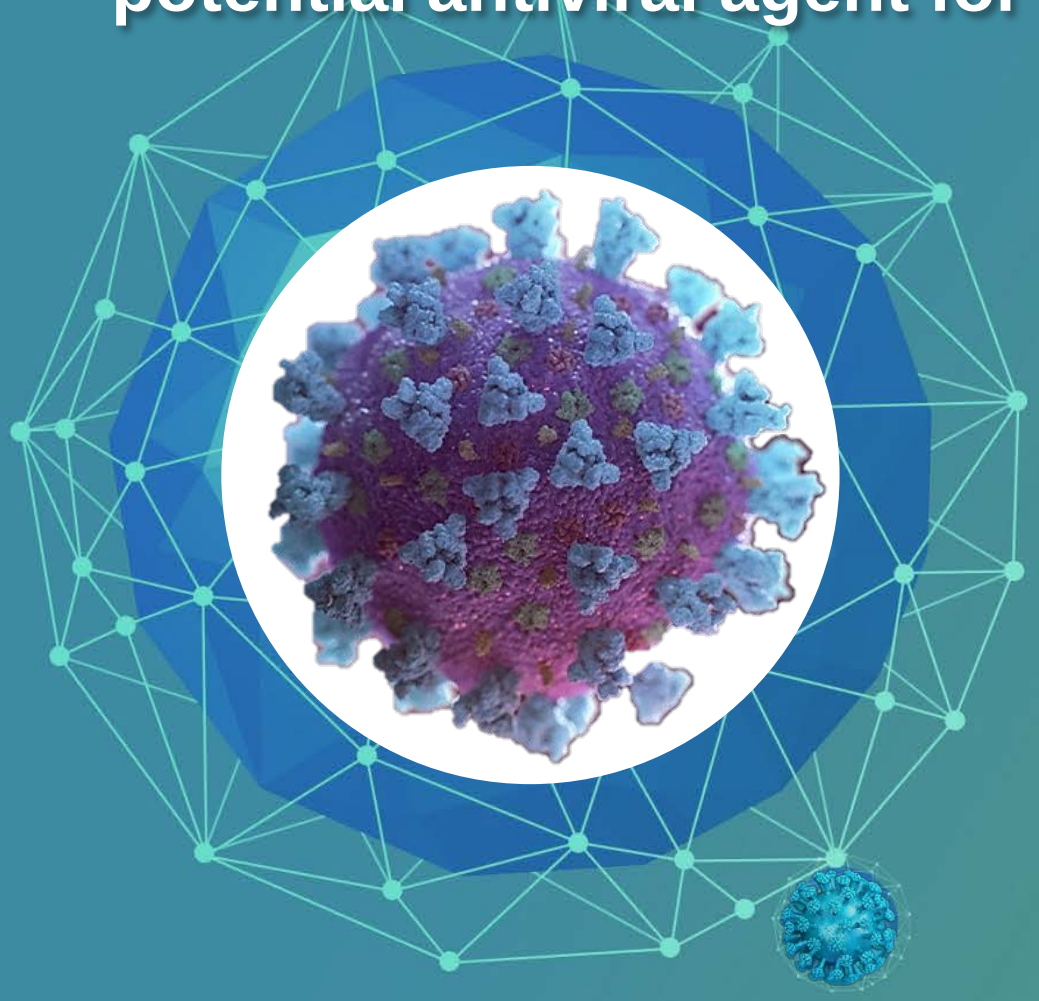
港大科學家發現金屬鉍藥物可作為潛在新冠病毒抑製劑

HKU discovers the metallodrug ranitidine bismuth citrate as a potential antiviral agent for COVID-19

