**As a further example of scientific uncertainty, therapeutic approaches with directly opposing actions are being promulgated. As an example, with granulocyte-macrophage colony-stimulating factor, both direct activation and inhibition are being targeted. If modulation in one direction proves successful, the counter approach may well harm. A further possibility is that both are efficacious, albeit at different time points in the disease process; to our knowledge, the critical issue of timing is not being addressed. Although the scientific merits behind these contrasting approaches have been eloquently argued, the challenge lies in determining the Goldilocks effect (5). The intricacy behind the pleiotropic biology of these drug targets and the unknown trade-offs between advantage and detriment in a complex multisystem disease cannot be underestimated.**

Publication bias for positive results in small case series may also provide a false reassurance of the safety and efficacy of an experimental intervention. Similar issues arise at the other end of the spectrum. Although buoyed by the impressive outcome improvements achieved by low-dose dexamethasone within the large-scale RECOVERY (Randomised Evaluation of COVID-19 Therapy) study, the explanation for many unexplained findings in this study remained unresolved such as the disparate effects depending on sex, age, illness severity, and timing of intervention (6).

Well-meaning attempts to intervene should not take priority over understanding of the pathogenic mechanisms underlying impaired viral clearance and the development of organ failure. The use of theranostic biomarkers may identify patients most likely to benefit and to subsequently monitor for treatment effects. Risk stratification can also be performed using routinely collected clinical parameters (7). This will enable trial enrichment, targeting patients most likely to benefit and not exposing those patients unlikely to benefit to potential detriment.

Decades of sepsis research exploring immunomodulatory therapies have fallen short of expectation and, in some cases, resulted in harm (8). It has been convenient to blame the intervention rather than acknowledging flaws in the underlying scientific rationale or study design. We fear that COVID-19 may be a case of déjà vu and argue for a measured approach based on sound science.

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Figure 1. Summary of biological therapies undergoing randomized controlled trials in coronavirus disease (COVID-19). A3AR = adenosine A3 receptor; JAK = Janus kinase; L-MOD = leukocyte modulator hemopuffusion; MAPK = mitogen-activated protein kinase; NF-kB = nuclear factor-kB; NLRP-3 = NOD-, LRR-, and pyrin domain-containing protein 3; NRP-2 = neuropilin 2; PD-1 = programmed cell death protein 1; PTK2B = phosphoinositide 3-kinase; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; STAT = signal transducer and activator of transcription; TREM-1 = triggering receptor expressed on myeloid cells-1; VEGF = vascular endothelial growth factor.

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