## 2.18 Exploring Metal-Derived Therapeutics For Combating COPD Exacerbations

Megan O'Shaughnessy[1], Laura Diez[1], Orla Howe[2], Orla Sheils[1,3], Anne-Marie Baird[1]

[1.] Trinity College Dublin

[2.] Technological University Dublin-City Campus

[3.] St. James's Hospital

With rising antimicrobial resistance challenging conventional antibiotic use, metal-derived drugs are potential alternatives, with their alternative and multi-modal mechanism of action. In this study, the antibacterial and anti-biofilm activity profiles of $\{[Cu(3,6,9\text{-tdda})(phen)_2]\cdot 3H_2O\cdot EtOH\}_n$ (Cu-tdda-phen), $\{[Mn(3,6,9\text{-tdda})(phen)_2]\cdot 3H_2O\cdot EtOH\}_n$ (Mn-tdda-phen) and $[Ag_2(3,6,9\text{-tdda})(phen)_4]\cdot EtOH$ (Ag-tdda-phen) (3,6,9-tdda = 3,6,9-trioxaundecanedioic acid; phen = 1,10-phenanthroline) was assessed against clinical *Haemophilus influenzae, Streptococcus pneumoniae* and *Pseudomonas aeruginosa* isolates from COPD patients. The metal-tdda-phen complexes demonstrated heightened activity in comparison to established antibiotics against clinical isolates in relation to planktonic growth, biofilm formation and established biofilms, with reductions in biofilm exopolysaccharide and extracellular DNA (eDNA), therefore suggesting these as targets. Metal-tdda-phen complexes were selectively toxic towards lung cancer (SKMES-1) and COPD (HBEC4 cells exposed to cigarette smoke extract) cell lines in comparison to normal cell line (HBEC4). The therapeutic potency of the metal-tdda-phen complexes was further assessed in an *in vivo* model using *Galleria mellonella* larvae challenged with the *P. aeruginosa* clinical isolates. The metal complexes were well tolerated by the *G. mellonella* and affected the host's immune response by stimulating immune cells (hemocytes) and enhancing the expression of immune-related peptides, transferrin (iron-binding protein) and IMPI (inducible metalloproteinase inhibitor). Therefore, this work highlights the antibacterial capabilities of metal-derived drugs both *in vitro* and in a pre-clinical *in vivo* model.

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