Development of bismuth drugs for the treatment of microbial infections

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Summary of the Impact

Prof. Hongzhe Sun’s research has made international impact on the development of inorganic pharmaceutics and providing prospective therapeutic options for major diseases.

- He determined the structure of bismuth drugs in gastric fluid and systematically deciphered their anti-*Helicobacter pylori* mode of mechanism, which has been embodied in the textbook and utilized as the principle of bismuth-based antiulcer drugs development in China.

- He firstly proposed bismuth drug as anti-SARS-CoV agent in 2007 and demonstrate their *in vivo* potency against SARS-CoV-2 during COVID-19 pandemic, which provided the base of phase 3 clinical trial on COVID-19 patients treated with oral bismuth in China.

- He initiated the area of bismuth drug as antimicrobial resistance breaker for the treatment of (multi)drug-resistant bacterial infections.
Underpinning Research

✓ We have >200 publications

✓ >4 patent granted/filed

✓ 1 RIF grants
  2 CRF grants
  3 ITF grants

... UC Berkeley Earl L Muetterties Memorial Lectureship (2018)

WuXi AppTech Life Science & Chemistry Research Award (2016)

Norman & Cecilia Yip endowed Professorship in Bioinorganic Chemistry
Outline of underpinning Research

Deciphering of bismuth drugs in simulated gastric acid and their mode of action against *Helicobacter pylori*

—Since 2002, project leader

Development of bismuth drug as antiviral agents

—Since 2003, project leader,
  cooperator: Prof. Kwok-Yung Yuen, Prof. Jiandong Huang, Prof. Bojian Zheng, Dr. Shuofeng Yuan

Overcoming antimicrobial resistance by bismuth drugs

—Since 2014, project leader
  cooperator: Dr. Richard Yi-Tshun Kao, Dr. Pak-Leung Ho
Bismuth citrate structure was highlighted in the cover of *Metal Ions in Biological System* (2004, 41), and also used in the promotion leaflet of Livzon’s product.

To form protective coating

15.3 Å

(Sun et al, *JACS* 2003, 125, 12408)
Bismuth drugs are effective against SARS-CoV-2 (therapeutic index > 900)

Bismuth suppresses the replication of the virus in animal model

Selectivity index: RBC = 975 in cell infection model

RBC inhibits viral helicase activity and suppresses replication of SARS-CoV-2 in vitro

Target zinc-finger domain of viral helicase

\[ IC_{50} = 0.70 \, \mu M \]

RBC lowers viral loading in both lung and nasal turbinate in hamster infection model

\( \text{Viral loading} \quad >10x \)

\( \approx \text{Remdesivir} \)

(DMSO, Remdesivir, RBC)

(Yuan SF, Wang RM, Chan JFW, ... Yuen KY, Sun H, Nature Microbiol 2020, 5, 1439)
New approach to fight against infection by superbugs: metallodrugs

- Bismuth drugs are selectively toxic to microbes based on metallome studies.
- Bismuth drug inactivate key resistant determinant NDM-1 in superbugs.

‘Kill two birds with one stone’ (一石二鸟)

CBS restore β-lactam antibiotics against NDM-1+ superbugs

In vivo effectiveness

Sun, Wang, Li, Kao, Zhang, US patent: 10,201,518 B2
Partial work was selected in the *Inorganic Chemistry* textbook (Armstrong et al, Oxford University Press, 2014)


Rehder D. “*Bioinorganic Chemistry*”, Oxford University Press, 2014, p42
Impacts Achieved

>37k accesses
>50 medium reported

Local Top Ten innovation and technology news in 2020 (Hong Kong)

- >37k accesses
- >50 medium reported

Related patent filed providing scientific basis for the phase III/IV clinical trial on COVID-19 patients treated with oral bismuth drugs (ChiCTR2000030398 and NCT04811339)
Acknowledgement

- Past and present members of the group, collaborations
- RGC and ITF
- Livzon Pharmaceutical Group
- Norman & Cecilia Yip Foundation