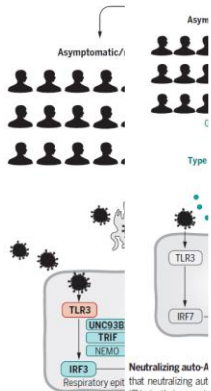
RESEARCH ARTICLE SUMMARY

RESEARCH ARTICLE CORONAVIRUS Autoantibodies with life-threatening

Paul Bastard¹ et al.

INTRODUCTION: Clinical severe acute respiratory infection to rapid life-threatening (COVID-19) pneumonia being male, being older, medical conditions cannot explain a relatively rare subgroup. Given the pandemic in terms of clinical variability remain graphic category. Discussed and detailed molecular, or body-level mechanisms and COVID-19 is of the utmost importance.

RATIONALE: We establish Genetic Effort (www.ce



Inborn errors of TLR3 and threatening COVID-19 pneumonia which underlie critical influenza encoding biochemically related are encoded by genes with Bastard et al., *Science*

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News & views

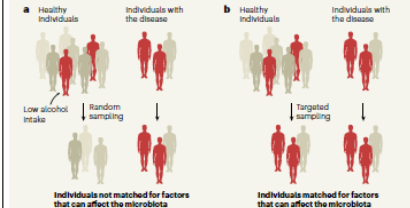


Figure 1 | Comparing populations to assess connections between gut microbes and human disease. Vukjovic-Cvijin et al. identified factors that affect the composition of gut microbes (termed microbiota) and that differ in prevalence between populations with and without a specific disease. a, For example, the proportion of individuals who have low levels of alcohol intake might differ between the healthy and ill populations. A random sampling of individuals for comparison that does not take this factor into account might mean that microbiota differences that seem to be associated with disease status arise because of this factor. b, The authors instead compared individuals matched for factors that can affect the microbiota. However, such sampling might select individuals not representative of a healthy population.

years of heavy smoking, will not provide a truly healthy control group. With that in mind, people with inflammatory bowel disease should not be matched with a healthy matching group on the basis of bowel movement quality. Nor should people who have type 2 diabetes be matched with a healthy cohort on the basis of blood levels of the glycoprotein HbA1c, which offers a way of assessing long-term excess sugar levels (something that the authors don't do). Researchers should also be suspicious of matching people who have type 2 diabetes with a healthy cohort on the basis of body mass index.

In an effort to address this issue, the authors repeated their analysis using a smaller cohort, in which none of the individuals in the healthy group self-reported any type of disease at all (the previous criterion for healthy individuals was just those who did not self-report the specific disease of interest). They found similar associations between disease status and the physiological and lifestyle differences, although these associations were now either less statistically significant than in the original analysis or no longer significant. Unfortunately, removing individuals with any self-reported disease does not rule out matching the people from the disease cohort with control individuals who might nevertheless be undiagnosed, or whose disease status might be borderline; this could happen if, for example, people who have diabetes are matched with those who are pre-diabetic. This problem, whose scope extends beyond this study, raises a key question for all medical studies: what constitutes a healthy cohort? Finally, it is important to remember that

may underlie critical COVID-19. We searched for auto-Abs against type I IFNs in 987 patients hospitalized for life-threatening COVID-

diabetes, then a causal effect exists between the microbiota and the disease; but this will not be seen after matching individuals on their level of alcohol consumption. The same will be true if inflammatory bowel disease results in the types of microbiota change that cause diarrhoea, and individuals are matched on their bowel movement quality. Thus, Vukjovic-Cvijin and colleagues' results do not rule out the microbiota having a causal effect. The question of causality between the microbiota and human disease is a central topic in studies in this area. These findings will certainly continue to fuel research in the field for years to come, and Vukjovic-Cvijin et al. have taken a step forward for our thinking about this issue.

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1. Sender, R., Fuchs, S. & Milo, R. *Cell* **144**, 337–340 (2016).
2. DeStefano, R. & Perkins, S. L. *Welcome to the Microbiome* (Yale Univ. Press, 2015).
3. Honda, K. & Littman, D. R. *Nature* **535**, 75–84 (2016).
4. Garret, W. C., Glick, L. K., Pritchard, L. W. & Knight, R. *Cell* **143**, 1038–1040 (2015).
5. Vukjovic-Cvijin, I. et al. *Nature* **569**, 448–454 (2020).
6. Schulzweinstein, J. I. *Case-Control Studies: Design, Conduct, Analysis* (Oxford Univ. Press, 1982).
7. Reis, S. & van der Laan, M. J. *Int. J. Biostat.* **5**, 1 (2006).
8. Costanza, M. C. *Pract. Med.* **34**, 425–433 (1995).

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Immunology

Interferon deficiency can lead to severe COVID

Eric Maffro & Akiko Iwasaki

Understanding what contributes to the development of severe COVID-19 would be of great clinical benefit. Analysis of people in whom this occurred pinpoints a key role for the signalling pathway mediated by type I interferon proteins.

Infection with the SARS-CoV-2 coronavirus results in diverse outcomes for COVID-19, with the disease tending to be more severe and lethal for older males^{1,2}. Yet some young people can also have severe COVID-19. What determines susceptibility to this disease? Writing in *Science*, Zhang et al.³ and Bastard et al.⁴ shed light on a key factor that affects whether life-threatening COVID-19 develops. The studies implicate deficiencies in interferon proteins, specifically, type I interferons (IFN-I). Such deficiencies might arise, as Zhang and colleagues report, through

inherited mutations in genes encoding key antiviral signalling molecules, or, as Bastard and colleagues describe, by the development of antibodies that bind to and 'neutralize' IFN-I. Among people who developed severe COVID-19, such neutralizing antibodies were mostly in older males.

The IFN-I family includes IFN- α , IFN- β and IFN- ω . These molecules provide innate immune defences—they mount an initial rapid antiviral response. IFN-I proteins are a type of immune-signalling molecule called a cytokine; they are induced when a cell detects viral

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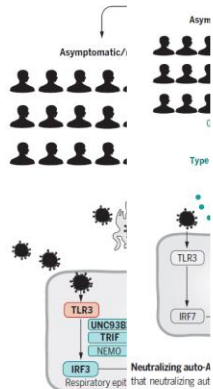
RESEARCH

RESEARCH ARTICLE SUMMARY

CORONAVIRUS

Autoantibodies with life-threatening errors

Qian Zhang et al. **INTRODUCTION:** Clinical severe acute respiratory virus 2 (SARS-CoV-2) is silent infection to lethal 2019 (COVID-19). Epidemic identified three risk factors being male, being older medical conditions cannot explain a relatively rare life-threatening group. Given the pandemic in terms of understanding the life-threatening (COVID-19) is of the utmost importance. **RATIONALE:** We establish Genetic Effort (www.ce



Inborn errors of TLR3 and threatening COVID-19 pneumonia which underlie critical infection encoding biochemically related are encoded by genes with: Bastard et al., *Science*

Zhang et al., *Science* 370, 422 (2020) 23 October

RESEARCH

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News & Views

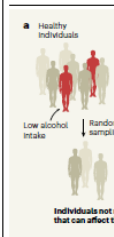


Figure 1 | Comparing population Vukjovic-Cvijin et al. identify and that differ in prevalence proportion of individuals with populations. A random sampling might mean that microbiota factor. b. The authors instead However, such sampling might

