Researchers report potential broad-spectrum anti-coronavirus cocktail therapy

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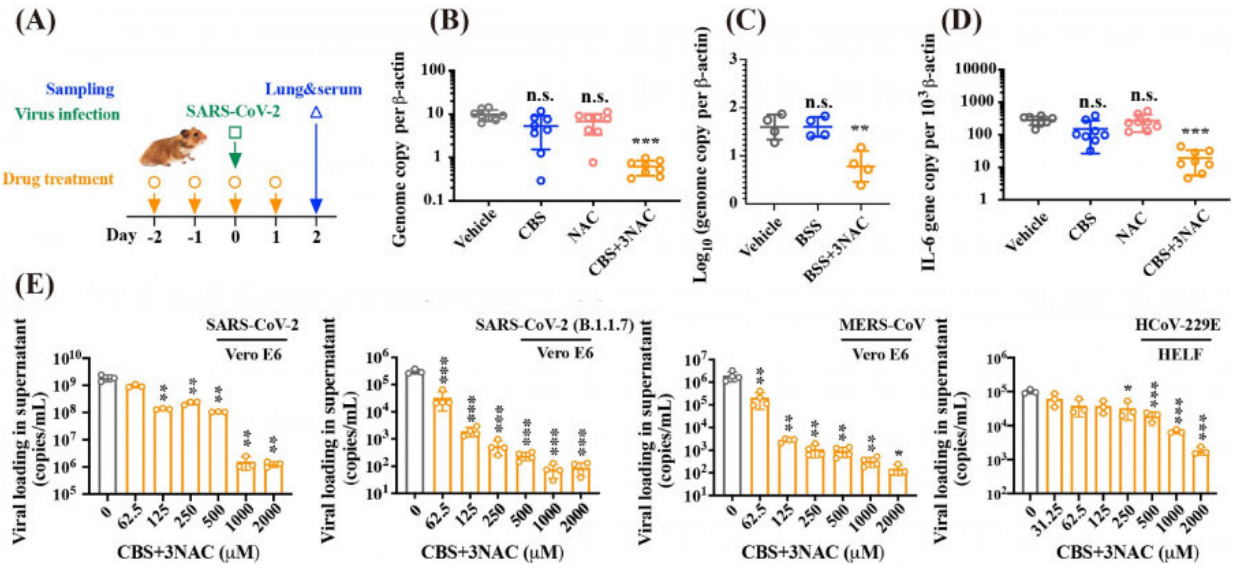


Combinatorial CBS and NAC exhibit broad-spectrum anti-CoVs potency both in vitro and in vivo. (A) Scheme depicting the therapeutic treatment via oral administration of vehicle, CBS (300 mg/kg) or BSS (300 mg/kg), NAC (370 mg/kg) and CBS (300 mg/kg)+3NAC (370 mg/kg) or BSS (300 mg/kg)+3NAC (405 mg/kg), given at Day -2, -1, 0 and 1 and the hamsters were challenged by virus at Day 0; Tissue samples were collected at two days after infection. (B) Viral yield in lung tissue of hamster receiving treatment of vehicle, CBS, NAC, and CBS+3NAC. (C) Viral yield in lung tissue of hamster receiving treatment of vehicle, BBS, and BSS+3NAC. (D) Cytokine IL-6 gene expression level. (E) CBS+3NAC suppressed replication of human-pathogenic coronaviruses in human cellular models in a dose-dependent manner, specifically for SARS-CoV-2 in Vero E6 cells; SARS-CoV-2 (B.1.1.7 variant) in Vero E6 cells; MERS-CoV in Vero E6 cell and HCoV-229E in HELF cell. Credit: The University of

A research team led by Professor Hongzhe Sun, Norman & Cecilia Yip Professor in Bioinorganic Chemistry from the Department of Chemistry, Faculty of Science, the University of Hong Kong (HKU), in collaboration with Dr. Shuofeng Yuan, Assistant Professor from the Department of Microbiology, Li Ka Shing Faculty of Medicine, discovered that orally administrated bismuth drug colloidal bismuth subcitrate (CBS) together with N-acetyl cysteine (NAC) could be a broad-spectrum anti-coronavirus cocktail therapy.