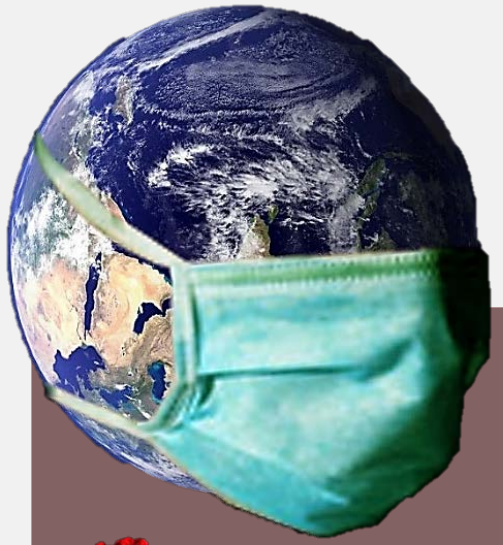


香港大學化學系、微生物學系

孫紅哲教授、袁國勇教授 研究團隊

Prof. Hongzhe SUN,
Department of Chemistry, HKU

Prof. Kwok-yung YUEN,
Department of Microbiology, HKU



新型冠狀病毒肆虐全球：*該何去何從?*

COVID-19 Pandemic: *What can we do?*

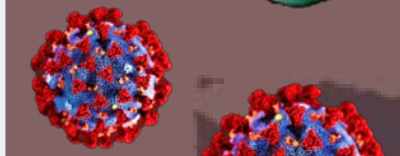
截止2020年10月12日：

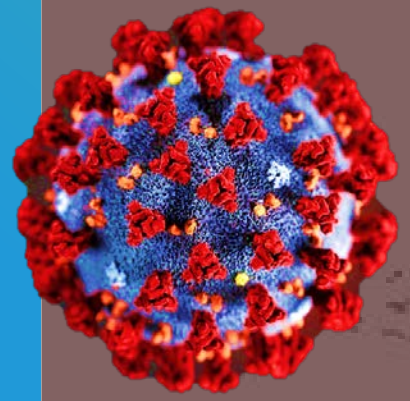
全球確診人數逾3,500萬
Confirmed cases

> 35 million world-wide (US>7 million)

全球死亡人數破百萬
Confirmed cases

➢ 1 million worldwide (US >200,000)





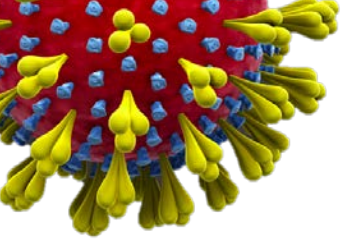
我們能做什麼?

❒ 盡快篩選抗新冠病毒的臨床藥物（老藥新用）！

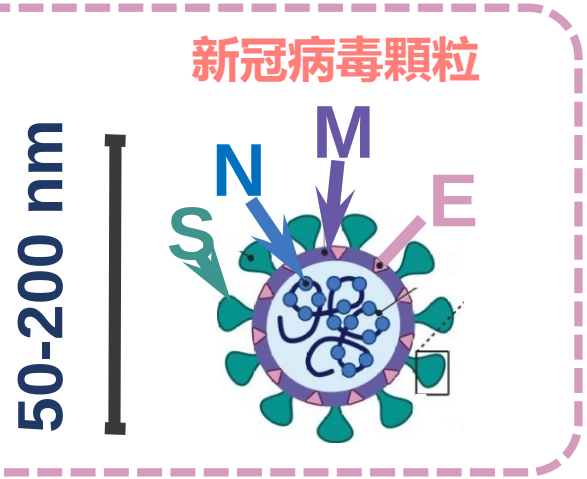
Screening clinically used drugs (repurpose old drug) for immediate use!