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Science Immunology

CORONAVIRUS

Autoantibodies of uninfected ~20% of COVID-19 patients

Paul Bastard^{1,2,3*}, Adri Manry^{1,2,3*}, Eleftherios Blietzis^{1,2,3*}, Alba Parra-Masloskaja^{1,2,3*}, Nicola Borrero^{4,5}, Alexandre Cognasse^{6,7,8,9}, Jesus Ti Jacques G. Riviere⁶, Ju Bruno Megarbane^{10,11}, Manuel Anaya¹², Jord Castagnoli^{13,14}, Ottavio Marcela Moncada-Velázquez^{15,16}, Dany Am Nussbaum¹⁷, Tayfun C Santana^{18,19}, Stéphane Kuroiwa²⁰, Christine Barretros²¹, Elena Dor Sahant²², Ivan Tance Vidau^{23,24}, Stuart G. I Nell Y. Kann²⁵, Anna Rutger Koning²⁶, Luis Monneret^{27,28}, Michel David Hagin^{29,30}, Joe Bourke³¹, Rabih Hal Sedkaoui³², Suzan Ali Vinh^{33,34}, Sisse Rye O N. Spaan^{35,36}, Laurent P. Lifton^{37,38,39}, Shri Response to COVID G James's Hospital, SAI The Milieu Intérieur (COVID Human Genet Sang study group, M Vandreaos⁴⁰, Olyvie James Mond⁴¹, Stéphi Mentre^{42,43,44,45}, Marl Solanich⁴⁶, Sophie Si Gregersen⁴⁷, Lorenzo Kal Kisand⁴⁸, Satoshi Tiberghien^{49,50}, Qian

¹Laboratory of Human Genetics of Institute, Paris, France; ²St. Giles Virology and Infectious Diseases, T University, Hiroshima, Japan; ³Hebron Barcelona Hospital Carr University of Tartu, Tartu, Estonia

First release: 19 August 20

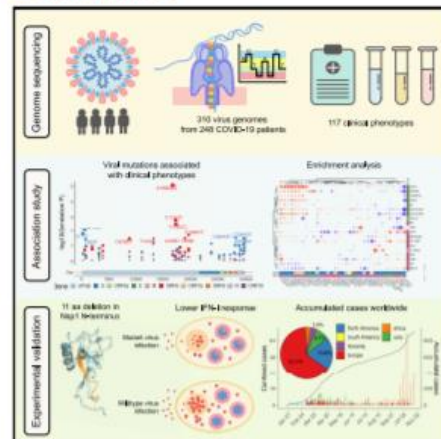
may underlie critical COVID-19. We searched for auto-Abs against type I IFNs in 987 patients hospitalized for life-threatening COVID-19.

Article

Cell Host & Microbe

Genomic monitoring of SARS-CoV-2 uncovers an Nsp1 deletion variant that modulates type I interferon response

Graphical Abstract



Highlights

- SARS-CoV-2 genome sequencing and phylogenetic analyses identify 35 recurrent mutations
- Association with 117 clinical phenotypes reveals potentially important mutations
- Δ500-532 in Nsp1 coding region correlates with lower viral load and serum IFN-β
- Viral isolates with Δ500-532 mutation induce lower IFN-I response in the infected cells

Authors

Jing-wen Lin, Chao Tang, Han-cheng Wei, ..., Jia Geng, Binwu Ying, Lu Chen

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In Brief

Bringing together epidemiological, genetic, and clinical data, Lin et al. identify viral mutations that associate with clinical phenotypes. The 500-532 locus in the Nsp1 coding region is a deletion hotspot in the SARS-CoV-2 genome, and deletion variants lead to lower IFN-I response. Prevalence of 500-532 deletion variants is accumulating worldwide.

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RESEARCH

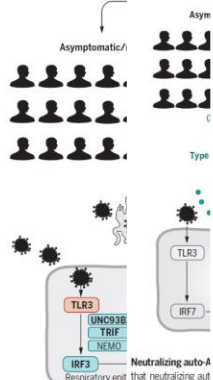
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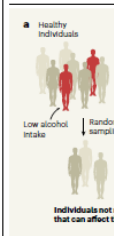


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Science Immunology

CORONAVIRUS

Autoantibody of uninfected ~20% of COVID-19

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First release: 19 August 20

may underlie critical COVID-19 for auto-Abs against type 1 II Hanta breath alcohol for life-threa



Article SARS-CoV-2 Nucleocapsid Protein Interacts with RIG-I and Represses RIG-Mediated IFN-β Production

Keli Chen^{1,†}, Feng Xiao^{1,†}, Dingwen Hu¹, Weiwei Ge¹, Mingfu Tian¹, Wenbiao Wang², Pan Pan², Kailiang Wu¹ and Jianguo Wu^{1,2,3,4,5,6}

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[†] These authors contribute equally to this work.

Abstract: SARS-CoV-2 is highly pathogenic in humans and poses a great threat to public health worldwide. Clinical data shows a disturbed type I interferon (IFN) response during the virus infection. In this study, we discovered that the nucleocapsid (N) protein of SARS-CoV-2 plays an important role in the inhibition of interferon beta (IFN-β) production. N protein repressed IFN-β production induced by poly(I:C) or upon Sendai virus (SeV) infection. We noted that N protein also suppressed IFN-β production, induced by several signaling molecules downstream of the retinoic acid-inducible gene I (RIG-I) pathway, which is the crucial pattern recognition receptor (PRR) responsible for identifying RNA viruses. Moreover, our data demonstrated that N protein interacted with the RIG-I protein through the DExD/H domain, which has ATPase activity and plays an important role in the binding of immunostimulatory RNAs. These results suggested that SARS-CoV-2 N protein suppresses the IFN-β response through targeting the initial step, potentially the cellular PRR-RNA-recognition step in the innate immune pathway. Therefore, we propose that the SARS-CoV-2 N protein represses IFN-β production by interfering with RIG-I.

Keywords: coronavirus disease 2019; COVID-19; severe acute respiratory syndrome coronavirus 2; SARS-CoV-2; nucleocapsid; interferon; IFN; retinoic acid-inducible gene I; RIG-I

1. Introduction

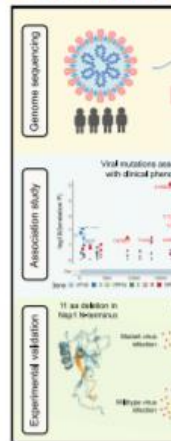
Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as a pandemic by the World Health Organization (WHO) on 11 March 2020 [1]. The viral infection poses a huge threat to the global public health. Globally, as of 5:13 p.m. CET, 19 November 2020, there have been 55,928,327 confirmed cases of COVID-19, including 1,344,003 deaths, reported to the WHO (<https://covid19.who.int/>). SARS-CoV-2 is an enveloped, non-segmented, positive-sense RNA virus in the Coronaviridae family, *Orthocoronavirinae* subfamily, *Betacoronavirus* genus, and *Sarbecovirus* subgenus [2,3]. SARS-CoV-2 is a novel β-coronavirus and zoonotic coronavirus, following the previously identified respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [4].