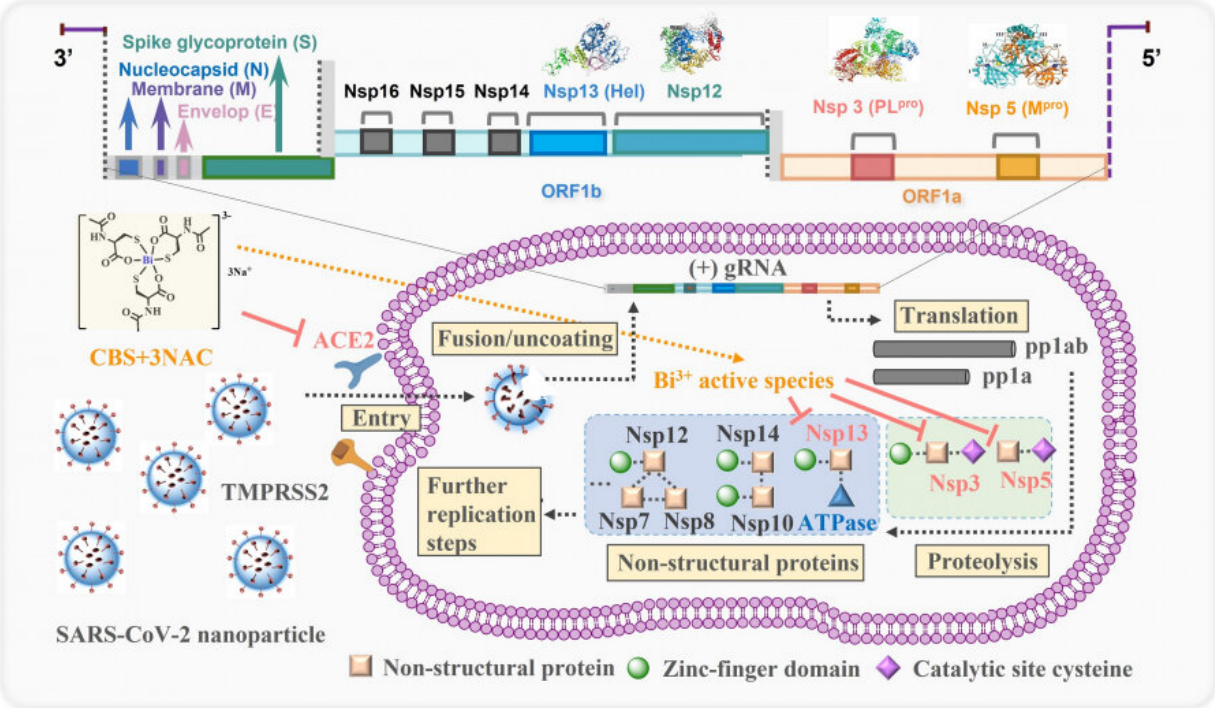
Oral administration of the cocktail suppresses the replication cycle of the virus, reduces viral loads in the lung and ameliorates virus-induced pneumonia in a hamster infection model. Not only could NAC stabilize bismuth-containing metallodrugs at stomach-like conditions but also enhance the uptake of bismuth drugs in tissues (e.g. lung) and antiviral potency through oral administration. Bismuth subsequently suppressed virus replication of a panel of clinically relevant coronaviruses, including Middle East respiratory syndrome-related coronavirus (MERS-CoV), Human coronavirus 229E (hCoV-229E) and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its alpha variant (B.1.1.7) by inactivating multiple essential viral enzymes. The findings provided insights into the development of inorganic pharmaceutics and a new therapeutic approach for viral infections. The ground-breaking findings have been published in the journal, *Chemical Science* and a related patent has been filed in the US.

Background

SARS-CoV-2 is the causative agent of the Coronavirus Disease 2019 (COVID-19) pandemic which leads to around five million confirmed

cases, including 323,000 deaths globally. Although several vaccines have been approved for emergency use worldwide, increasing cases of people getting infected with COVID-19 are reported despite being fully vaccinated. The emergence of SARS-CoV-2 variants like Omicron and Delta variants associated with enhanced transmissibility and reduced sensitivity to vaccine-induced protection poses a continuous threat to global health. There is an urgent need for safe and effective therapeutic options for COVID-19 which remain scarce.