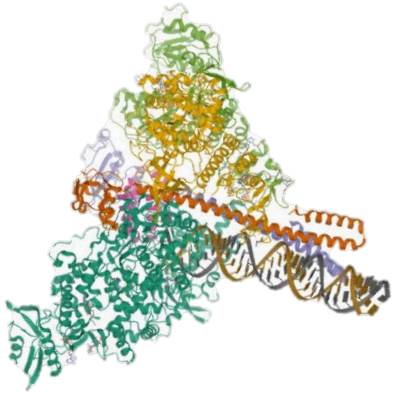
❒ 盡快研發新型抗新冠病毒藥物和疫苗

Develop novel anti-SARS-CoV-2 drugs and vaccines



新型冠狀病毒的結構基因组
Structural genomics of SARS-CoV-2

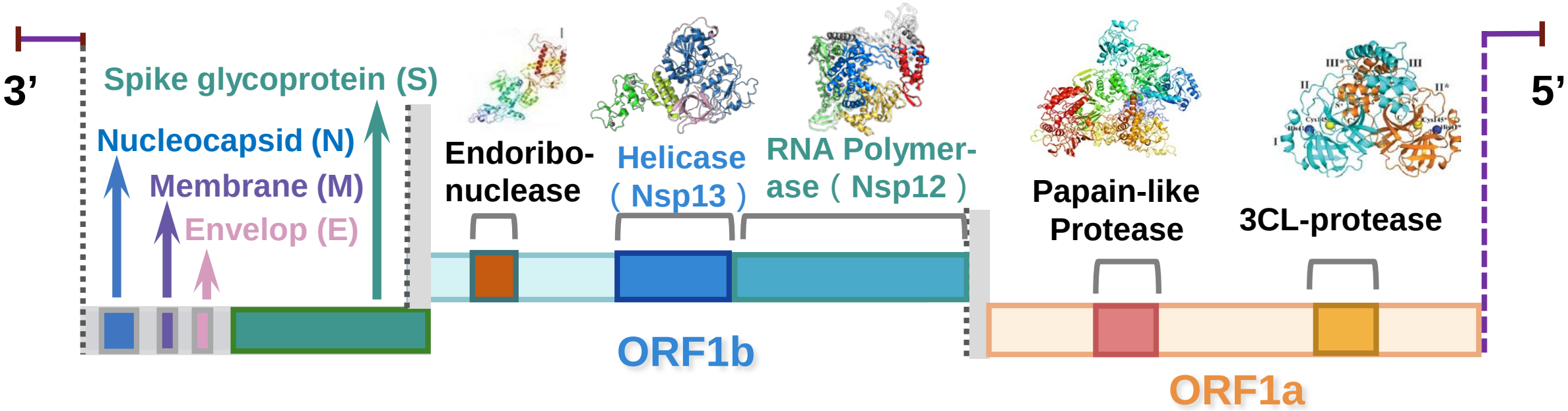


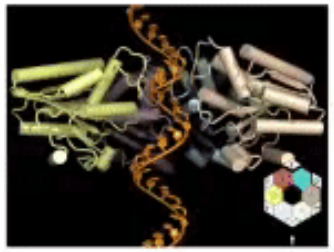


病毒複製的「指揮官」

新冠病毒複製轉錄複合體（解旋酶+RNA 聚合酶）

SARS-CoV-2 replication transcription complex-Helicase（Helicase+RNA Polymerase）