The viral genome sequence is about 29,903 nt and has 5' and 3' terminal sequences that are typical of *Betacoronavirus* with a short untranslated (UTR) 5' and 3' terminus. The order of the genes (5' to 3') is replicase ORF1ab, spike (S), envelope (E), membrane (M), nucleocapsid (N), and accessory proteins ORF3a, ORF6, ORF7a, ORF7b, ORF8, ORF9a, and ORF9b [5,6]. ORF1ab is further cleaved into 15 nonstructural proteins (NSP1–10, 12–16) by

Cell Host & Microbe

Genomic m Nsp1 deleti interferon r

Graphical Abstract



Highlights

- SARS-CoV-2 genome identify 35 recurrent
- Association with 117 important mutations
- Δ500-532 in Nsp1 ct load and serum IFN-β
- Viral isolates with Δ500-532 mutation induce lower IFN-β response in the infected cells



Citation: Chen, K.; Xiao, F.; Hu, D.; Ge, W.; Tian, M.; Wang, W.; Pan, P.; Wu, K.; Wu, J. SARS-CoV-2 Nucleocapsid Protein Interacts with RIG-I and Represses RIG-Mediated IFN-β Production. *Viruses* 2021, 13, 47. <https://doi.org/10.3390/v13101047>

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Growing body of evidence supporting rationale to assess SNG001 in COVID-19 patients

RESEARCH

RESEARCH

RESEARCH ARTICLE SUMMARY

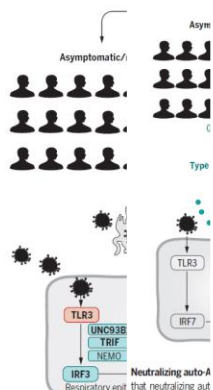
CORONAVIRUS

Autoantibodies with life-threatening inborn errors

Paul Bastard^{1,2} et al.

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RATIONALE: We establish Genetic Effort (www.ceff.fr)



Inborn errors of TLR3 and IRF7 which underlie critical innate encoding biochemically related are encoded by genes with

Zhang et al., *Science* 370, 422 (2020) 23 October

RESEARCH

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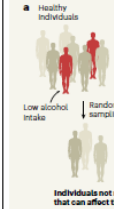


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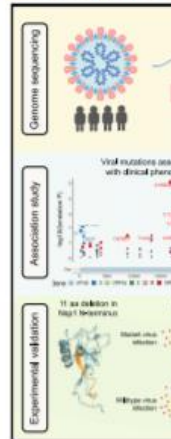
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- Viral isolates with Δ500-532 mutation ir response in the infected cells



Article

SARS-CoV-2 Represses

Keli Chen^{1,2}, Fei and Jianguo Wu^{1,2}

¹Dermatology Hospital, Southern Medical University, Guangzhou, China
²Department of Molecular Biology and Biotechnology, School of Biological Sciences, College of Agriculture and Natural Sciences, University of Cape Coast, Cape Coast, Ghana

* Guangzhou Provincial Key Laboratory of Tropical Disease Research, School of Public Health, Southern Medical University, Guangzhou, China

ARTICLE INFO

Keywords: SARS-CoV-2, Open reading frame 8, Open reading frame 8 genotypes, Endoplasmic reticulum stress, Interferon beta

Check for updates

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The ORF8 protein of SARS-CoV-2 induced endoplasmic reticulum stress and mediated immune evasion by antagonizing production of interferon beta

Farooq Rashid¹, Emmanuel Enoch Dzakah^{2,3}, Haiying Wang⁴, Shixing Tang^{2,3,4,*}

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causal agent of the COVID-19 pandemic and is phylogenetically related to the 2002–2003 severe acute respiratory syndrome coronavirus (SARS-CoV) and other bat-related SARS-CoVs (Corman and Geurts, 2020; Chan et al., 2020). Several proteins of SARS-CoV can trigger endoplasmic reticulum (ER) stress and unfolded protein responses (UPR) to maintain cellular homeostasis (Mitsukida et al., 2009; Song et al., 2009; Shi et al., 2019). The suppression of primary interferon (IFN) production and signaling has been observed in subjects infected with SARS-CoV-2 (Yoon et al., 2020). However, studies that investigate the role of the individual viral proteins of SARS-CoV-2 in the regulation of ER stress and innate immune suppression need to be conducted. ER is responsible for the correct folding and maturation of a large number of proteins (Rashid et al., 2017). Protein folding is both sensed

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ARTICLE INFO



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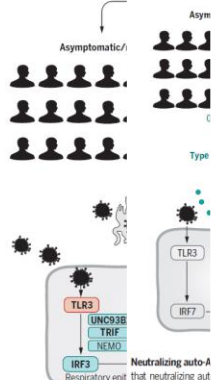
RESEARCH

RESEARCH

RESEARCH ARTICLE SUMMARY

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News & Views

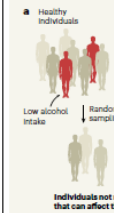


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Science Immunology

CORONAVIRUS Autoantibodies of uninfected ~20% of COVID-19

Paul Bastard^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000}

The Million Interieur COVID Human Genet Sang study group, M Vandreaux¹⁰⁴, Olivier James Mon¹⁰⁵, Stéphi Ment^{106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000}

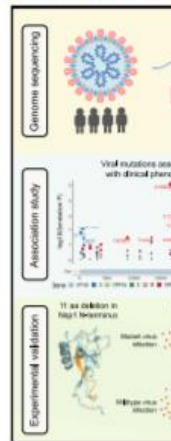
First release: 19 August 20

may underlie critical COVID-19 for auto-Abs against type I I

Cell Hosts & Microbes

Genomic m Nsp1 deletion interferon r

Graphical Abstract



Highlights

- SARS-CoV-2 genomic identify 35 recurrent
- Association with 117 important mutations
- Δ500-532 in Nsp1 c-terminal and serum IFN-β
- Viral isolates with Δ500-532 mutation response in the infected cells



Article SARS-CoV-2 Represses

Keli Chen^{1,2,3}, Fei and Jianguo Wu



OPEN ACCESS

Citation: Chen, K., Xia Gu, W., Tian, M., Wang, Wu, K., Wu, J. SARS-CoV-2 Nucleocapsid Protein Inhibits IRF3 and IRF7 Production. *Virus* 47. <https://doi.org/10.3389/fviro.2020.00047>

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Publisher's Note: MED with regard to jurisdic in published maps a nullifications.

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Revisiting Pleiotropic Effects of Type I Interferons: Rationale for Its Prophylactic and Therapeutic Use Against SARS-CoV-2

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The pandemic distribution of SARS-CoV-2 together with its particular feature of inactivating the interferon-based endogenous response and accordingly, impairing the innate immunity, has become a challenge for the international scientific and medical community. Fortunately, recombinant interferons as therapeutic products have accumulated a long history of beneficial therapeutic results in the treatment of chronic and acute viral diseases and also in the therapy of some types of cancer. One of the first antiviral treatments during the onset of COVID-19 in China was based on the use of recombinant interferon alpha 2b, so many clinicians began to use it, not only as therapy but also as a prophylactic approach, mainly in medical personnel. At the same time, basic research on interferons provided new insights that have contributed to a much better understanding of how treatment with interferons, initially considered as antivirals, actually has a much broader pharmacological scope. In this review, we briefly describe interferons, how they are induced in the event of a viral infection, and how they elicit signaling after contact with their specific receptor on target cells. Additionally, some of the genes stimulated by type I interferons are described, as well as the way interferon-mediated signaling is torpedoned by coronaviruses and in particular by SARS-CoV-2. Angiotensin converting enzyme 2 (ACE2) gene is one of the interferon response genes. Although for many scientists this fact could result in an adverse effect of interferon treatment in COVID-19 patients, ACE2 expression contributes to the balance of the renin-angiotensin system, which is greatly affected by SARS-CoV-2 in its internalization into the cell. This manuscript also includes the relationship between type I interferons and neutrophils, NETosis, and interleukin 17. Finally, under the subtitle of "take-home messages", we discuss the rationale behind a timely treatment with interferons in the context of COVID-19 is emphasized.

