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immobilization, and even death [4]. This underscores a central role for UPP in the maintenance of tegument integrity and survival in schistosomes. Considering the importance of UPP in both larval and adult worm stages [9,10], Wang et al. then sought to evaluate its druggability. By filtering databases and chemical libraries, a series of compounds were therefore selected by their potential to inhibit UPP components. This last and most exciting approach allowed the identification of p97, a central component in the UPP, as a novel target for drug development. In sum, this article sheds light on the usefulness of large-scale RNAi for unraveling complex cellular pathways and exploring their potential benefit in the field of schistosomiasis.

Altogether, these two illuminating articles provide an unprecedented foundation for a better understanding of multiple aspects of schistosome biology and, as a consequence, unveil hidden drug targets. Notably, these findings have highlighted some pre-existing pharmacological agents, thus accelerating the discovery of unexpected highly effective anthelmintic compounds. It is also important to underline the considerable value of the state-of-the-art methods used here in order to identify other clinical drug candidates with selective activity on these worms (and thus with limited side effects). One future avenue for investigation may concern reproductive biology (i.e., egg production) of schistosomes because such therapeutic intervention would combine the advantage of reducing the pathology with a limitation in transmission. The latest exciting developments in functional genomic technologies (especially CRISPR-Cas9) will undoubtedly stimulate further fruitful research into this important area of schistosome biology and greatly help disease control and the development of innovative therapeutic strategies.

Resources

1. www.collinslab.org/schistocyte/

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Artemisinin-based combination therapies (ACTs) have demonstrated in vitro inhibition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Artemisinins have also shown anti-infectious effects, including inhibition of interleukin-6 (IL-6) that plays a key role in the development of severe coronavirus disease 2019 (COVID-19). There is now sufficient evidence for the effectiveness of ACTs, and in particular artemesitane/pyronaridine, to support clinical studies for COVID-19 infections.

Drug Repurposing Accelerates the Discovery of New Cures

Using a drug that works for one disease to treat an unrelated condition can reduce suffering and save lives. Antimalarials provide abundant examples of such successes. When quinidine was purified from cinchona alkaloids, earlier empirical observations on its antiarrhythmic properties led Walter Frey to conclude that it was the most effective of the four cinchona alkaloids in 1918. A merchant first proposed examining cinchona alkaloids to treat arrhythmias because he noticed that when he took quinine to prevent malaria his heart irregularities resolved. Quinine was being used to treat discoid lupus erythematosus with indifferent results until Francis Page (a Registrar at the Middlesex Hospital in London) described the beneficial effects of mepacrine (an antimalarial agent that is structurally related to chloroquine and was used during World War II) in most of 18 patients. A few years later, building on chloroquine’s success as an antimalarial in the late 1940s, hydroxychloroquine was also
During Stages 1 and 2 of infection there is viral replication, which may be targeted by Artesunate. It has also shown studies comparing (4 Vero > 33.0–2.0 [4] Vero Between 4.0–5.0 & 2.0–2.5 [4] Vero > 0.5–1.0 [4] Vero Between 4.1–2.5 & 2.0–1.3 [4] 50). In vitro infections. It has shown that pyronaridine and artesunate are more potent than hydroxychloroquine effectiveness against SARS-CoV-2 show that pyronaridine and artesunate are more potent than hydroxychloroquine [3] in the human lung epithelial cell line Calu-3 (Table 1). Another ACT, mefloquine-artesunate has also shown potent antiviral activity against SARS-CoV-2 [4] with increased drug concentration in lung tissue, a potential clinical advantage in COVID-19 (Table 1).

Antimalarials as Potential Therapeutic Agents for COVID-19
Are there any other promising antimalarials that might be worth investigating in the management of COVID-19? Pyronaridine (a mepacrine nucleus with an amodiaquine-like addition) was first made in 1970 at the Institute of Chinese Parasitic Disease and used as an antimalarial monotherapy given orally and parenterally to treat chloroquine-resistant Plasmodium falciparum infections. It has since been combined with artesunate (in a 3:1 ratio) to form an ACT that is safe and which cures otherwise multidrug-resistant infections [2]. In vitro studies comparing pyronaridine, artesunate, and hydroxychloroquine effectiveness against SARS-CoV-2 show that pyronaridine and artesunate are more potent than hydroxychloroquine [3].

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tract as a viral pneumonia (Stage 2). Around day 7–10, the detectable upper respiratory viral load decreases, antibody responses are generated, and patients start to recover. However, at 7–14 days a small proportion of patients develop a cytokine release syndrome (CRS)/cytokine storm (CS), the hallmarks of which appear to be elevated host markers of inflammation [e.g., increased C-reactive protein (CRP), ferritin, D-dimers] and lymphopenia. Patients experiencing CRS often develop progressive respiratory failure (Stage 3) that can then lead to acute respiratory distress syndrome (ARDS) and multiorgan failure (MOF) (Stage 4).