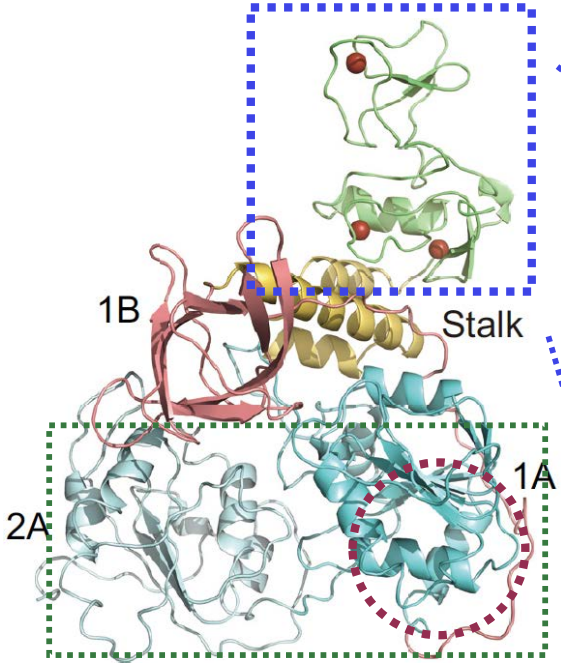


靶向新冠解旋酶:*含鉍金屬藥物?*

Targeting SARS-CoV-2 Helicase：*Bismuth drug ?*

解旋酶晶體結構

Protein crystal structure

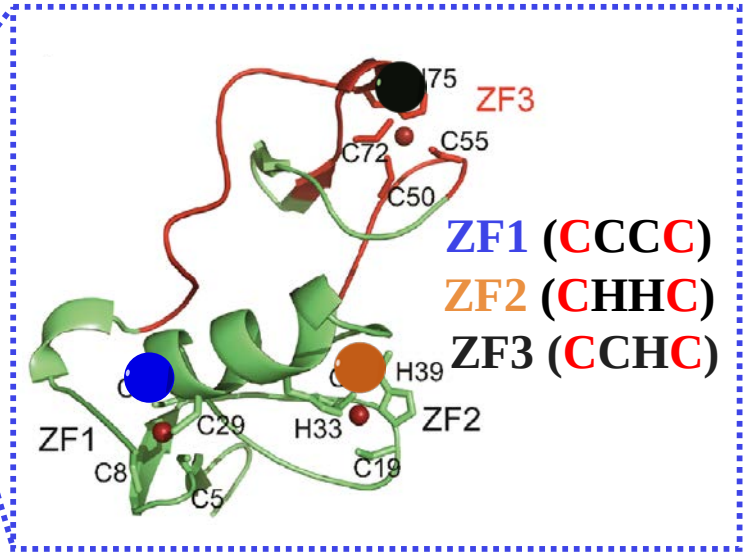


核酸底物識別位點

Substrate recognition site

鋅指結構域

（Zinc-finger domain）

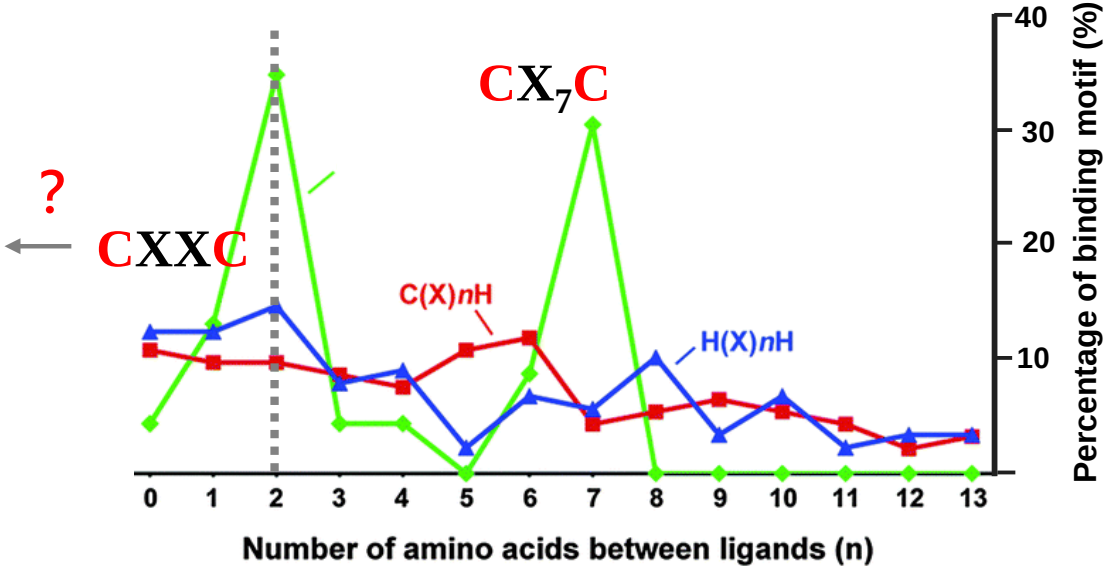


ATP的結合位點（預測）

Putative ATP binding site

含鉍藥物鉍在幽門螺旋桿菌中的結合蛋白基序

Bismuth-binding motif in *Helicobacter pylori*