Keywords: Type I interferons, SARS-CoV-2, COVID-19, ACE2, neutrophil-mediated inflammation



ino acids with two g-2 as well as the acrh is and the inhibition of we capable of inducing 6 (ATF6) and inostol-1 branch of ER stress resion of SARS-CoV-2 sating the production polyeytidylic acid (poly r factor 3 (IRF3), after aV-2 self proteins could y, and functions as an at not to be affected by

be host against ess. Therefore, sisting type I 9 severity. We rponse during FN-mediated duced that the option against

78 and GRP94 (Sic- correctly, ER stress is). Cells respond to ER e UPR (Rashid et al., ped mechanisms to 2009; Kozier et al., individual proteins of have been shown to Shi et al., 2009; Song pathways has impo- reduction (Matsuno

'AMPs), such as viral host pattern recogni- d., 2014). These are rs such as IRF3 and

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Growing body of evidence supporting rationale to assess SNG001 in COVID-19 patients

RESEARCH ARTICLE SUMMARY

RESEARCH ARTICLE
CORONAVIRUS
Inborn errors with life-threatening COVID-19

Qian Zhang et al.
INTRODUCTION: Clinical severe acute respiratory virus 2 (SARS-CoV-2) infection to rapid life-threatening COVID-19 pneumonia (COVID-19) in being male, being older medical conditions. How clinical variability remain graphic category. Discov and detailed molecular, or body-level mechanisms of COVID-19 is of the utmost importance.
RATIONALE: We establish Genetic Effort (www.ce

News & views

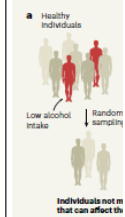


Figure 1 Comparing population groups that differ in prevalence of individuals with inborn errors. A, Healthy individuals. B, Individuals with inborn errors. A random sample might mean that microbiome factor. B, The authors instead However, such sampling might

years of heavy smoking, a healthy control group. With that in mind, peo tory bowel disease sho with a healthy matching bowel movement quali who have type 2 diabete healthy cohort on the ba the glycoprotein HbA1c, assessing long-term excc thing that the authors de should also be susceptio who have type 2 diabetes on the basis of body mas an effort to address the specific disease of r similar associations bet and the physiological ences, although these as either less statistically si original analysis or no Unfortunately, remov any self-reported disea matching the people fro with control individuals less be undiagnosed, or might be borderline. If for example, people w matched with those w This problem, whose sci this study, raises a key qu studies: what constitute Finally, it is importan

ScienceImm
CORONAVIRUS
Autoantibodies of uninformed individuals ~20% of total population

Paul Bastard^{1,2,3*}, Manry^{1,2,4}, Eliehn Rizien^{1,2,4}, Alba P. Maslowska^{1,2,4}, N Borrero⁵, Alexar Cognasse^{6,7,8,9}, Jes Jacques G. Rivière Tomohiro Morito Bruno Megarban Manuel Anaya¹⁰, Castagnoli^{11,12}, O Marcela Bonaced Conillabala¹³, Dar Nussbaum¹⁴, Tay Santana^{15,16}, Stéé Kurolo¹⁷, Chris Barreiros¹⁸, Elen Sahane¹⁹, Ivan T Vidau^{20,21}, Stuar Nell²², Y. Kann²³, J Rutger Koning²⁴, Monneret^{25,26}, M David Hagin^{27,28}, Bourke²⁹, Rabih Sedkaoui³⁰, Suza Vinh^{31,32}, Sisse R N. Spaan^{33,34}, Lat P. Lifton^{35,36,37}, Response to COV James's Hospital The Millieu Inter COVID Human C Sang study group Vandreakos³⁸, C James Mon^{39,40}, Mentre^{41,42,43,44}, J Solanich¹⁵⁰, Sopl Gregersen⁴⁵, Lot Kal Kisand⁴⁶, Sat Thiberghien^{47,48}, C

may underlie critical COVID-19 response in the affected cases

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-021-01068-6

Harnessing Type I IFN Immunity Against SARS-CoV-2 with Early Administration of IFN-β

Donald C. Vinh¹ · Laurent Abel^{2,3,4} · Paul Bastard^{2,3,4} · Matthew P. Cheng¹ · Antonio Condino-Neto⁵ · Peter K. Gregersen⁶ · Filomeen Haerynck⁷ · Maria-Pia Cicalese⁸ · David Hagin⁹ · Pere Soler-Palacin¹⁰ · Anna M. Planas¹¹ · Aurora Pujol^{12,13} · Luigi D. Notarangelo¹⁴ · Qian Zhang¹⁵ · Helen C. Su¹⁶ · Jean-Laurent Casanova^{2,3,4,15} · Isabelle Meys^{16,17} · On behalf of the COVID Human Genetic Effort

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Introduction

Since December 2019, over 150 million individuals have been infected with SARS-CoV-2 globally. While most cases (>95%) are asymptomatic or mild, a small proportion develop moderate, severe, or critical COVID-19 pneumonia requiring hospitalization, at times in the intensive care unit [1]. At least 2 million patients have already died [2]. The main epidemiological risk factor associated with critical pneumonia or death is age > 65 years; however, life-threatening COVID-19 has also affected younger people, albeit sporadically. Studies have suggested that type I interferon (IFN) immunity contributes to the control of SARS-CoV-2 infection [3–8]. Notably, inborn

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REVIEW
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on production by

ng^{1,2,3}, Li Li¹, Lili Ren^{1,2,3}

mpared with some other (that SARS-CoV-2 nsp12, the viral attenuated Sendai virus (SeV)- or promoter activation triggered by pressed the nuclear translocation rase activity of nsp12. Given nunity and thus provides insights

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connected by an interface domain,⁷ is catalytic residues (amino acids MS-CoV-2 RdRp has a GDD module size residues function as catalytic s, such as HCV NS5B and poliovirus synthesis activity, RdRps of enterococcal phages, and Langkat virus nase response through inhibition or of IFN-β or other cytokines.^{10–12} as a is involved in modulating the host ified that nsp12 could inhibit SeV-nt, but the underlying mechanism

critical for the initial detection and After a cell is infected by a pathogen, s, such as RIG-I-like receptors (RLRs) pize pathogen-associated molecular ly to activate the innate immune scible gene 1 (IRG-1 and melanoma 45) are two cytoplasmic RLRs that i mitochondrial antiviral signaling recognition.^{19–21} MAVS then initiates l multiple kinases, which lead to the regulatory factor 3/7 (IRF3/7).²² After tization, IRF3/7 translocates to the lution of IFN-α/β.^{24,25}

King Union Medical College, Beijing 100730, PR China; Beijing 100730, PR China; "Chitonghe g 100730, PR China and "Biomedical Promoting soft of Life Sciences, Peking University, Beijing

its of Type Its tic Use

inga-Acosta²

litical Diabon, Havana, Cuba; Real Diabon, Havana, Cuba; search Director, Center for Genetic

its particular feature of accordingly, impairing the nial scientific and medical rapetic products have y the treatment of chronic of cancer. One of the first was based on the use of it, not only as therapy but l. At the same time, basic tributed to a much better sored as antivirals, actually briefly describe interferons, w they elicit signaling alter ally, some of the genes way interferon-mediated SARS-CoV-2. Angiotensin sone genes. Although for ferson treatment in COVID- rinin-angiotensin system, to the cell. This manuscript neutrophils, NETosis, and isages", we discuss the ie context of COVID-19

rd Information

1/2021 | Volume 12 | Article 603228



ino acids with two ge-2 as well as the arrib- us and the inhibition of us capable of inducing 6 (ATF6) and inostif- f branch of ER stress ransition of SARS-CoV-2 ransition the production poly(ADP-ribose) (PAR) factor 3 (PARF3), after y-2 with proteins could y, and functions as an ot to be affected by

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individual proteins of have been shown to Shi et al., 2009; Song pathways has impor- reduction (Matsuno like protein (S) me-2 receptor (IC) [1–3]. The hrome protease induces proteasome entry n releases viral (the cytoplasm oligomerase, fol- replicated viral ioli apparatus sis [1–4]. y a huge role in y to viral entry.