Interleukin-6 (IL-6) is promptly and transiently produced in response to tissue injury and infection, stimulating acute-phase responses, hematopoiesis, and immune reactions, which contribute to host defense [5]. In chronic inflammation and autoimmune diseases, dysregulated continual synthesis of IL-6 leads to significant pathophysiological effects. Apart from IL-6, other proinflammatory cytokines, such as IL-1, interferon-gamma (IFN-γ) and tumor necrosis factor (TNF) are produced during CRS/CS and contribute to pathophysiological processes that result in MOF. Although rare, symptoms similar to Kawasaki disease are another delayed immunological manifestation of SARS-CoV-2 infection in children [6].

In patients admitted to intensive care units, around 60–70% develop ARDS, followed by shock (30%), myocardial dysfunction (20–30%), and acute kidney injury (10–30%). In these critically ill patients, between 42 and 100% will require mechanical ventilation. Risk factors for developing severe COVID-19 disease include older age, male sex, comorbidities (including chronic lung disease, cardiovascular disease, diabetes, obesity, cancer, and organ transplantation). Genetic factors and ethnicity may also play a role [7]. Several therapeutic agents have been proposed for the treatment of CRS, including corticosteroids, intravenous immunoglobulin, selective cytokine blockade, and Janus kinase (JAK) inhibition [8].

The RECOVERY trial has shown a mortality benefit of dexamethasone in patients with moderate and severe COVID-19, supporting the importance of anti-inflammatory interventions to manage the complications of CRS. Tocilizumab is an anti-IL-6 antibody that binds membrane-bound and soluble IL-6 receptors, blocking IL-6 from exerting its proinflammatory effects. It is currently licensed for the treatment of CRS related to chimeric antigen receptor (CAR)-T cell therapy and rheumatoid arthritis. Tocilizumab has also been trialed in different studies to treat severe COVID-19, including the specific features of CRS [9], and may be beneficial in reducing mortality and morbidity, although more studies are needed.

Artemisinins as Potential Therapeutic Agents for COVID-19

In addition to their in vitro SARS-CoV-2 effects, as noted earlier, artemisinins, including artesunate, also have anti-inflammatory properties. These include those directed at IL-6-mediated pathways. The anti-inflammatory effects of artesunate in a range of disease states are detailed later and suggest that artemisinins may be beneficial in managing COVID-19 patients.

In a rat model of hemorrhagic shock, artesunate attenuated the expression of proinflammatory proteins IL6, TNF-α, NF-κB, and nitric oxide synthase (NOS). This protected against MOF [11]. Pathway analysis by RNAseq supported an effect of artesunate on the protein kinase B (PKB or Akt)-survival pathway, resulting in IL-1 receptor-associated kinase 1 (IRAK1) downregulation. Treating rats with artesunate enhanced the phosphorylation (activation) of endothelial (e)NOS and Akt as well as the phosphorylation (inhibition) of glycogen synthase kinase-3β (GSK-3β). Akt activation is linked to the prevention of a range of organ injuries and phosphorylates estrogen receptor (ER) at Ser117 enhancing production of nitric oxide (NO). This is pivotal to preserve microvascular perfusion and prevent MOF.

Artesunate in Models of Acute Lung Injury and Nephritis

In a rat model of LPS-induced lung injury, artesunate reduced levels of IL-6, IL-1β, and TNF-α. TLR4 expression and NF-κB activation were also attenuated by artesunate, which upregulated expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) [12]. In another rat model [13], artesunate inhibited renal reperfusion-stimulated lung inflammation by attenuating serum and pulmonary IL-6, macrophage-inflammatory protein 2 (MIP-2), prostaglandin E2 (PGE2), NO and malondialdehyde (MDA) levels, and activated the HO-1 pathway.

In a rat model of nephritis, artesunate attenuated IL-6 levels, TNF-α, transforming growth factor (TGF)-β1, TLR4, and NF-κB expression [14]. Artesunate also ameliorated high glucose-induced injury in rat glomerular mesangial cells via suppression of the TLR4/NF-κB/nod-like receptor protein 3 (NLRP3) inflammasome pathway [15].
Concluding Remarks
There is sufficient evidence for the antiviral and anti-inflammatory effects of antimalarials to support further clinical therapeutic studies for COVID-19 infections. In particular, pyronaridine has demonstrated in vitro antiviral effects on SARS-CoV-2 in a human lung epithelial cell line, while artemesine, in addition to similar antiviral effects, has anti-inflammatory effects via IL-6 mediated pathways in other disease states that suggest it may be beneficial in the treatment of COVID-19 (Table 1, Figure 1). Thus, the ACT artemesine/pyronaridine deserves further investigation as a COVID-19 treatment option. The safety of this antimalarial combination is established in malaria in children and adults, providing some reassurance for studies in COVID-19. Several Phase II studies are being implemented, and their design may benefit from the varied mechanisms of action that have been outlined, including assessment of the broad-spectrum anti-inflammatory properties of artemesine. In addition, care should be taken to test this combination with rigor and not over promise its potential so as to avoid the issues that surrounded the treatment of COVID-19.

Acknowledgements
H.M.S. is supported by the Wellcome Trust Institutional Strategic Support Fund (204802/Z/16/2) awarded to St George's University of London.

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