Sun. Chem. Commun., 2015,51, 16479

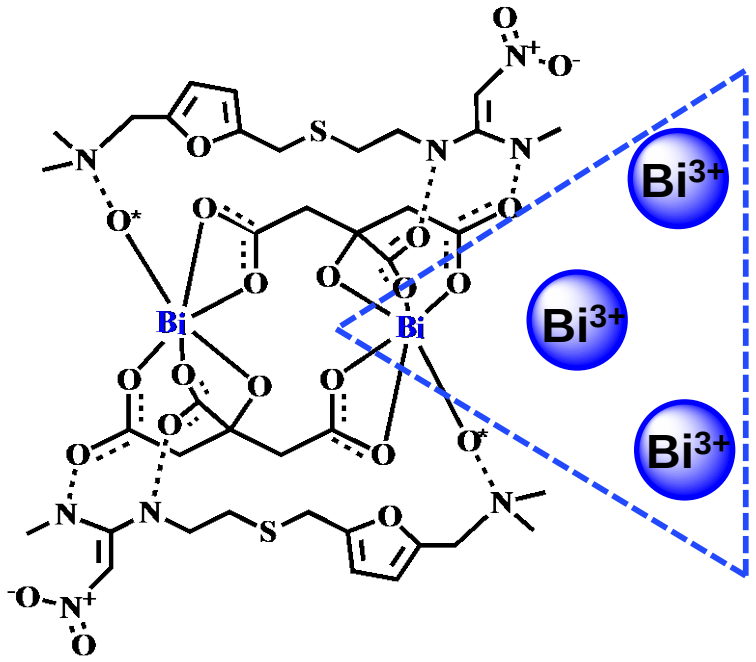
基於蛋白結構分析，對含鉍及相關的金屬藥物進行篩選！

Screen on bismuth drugs and related metallodrug based on structural analysis

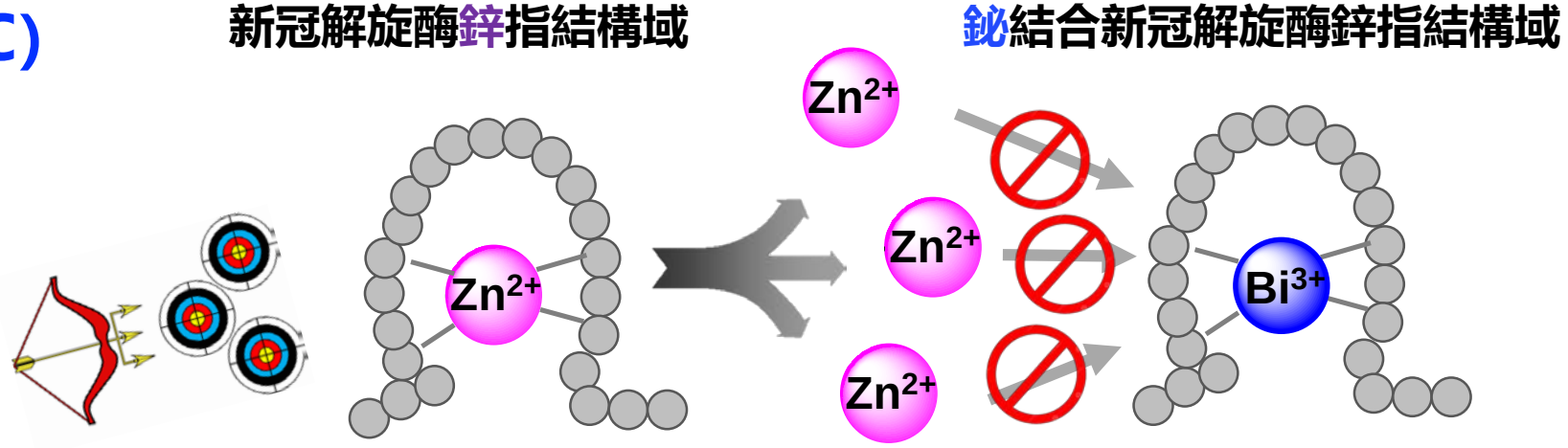
枸櫞酸鉍雷尼替丁：*強力新冠解旋酶抑制劑*

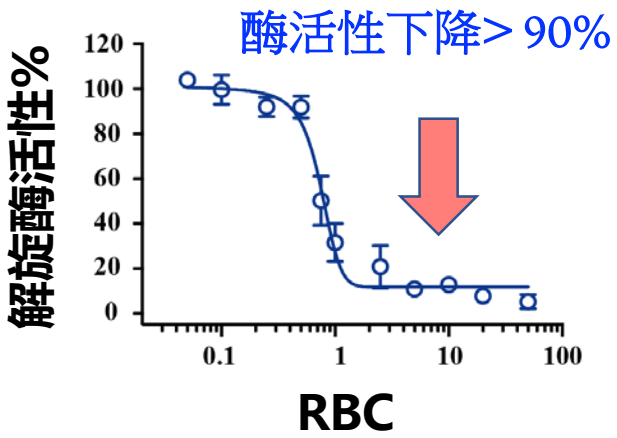
Ranitidine bismuth citrate：*Potent SARS-CoV-2 helicase inhibitor*