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Growing body of evidence supporting rationale to assess SNG001 in COVID-19 patients

RESEARCH

RESEARCH

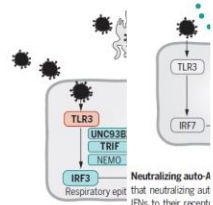
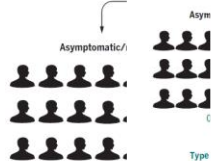
RESEARCH ARTICLE SUMMARY

RESEARCH ARTICLE CORONAVIRUS Autoantib with life-threatening Inborn errors with life-threatening

Qian Zhang et al.

INTRODUCTION: Clinical severe acute respiratory virus 2 (SARS-CoV-2) infection to rapid life-threatening (COVID-19) pneumonia being male, being identified three risk factors being male, being elderly medical conditions. How clinical variability remain graphic category. Discov and detailed mechanism of body-level mechanisms and COVID-19 is of the utmost importance.

RATIONALE: We establish Genetic Effort (www.c



Inborn errors of TLR3 and threatening COVID-19 pneumonia which underlie critical immune encoding biochemically related are encoded by genes with Bastard et al., *Scienc*

Zhang et al., *Science* 370, 422 (2020) 23 October

News & views

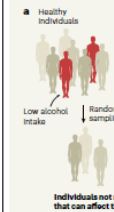


Figure 1 Comparing popul Vukjovic-Cvijin et al., identify and that differ in prevalence proportion of individuals with populations. A random sampl might mean that microbiota factor. B. The authors instead However, such sampling mig

years of heavy smoking, w healthy control group. With that in mind, peo tory bowel disease sho with a healthy matching bowel movement qualit who have type 2 diabete healthy cohort on the ba the glycoprotein HbA1C, assessing long-term exce thing that the authors d should also be susceptio who have type 2 diabetes on the basis of body mas an effort to address repeated their analysis in which none of the indi group self-reported any (the previous criteri uals was just those of the specific disease of Ir similar associations bet and the physiological ences, although these as either less statistically si original analysis or no Unfortunately, remov any self-reported disea matching the people fro with control individuals less be diagnosed, the might be borderline: f for example, people w matched with those w This problem, whose sci this study, raises key qu studies: what constitute Finally, it is importan

374 | Nature | Vol 581 |

Science |

CORONAVI Auto of uni ~20%

Paul Bastard^{1,2*}, E Bizen^{1,2,3*}, A Maslovska Borro^{4,5}, J Cognasse^{4,5}, Jacques G. Tomohiro⁶, Bruno Meg Manuel An Castagnol¹, Marcela M Conillabaly^{1,2}, Nussbaum⁶, Santana^{4,5,4}, Kurokawa⁷, Barreiros^{7,8}, Sahane^{7,8}, I Vidau^{9,10,11}, Nelli Y. Ka Rutger Kon Monneret¹², David Hag Bourke^{10,11}, I Sedkaoui¹¹, Vinh^{16,17}, S N. Spaan^{1,18}, P. Lifton^{19,20}, Response to James's Hill The Millie COVID Hu Sang study Vandreako James Mon Mentré^{16,24}, Solanich^{15,21}, Gregersen⁶, Kal Kisanth Tiberghien²²

¹Laboratory of Hu Institute, Paris, Fr Virology and Infec University, Hôsp d'Hebron Barcelo University of Tart

First release: |



viruses

Review

Dysregulated Interferon Response Underlying Severe COVID-19

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Academic Editor: Andrew Davidson Received: 27 October 2020; Accepted: 9 December 2020; Published: 13 December 2020

Abstract: Innate immune interferons (IFNs), including type I and III IFNs, constitute critical antiviral mechanisms. Recent studies reveal that IFN dysregulation is key to determine COVID-19 pathogenesis. Effective IFN stimulation or prophylactic administration of IFNs at the early stage prior to severe COVID-19 may elicit an autonomous antiviral state, restrict the virus infection, and prevent COVID-19 progression. Inborn genetic flaws and autoreactive antibodies that block IFN response have been significantly associated with about 14% of patients with life-threatening COVID-19 pneumonia. In most severe COVID-19 patients without genetic errors in IFN-relevant gene loci, IFN dysregulation is progressively worsened and associated with the situation of pro-inflammation and immunopathy, which is prone to autoimmunity. In addition, the high correlation of severe COVID-19 with seniority, males, and individuals with pre-existing comorbidities will be plausibly explained by the coincidence of IFN aberrance in these situations. Collectively, current studies call for a better understanding of the IFN response regarding the spatiotemporal determination and subtype-specificity against SARS-CoV-2 infections, which are warranted to devise IFN-related prophylactics and therapies.

Keywords: COVID-19; interferons; interferon signaling; SARS-CoV-2; immunopathy

1. Diverted Type I Interferon (IFN) Response Associated with Hyper-Inflammation

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the current pandemic of new coronavirus disease 2019 (COVID-19), shows an evolutionary success to adapt its infectivity and contagiousness to efficiently spread in human societies [1–6]. The prognosis of SARS-CoV-2-infected patients is very broad, with a vast majority of people (50–80% based on different research scenarios, CDC) only having mild symptoms like the common cold or asymptomatic [7]; however, still, the other significant numbers (averagely 20–50% based on different ethnicity and pre-medical conditions) may progress into severe respiratory and systemic syndromes, needing immediate hospitalization and critical care [8–12]. The case fatality rate of COVID-19 ranges from 1.7–13.0% in different countries [7]. Except for the pathogenic impact of viral infection, major pathologies underlying severe COVID-19 come from the dysregulation of vast immune factors at both the cellular and molecular levels. For example, severe COVID-19 patients display macrophage overreaction (also known as macrophage activation syndrome (MAS)) and lymphopenias of effective lymphocytes, including neutrophils, CD4 T cells, and natural killer (NK) cells [13–15]. At the molecular level, hyper-regulation of pro-inflammatory mediators (including IL-6, TNF α , S100A8/9, and C-reactive protein), a significant decrease of human leukocyte antigen D-related (HLA-DR) gene expression in CD14 monocytes, and dysregulated antiviral interferon (IFN) response have been reported in COVID-19 patients with critical illness [13–15]. In this review, we focus on the determinant role of dysfunctional