Remdesivir was the first drug approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19. However, patients can only receive remdesivir treatment via intravenous route as in-patients as the oral formulation of this drug is still not available. For most COVID-19 patients with mild to moderate disease, an orally available anti-SARS-CoV-2 drug would help to facilitate out-patient treatment and reduce the burdens of healthcare facilities. Even though the US FDA issued emergency use authorisation for the oral tablet-form candidates from pharmaceutical giants Pifzer and Merck which reported significant reduction of the risk of hospitalization or death, their antiviral efficacy, long-term safety and worldwide availability spark uncertainties. Therefore, it is of utmost urgency for renewed efforts to evaluate the existing repertoire of FDA-approved drugs on a wider scale and by a novel strategy.



Proposed mechanism of action for orally administrated colloidal bismuth subcitrate together with N-acetyl cysteine as a broad-spectrum anti-coronavirus cocktail therapy. The pan-inhibitory activity of bismuth drugs against various CoVs may stem from their abilities to target multiple viral enzymes in the viral replication cycles. CBS as well as related metallodrugs could inactivate the viral cysteine protease through either targeting the key cysteine residue in the active site (PL^{pro} and M^{pro}) or structural zinc-finger domain (PLpro and Hel) or even other zinc metalloproteins in human cells (ACE2) that are tightly associated with viral entry. Credit: The University of Hong Kong

Key findings

The research team previously screened a set of metallodrugs and related compounds and identified ranitidine bismuth citrate (RBC, commercial name: Pylorid), a drug in clinical use for the treatment of Helicobacter pylori infection, as a potent anti-SARS-CoV-2 agent both in vitro and in

vivo. Pylorid exhibited low cytotoxicity and protected SARS-CoV-2-infected cells with a high selectivity index which demonstrated the high clinical potential of bismuth(III)-drugs or other metallodrugs for the treatment of SARS-CoV-2 infection. The related works were published in *Nature Microbiology* in 2020.

RBC, as well as other related bismuth drug(s), e.g., colloidal bismuth subcitrate (CBS) and bismuth salicylate (BSS), acts to precipitate in gastric juice and form a protective coating on the gastric wall, which leads to a hindered absorption in gastrointestinal tract. The findings revealed that NAC could prevent the hydrolysis of CBS in simulated gastric juice buffer (pH 1.2) and sodium bicarbonate buffer (pH 9.2), which form a highly stable and water-soluble Bi(III) thiolate complex, $[Bi(NAC)_3]$. The combined use of NAC could significantly enhance the permeability of bismuth in parallel artificial membrane model, the human intestinal epithelial cancer cell line (Caco-2) model, and a modified ex vivo everted rat gut sac model. The thiolated bismuth could undergo fast thiol exchange with thiol groups in glycoproteins, which potentially increase both the lipophilicity and membrane permeability of bismuth, thus further enhancing the oral absorption of bismuth drugs. The in vivo pharmacokinetics data also consistently demonstrate that compared with the administration of CBS in the absence of NAC, the co-administration of CBS with NAC led to a remarkably improved bismuth uptake profile in both blood and lung tissues.

The studies demonstrated the oral efficacy of CBS+3NAC as well as BSS+3NAC on the suppression of SARS-CoV-2 replication in vivo as evidenced by the substantial reduction of viral loading in the lungs based on viral RNA genome copy number and the ameliorated virus-associated lung pathology after oral administration of CBS+3NAC. The therapeutic dosage of drugs induced only reversible nephrotoxicity and no systematic toxicities. More importantly, CBS+3NAC inhibits the replication of a broad range of epidemic and seasonal CoVs, including

SARS-CoV-2 (B.1.1.7), MERS-CoV, and hCoV-229E. The pan-inhibitory activity of bismuth drugs against various CoVs may stem from their abilities to target multiple key viral cysteine enzymes in the viral replication cycles, including papain-like protease (PL^{pro}), main protease (M^{pro}), helicase (Hel) and angiotensin-converting enzyme 2 (ACE2).

More information: Runming Wang et al, Orally administered bismuth drug together with N-acetyl cysteine as a broad-spectrum anti-coronavirus cocktail therapy, *Chemical Science* (2021). DOI: 10.1039/D1SC04515F

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