枸櫞酸鉍雷尼替丁 （RBC）

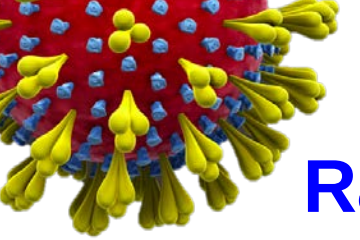


- ✓ 抗消化系统溃瘍藥物
- ✓ 臨床使用多年，安全性佳





鉍結合到新冠解旋酶上，剔除鋅離子並使其失活，且活性不可再恢復！

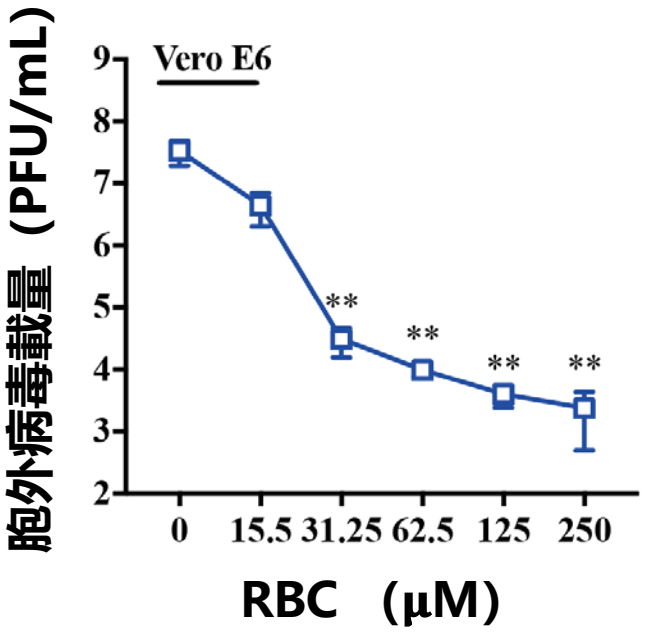


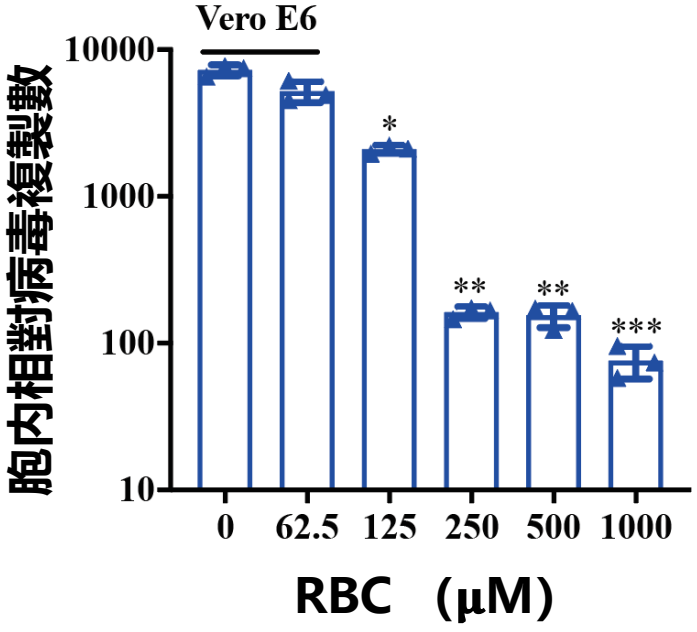
枸櫞酸鉍雷尼替丁：*強力抗新冠病毒劑*

Ranitidine bismuth citrate：*Potent anti-SARS-CoV-2 agent*

選擇指數（selectivity index，效力/毒性）

RBC：975！



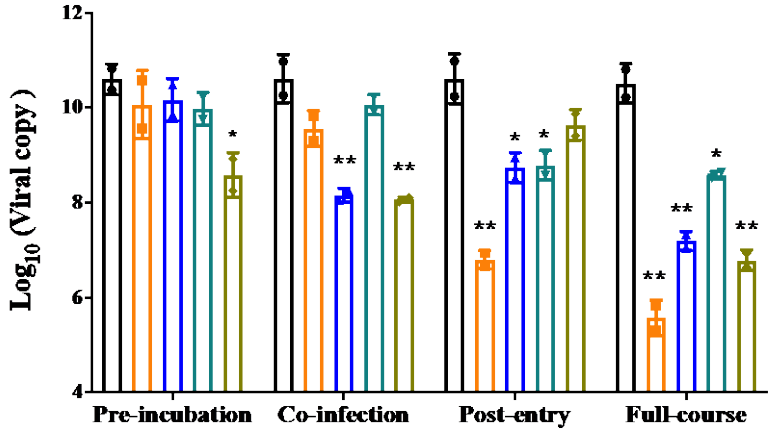


「神藥」瑞德西韋

Remdesivir

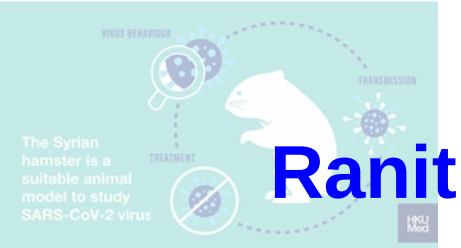
細胞層面選擇指數： ~130

Cell Research , 30, 269–271(2020)



RBC在細胞層面毒性極低，並能大幅度降低受新冠病毒感染細胞的病毒載量！

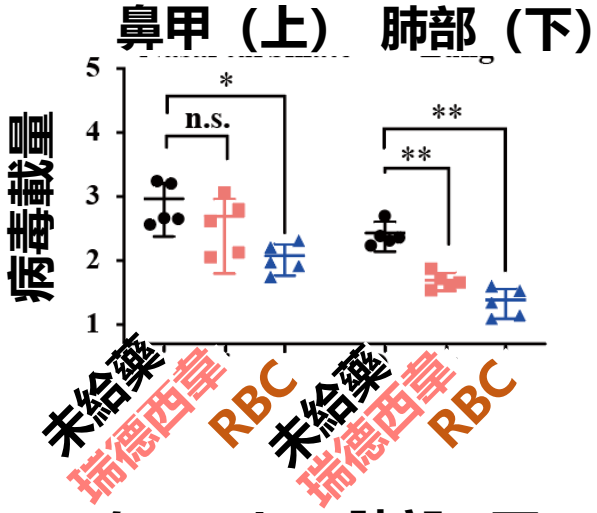
RBC可能存在多種抗病毒機制

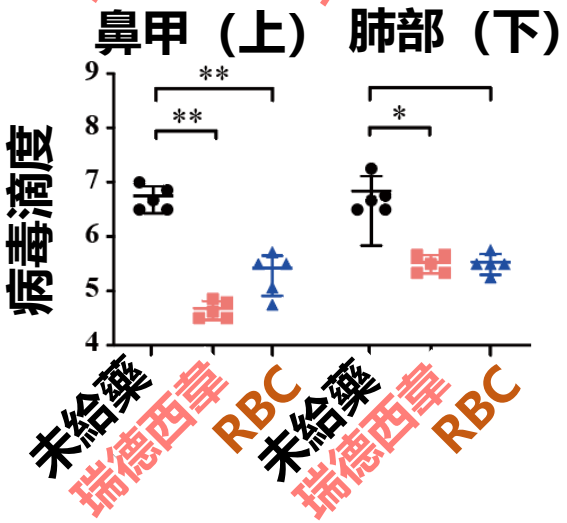


枸櫞酸鉍雷尼替丁：*強力抗新冠病毒劑*

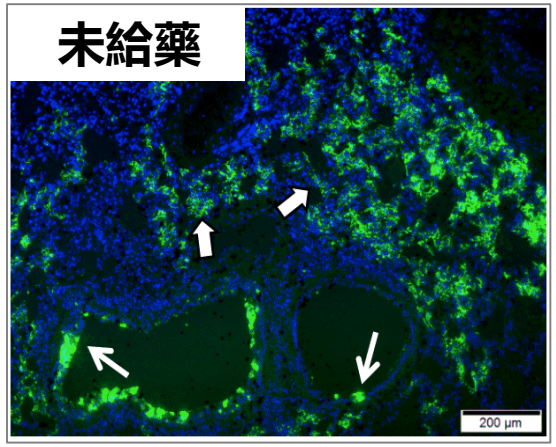
Ranitidine bismuth citrate：*Potent anti-SARS-CoV-2 agent*