Viruses 2020, 12, 1433; doi:10.3390/v12121433

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Review

on production by

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Review

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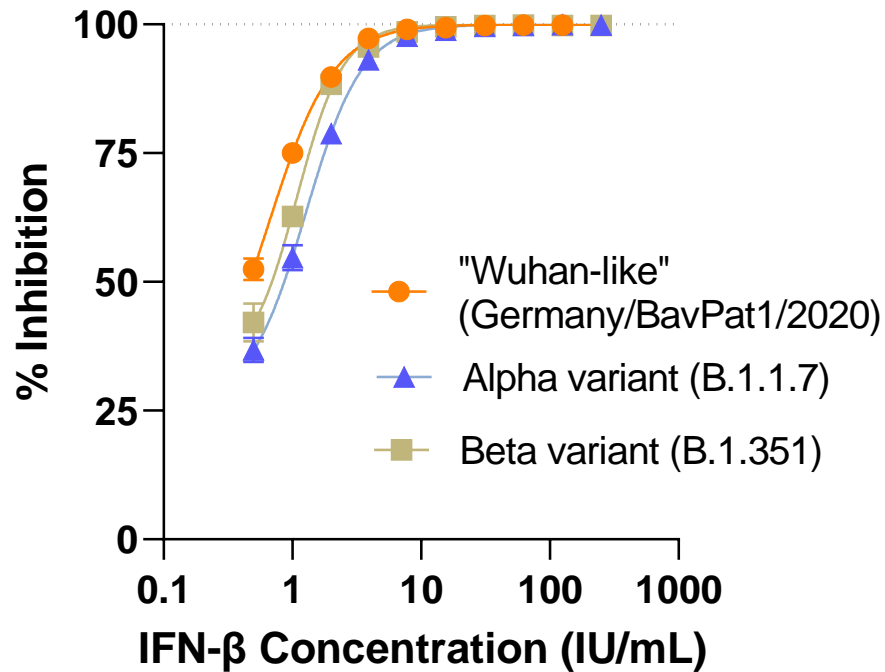
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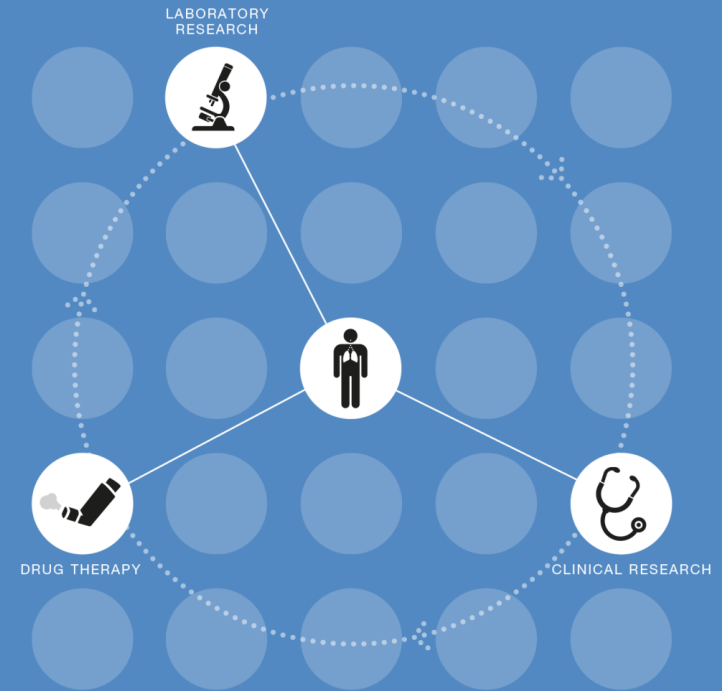
Viruses 2020, 12, 1433; doi:10.3390/v12121433

Antiviral activity of SNG001 against SARS-CoV-2 variants in a cell-based assay



- SNG001 demonstrates similar antiviral potency against different SARS-CoV-2 variants

Clinical trial progress in COVID-19 and preparations for success



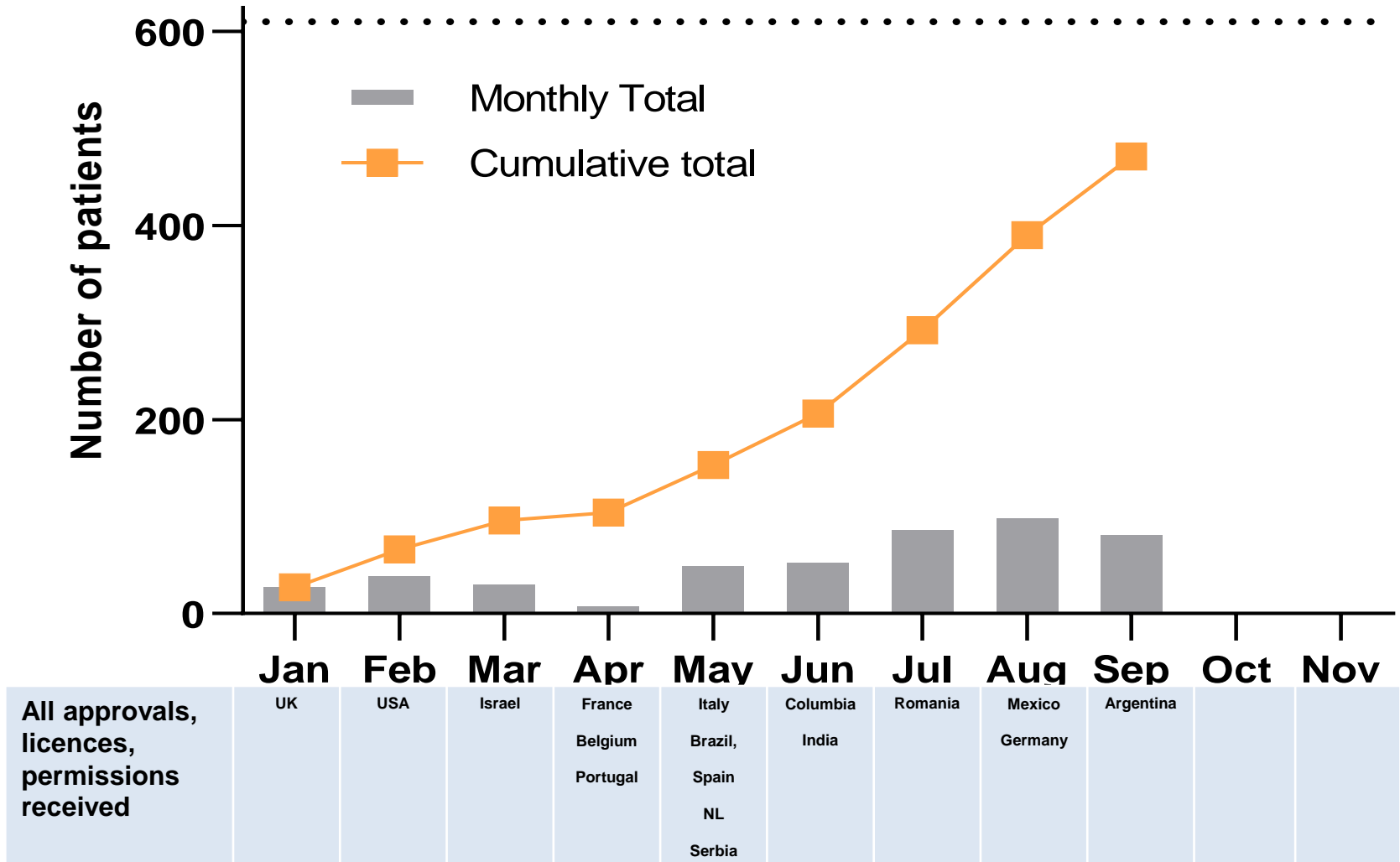
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SPRINTER Phase III trial

