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Citation	The 12th International Symposium on Applied Bioinorganic Chemistry (ISABC12), Guangzhou, China, 3-6 December 2013.
Issued Date	2013
URL	http://hdl.handle.net/10722/203962
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Selective binding of Hpnl towards with Ni(II) and Bi(III)

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Histidine-rich protein Hpn and histidine- and glutamine-rich protein Hpn-like (Hpnl) in *Helicobacter pylori* have been corroborated to be crucial to nickel homeostasis.[1-3] Nickel supply to hydrogenases and ureases might be disrupted owing to the interaction of metallodrugs, such as bismuth antiulcer drugs, with Hpnl, which may subsequently disturb the functions of the essential metalloenzymes in *H. pylori*.[4]

In this work, fluorescent sensors CYHpnl and CYHpnl-1-48 were constructed and their interaction with metals were examined by Fluorescence Resonance Energy Transfer (FRET), utilizing enhanced cyan and yellow fluorescent proteins (eCFP and eYFP) as the FRET donor-acceptor pair.[5] CYHpnl and the C-terminus glutamine truncated CYHpnl (CYHpnl-1-48) exhibited a greater change in the FRET upon both Ni(II)- and Zn(II)-binding. CYHpnl demonstrated a larger increase in fluorescence after its interaction with Bi(III) and Ni(II) in CYHpnl-overexpressed bacteria. However, only Ni(II) induced FRET response in CYHpnl-1-48-overexpressed bacterial cells. Interestingly, interaction between CYHpnl and Bi(III) was unprecedentedly discovered in the presence of excess Bi(III) ions, which showed about 40% increase in fluorescence. Interaction between Bi(III) and CYHpnl was further investigated and the metallodrugs induced CYHpnl oligomerization was revealed. *In vitro* and intracellular FRET analyses on CYHpnl and CYHpnl-1-48 revealed a highly selective interaction of Hpnl towards Ni(II) among other metals, whereas the glutamine-rich C-terminus might affect the metal-binding properties of Hpnl, for instance the interaction with Bi(III). Selectivity towards Ni(II) elucidated the important role of Hpnl in nickel homeostasis[1] and interaction with Bi(III) implied that Bi(III) interacts with Hpnl in *H. pylori.*

This work was supported by the General Research Fund, the NSFC/RGC Joint Research Scheme of the Research Grants Council of Hong Kong (7049/09P and N_HKU75209, 7046/12P), and the University of Hong Kong (for an eSRT on Integrative Biology).

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