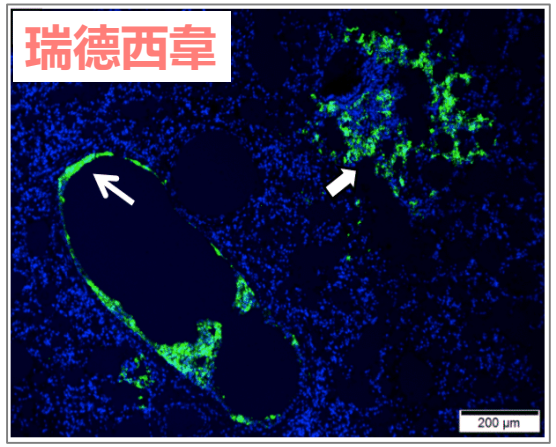
新冠感染倉鼠模型——觀測藥物治療後受新冠感染動物在上下呼吸道組織的病毒量

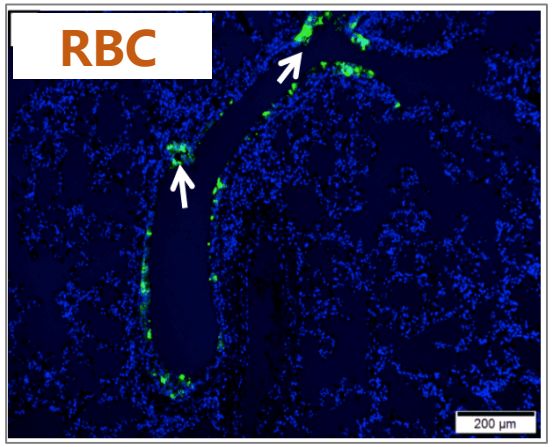




RBC治療後，受感染動物肺部新冠病毒量下降十倍！

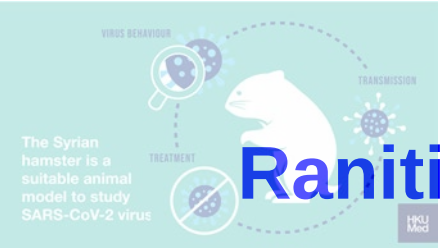






病毒N蛋白量顯著下降 ⬇ **絕大多數新冠病毒已在肺部被清除**

RBC在倉鼠模型中與瑞德西韋藥效相當！

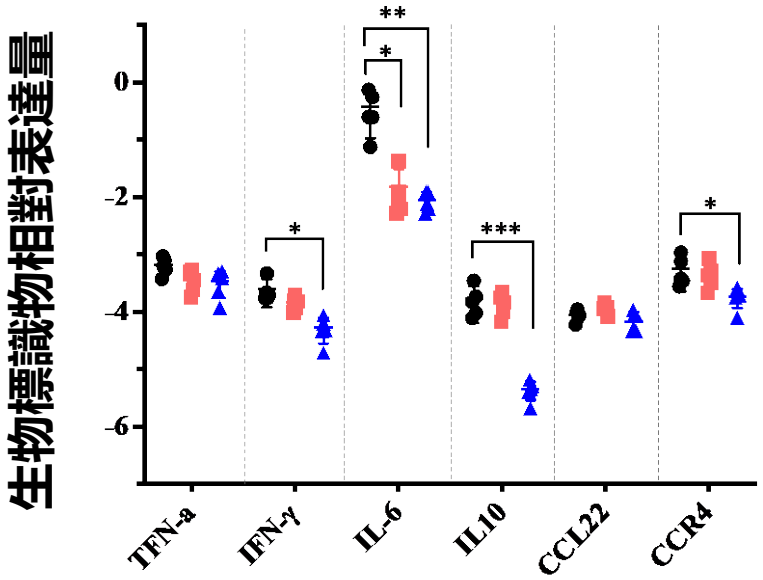


枸櫞酸鉍雷尼替丁缓解新冠引起的病症

Ranitidine bismuth citrate mitigates SARS-CoV-2 disease

選取新冠感染的重要的生物標識物（biomarker）
用於檢測生物體的生理健康水平

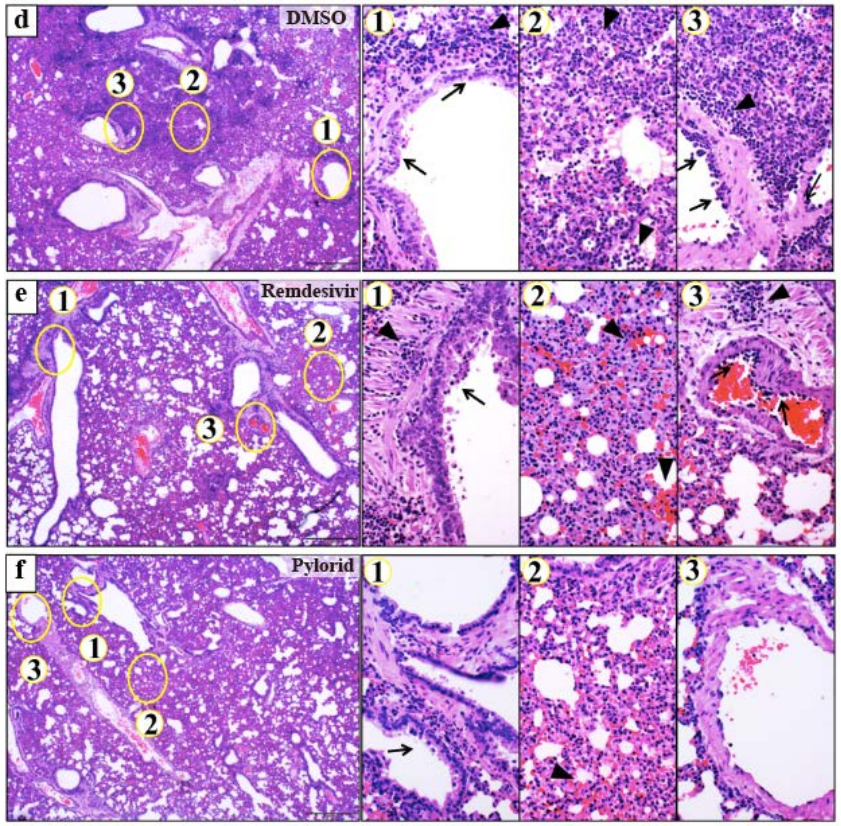
•未給藥 ▪瑞德西韋 ▴RBC



未給藥

瑞德西韋

RBC



RBC治療後，受新冠感染動物的炎症相關指標均出現下降

枸櫞酸鉍雷尼替丁抗新冠病毒感染療法的優勢

Advantage of RBC-based therapy for treating COVID-19 infection

強力 – 在細胞水平和動物模型中不差於瑞德西韋

安全 – 枸櫞酸鉍雷尼替丁已在臨床使用多年，可快速投入後期臨床試驗

穩定 – 水溶性佳，常溫儲存不變質，無需特殊儲存條件

徹底 – 新冠病毒解旋酶失活的過程不可逆，徹底使其失去複製能力

平價 – 相比現今高昂的抗新冠治療成本（瑞德西韋>3000 美元/療程），枸櫞酸鉍雷尼替丁的成本極為低廉

團隊研究成果已發表並已申請美國專利

The new findings has been published and in application for US patent

nature microbiology