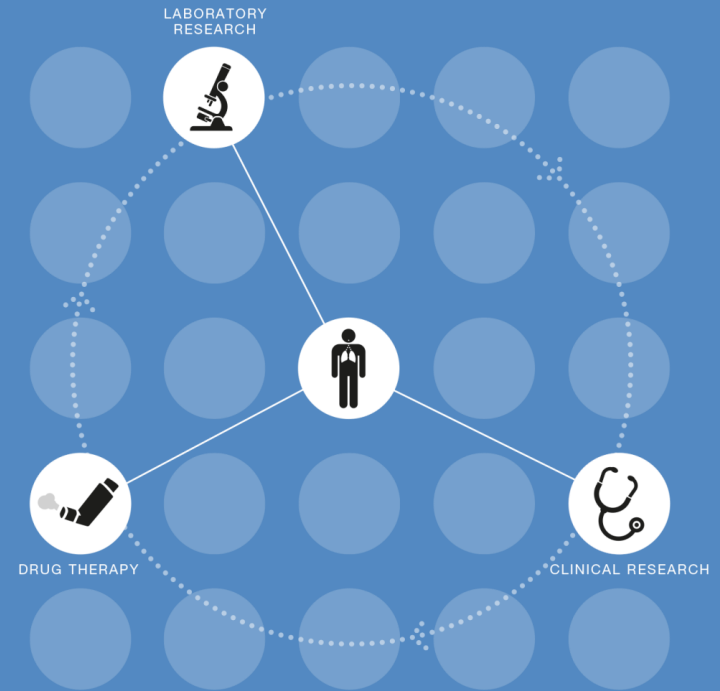
A randomised, double-blind, placebo-controlled, Phase III trial to determine the efficacy and safety of inhaled SNG001 for the treatment of patients hospitalised due to a confirmed SARS-CoV-2 infection

- 610 patients to be recruited (approaching 80% enrolment)
- 17 countries, >100 sites with new sites being added
- Core baseline data suggests similar to Phase II trial:
 - Mean and median age ~51 years
 - Mean and median duration of symptoms prior to initiation of treatment ~8 days
 - Vaccination status
 - Amendment made in May to allow inclusion of vaccinated patients
 - Since then (where approved) 25-30% of patients entering the trial are vaccinated

SPRINTER enrolment expected to complete in November, top line data in early 2022



Preparations in anticipation of a successful outcome of SPRINTER trial



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EUA preparedness

- Expand Synairgen team
- Assuming a positive outcome from SPRINTER
 - File for EUA in US (followed by BLA/MAA)
 - Action in-market support services from 3rd party COVID-experienced vendors who will provide:
 - Medical information for healthcare professionals
 - Patient support services
 - Pharmacovigilance/safety monitoring
 - Distribution

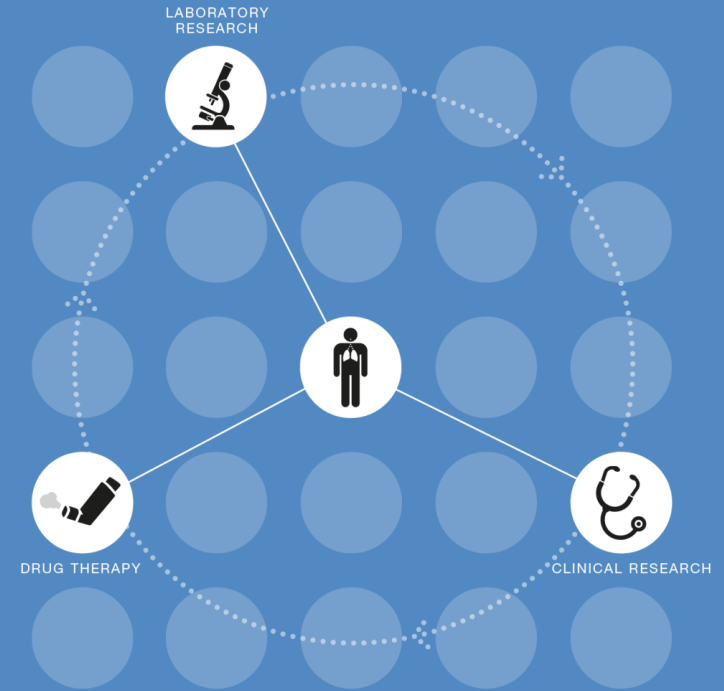
Increasing manufacturing capacity

- This will provide tens of thousands of treatment courses should an EUA be granted
- Multiple commercial scale drug substance batches have been completed by Akron
- Multiple commercial scale batches of prefilled glass syringes have been filled by Catalent
- Commercial scale blow fill seal run with Woodstock Sterile Solutions is underway (formerly a Catalent site)
- Potential to increase capacity to ~100,000 treatment courses per month.
 - Government support required to accomplish this larger scale of manufacturing operation

ACTIV-2 trial update

- ACTIV-2 is being conducted in the home setting
- US Government sponsored trial (conducted by the NIH) includes ~110 COVID-19 patients dosed with SNG001 in the first part of the trial
- Data being reviewed, decision to progress into larger second part of trial awaited

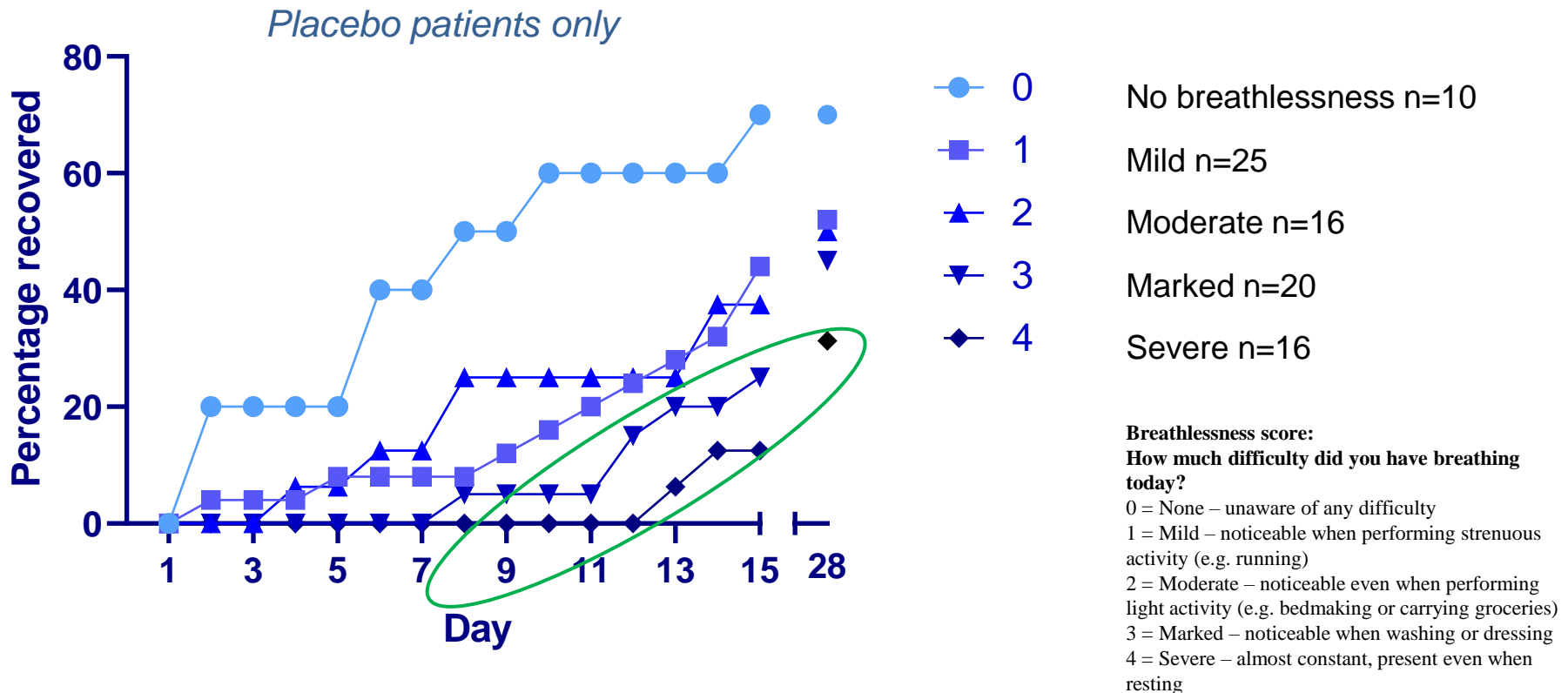
Relevant supporting clinical data generated in 2021



