Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Intestinal microbiome transfer, a novel therapeutic strategy for COVID-19 induced hyperinflammation?

In reply to, 'COVID-19: Immunology and treatment options', Felsenstein, Herbert McNamara et al. 2020′

To the Editor,

We read the focussed review authored by Felsenstein and colleagues with great interest and wish to add further perspective on a novel approach to immunotherapy in this patient population that has not previously been described.

In recent years several publications have demonstrated that a bi-directional dialogue exists between the host immune system and its resident hidden microbial majority, specifically the microbiome of the gut and other mucosal surfaces. Emerging evidence has led researchers to conclude that a gut-lung axis may exist and that perturbations of the gut microbiome can worsen outcomes in viral or bacterial animal models of respiratory infection [1]. Preliminary evidence suggests that this axis may influence compartmentalised and systemic inflammation in COVID-19 patients, which may in turn contribute to the wide spectrum of clinical severity observed in the literature [2]. Although mechanistically, these phenomena have yet to be fully elucidated, it has been shown that microbially-derived metabolites, such as short-chain fatty acids (SCFAs), can modulate host inflammatory responses, as well as promote tolerance and resistance to viral pathogens. For instance, one recent study showed that administration of the SCFA butyrate reduced persistent lung inflammation in an animal model of pneumonia [3]. These observations lead us to conclude that modulating the composition and functional outputs of the gut microbiota could in turn regulate the uncontrolled inflammation observed in COVID-19, and thereby representing a potentially attractive novel therapeutic option in this patient population.

Research has shown that the microbiome in critically ill patients is distinct to that of healthy controls and there is some precedence, albeit in an uncontrolled setting, for intestinal microbiome transfer (also known as faecal microbiota transplantation or FMT) being administered to patients with multiple organ dysfunction with successful outcomes, including those with severe viral infections [4]. In addition to aberrant cytokine production and dynamics, T-cell hyperstimulation is a proposed pathomechanism of severe viral influenza, which could also be relevant to COVID-19. Felsenstein and colleagues describe the blockade of proinflammatory cytokines such as interleukin-6 (IL-6) as being a promising host-targeted therapeutic option in COVID-19 patients. Although host immunological outcomes post-FMT have not been fully elucidated, several studies have shown reductions in IL-6 and other proinflammatory cytokines, such as TNF-alpha [5]. Furthermore, microbiota profiles in IBD patients who respond to FMT consistently, show a significant shift towards species of bacteria that are known to induce IL-10 production and induce T_{reg}-cells [6] These data align with a preclinical study that reported that a combination of 17 indigenous strains of Clostridia enhance T_{reg}-cell abundance and induce IL-10 [7]. When taken collectively, the available data insinuates that FMT - and indeed other less complex microbiome modulating therapeutic modalities, such as live biotherapeutic products (LBPs) - could be useful adjuvant immunomodulatory interventions when administered alongside agents currently under investigation, such as tocilizumab or dexamethasone, in patients with COVID-19 induced hyperinflammation.

The available evidence appears to instil cautious optimism for the investigation of FMT in COVID-19 patients as a means to modulate the dysfunctional immune system responses described by Felsenstein and colleagues. Despite the promise, we are of the view that any investigation must only take place in the context of properly controlled clinical studies to establish safety, tolerability and an effective dose schedule in what can be a rapidly deteriorating clinical picture. Although there are safety concerns associated with transferring a foreign antigenic load via the intestinal tract into patients who are fighting an infection, FMT has been applied to numerous intestinal and extra-intestinal disease indications, including immunocompromised and immunosuppressed patients, with a favourable short-term safety profile.

Finally, recent FMT safety alerts have highlighted that need for robust donor as well as controlled manufacturing procedures and facilities. Although it has yet to be convulsively proven, it is plausible that intact SARS-CoV-2 virions could be present in donated material. We are therefore of the view that donors and starting material should be screened for SARS-CoV-2 to safeguard patient safety. Specific expert recommendations regarding reorganisation of FMT services during the COVID-19 pandemic (including adaptations to donor screening, administration protocols and the continuation of FMT research studies) have recently been described [8].

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Authors contributions

James R. McIlroy prepared the first draft of the manuscript. All other authors contributed to manuscript review and revisions. Professor Julian R. Marchesi is the guarantor of the article.

Declaration of Competing Interest

JRM is a shareholder in and is an employee of EnteroBiotix Limited.

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James R. McIlroy[a,b,*], Benjamin H. Mullish[c], Simon D. Goldenberg[d], Gianluca Ianiro[e], Julian R. Marchesi[c,f]

[a] *EnteroBiotix Limited, Aberdeen Blood Transfusion Centre, Foresterhill, Aberdeen, United Kingdom*

[b] *School of Medicine, Medical Science & Nutrition, University of Aberdeen, Aberdeen, United Kingdom*

[c] *Division of Digestive Diseases, Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, London, United Kingdom*

[d] *Centre for Clinical Infection and Diagnostics Research, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom*

[e] *Digestive Disease Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy*

[f] *School of Biosciences, Cardiff University, Cardiff, United Kingdom*

E-mail address: j.mcilroy@enterobiotix.com (J.R. McIlroy).

[*] Corresponding author at: EnteroBiotix Limited, Aberdeen Blood Transfusion Centre, Foresterhill, Aberdeen, United Kingdom.