ARTICLES

https://doi.org/10.1038/s41564-020-00802-x

Check for updates

Metallodrug ranitidine bismuth citrate suppresses SARS-CoV-2 replication and relieves virus-associated pneumonia in Syrian hamsters

Shuofeng Yuan[1,6], Runming Wang[2,6], Jasper Fuk-Woo Chan[1,3,6], Anna Jinxia Zhang[1], Tianfan Cheng[4], Kenn Ka-Heng Chik[1], Zi-Wei Ye[1], Suyu Wang[2], Andrew Chak-Yiu Lee[1], Lijian Jin[4], Hongyan Li[2], Dong-Yan Jin[5], Kwok-Yung Yuen[1,3] and Hongzhe Sun[2]

團隊在後續的研究中已經發現更多有效的金屬藥物（包括新藥！）。目前正在積極尋找臨床試驗機會

化學-微生物-臨床醫學跨學科研究團隊
Key members of the research team

——攝於香港大學李嘉誠醫學院微生物學系新發傳染病國家重點實驗室前

右起: 微生物學系**陳福和**醫生、**袁碩峰**博士、**袁國勇**教授、化學系**孫紅哲**教授、**王潤銘**博士、**王素玉**小姐
From the right:
Dr Jasper F W CHAN, Dr Shuofeng YUAN, Professor Kwok-Yung YUEN, Professor Hongzhe SUN, Dr Runming WANG and Miss Suyu WANG.

特此鳴謝：香港研究資助局、國家重點研發計畫、基礎研究種子基金對本研究的大力資助以及眾多來自慈善基金、企業和個人的大力捐贈。