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Combined Hospital and Home cohorts from SG016 (placebo patients):

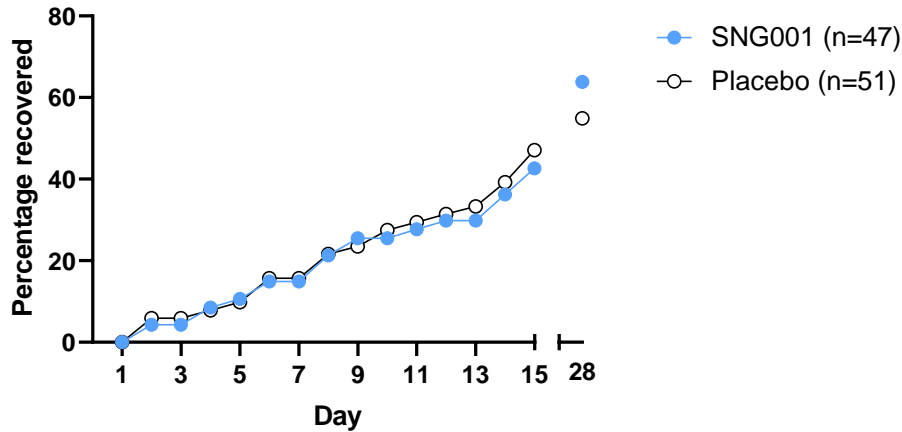
Recovery to level 1 'no limitation of activities' on the WHO Ordinal Scale is delayed in patients with marked or severe breathlessness



Combined Hospital and Home cohorts from SG016:

Recovery to Level 1 on the WHO Ordinal Scale in patients with or without marked/severe breathlessness at start of treatment

Recovery to level 1 on the WHO Ordinal Scale for patients with breathlessness <3 at start of treatment



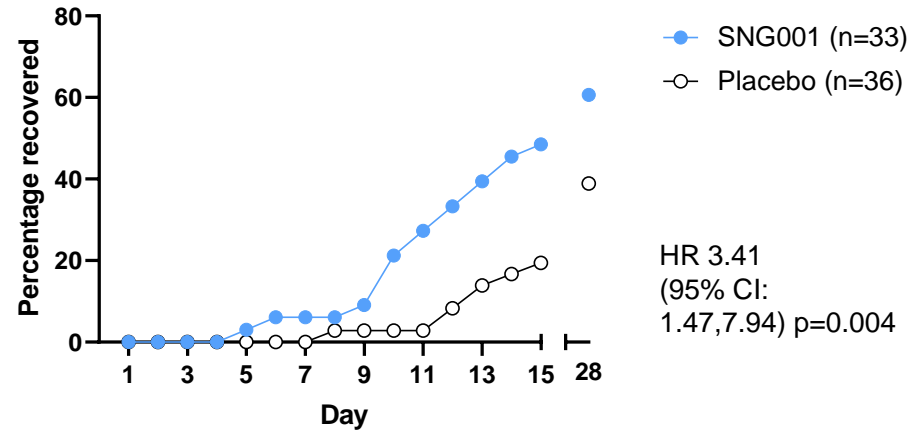
No significant difference in recovery rate between SNG001 and placebo in patients with breathlessness score of 0, 1, or 2.

Breathlessness score:

How much difficulty did you have breathing today?

- 0 = None – unaware of any difficulty
- 1 = Mild – noticeable when performing strenuous activity (e.g. running)
- 2 = Moderate – noticeable even when performing light activity (e.g. bedmaking or carrying groceries)
- 3 = Marked – noticeable when washing or dressing
- 4 = Severe – almost constant, present even when resting

Recovery to level 1 on the WHO Ordinal Scale for patients with breathlessness ≥3 at start of treatment

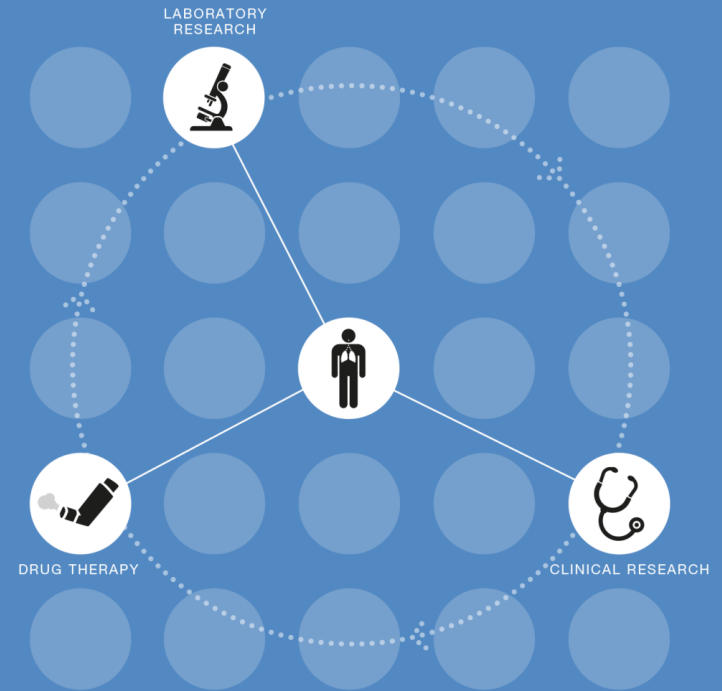


HR 3.41
(95% CI:
1.47,7.94) p=0.004

Breathless patients scoring 3 or 4 receiving SNG001 are more than 3 times as likely to recover than patients taking placebo.

Markedly or Severely breathless patients should be targeted for treatment with SNG001

Financial Summary



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Financial highlights for the 6 months ended 30 June 2021

- Loss before tax of £38.89 million (H1 2020: £5.07m loss)
 - R&D expenditure of £36.91 million (HY 2020: £4.47m) as Synairgen advanced its Phase III clinical trial and scaled up its manufacturing activities
 - Administrative expenses of £1.99 million (H1 2020: £0.60m) as Synairgen built up its management infrastructure and invested in pre-commercialisation activities
- R&D tax credits increased to £5.97 million from £1.11 million due to a scale up of qualifying activities
- Cash of £46.21 million (H1 2020: £10.88m)

Conclusions

- Urgent need for a broad-spectrum antiviral to treat severe viral lung infections
 - >10,000 hospitalisations per day in the US alone
- Increasing evidence underpinning the rationale to assess inhaled IFN- β for the treatment of COVID-19 patients
- Phase III SPRINTER trial expected to complete recruitment in November with topline data available early in 2022
- Positive data from SPRINTER to trigger:
 - EUA submission in the US
 - Distribution arrangements
 - ‘In-market’ support for health care workers and patients provided by COVID-experienced suppliers
- Potential beyond COVID-19 for:
 - Pandemic preparedness
 - Broad-spectrum antiviral for patients hospitalised due to severe viral lung infections