Investigation of gold drug candidates as immunomodulating agents for the treatment of malignant pleural mesothelioma

PI: Dr. Maria Babak,
Assistant Professor, Department of Chemistry,
City University of Hong Kong

Aims: The research institution aims to develop novel chemotherapeutic agents based on a gold metal and assess their capacity to trigger immune response in malignant pleural mesothelioma (MPM) tumors.

Background: MPM is an extremely rare cancer characterized by poor survival rates. MPM generally exhibits limited responsiveness to immunotherapeutic interventions.

Methodology:

Cell Study

1. MTT colorimetric test was applied to determine percentage of cell death.
2. Flow cytometry test was applied to determine 1) phagocytosis, 2) annexin V/PI staining, 3) calreticulin (CRT) staining and 4) HMGB1 staining.
3. Confocal microscopy was applied to determine CRT, HMGB1 and reactive oxygen species (ROS) detections.
4. Western blotting was applied to detect protein expression of HMGB1, Bip and C/EBP homologous protein (CHOP).
5. Luminescence assay was applied to determine extracellular ATP content.

Mice Study

1. MPM bearing mice were either injected with gold complexes or control vehicle to determine 1) liver and kidney toxicity, 2) tumor study and 3) organ distribution study.
2. Tumor study included 1) RNA sequencing and 2) histopathological staining of IBA1 and CRT.

Impact: Results of the project supported a superior role of the novel gold complexes compared to current standard-of-care treatment in term of higher efficacy and lower toxicity. The research institution is going to submit patent application in the name of PI and under CityU.

Result and Conclusion:

1. Successfully synthesized and characterized 35 cyclometalated gold (III) complexes containing dithiocarbamate ligands, with 25 of these complexes being previously unreported.
2. The ability to induce phagocytosis against MPM cells was strongly dependent on the cyclometalated scaffold and the overall lipophilicity of the complexes.
3. Necrosis was the main cell death mechanism indicated by both cell and mice studies and the leading gold complex was 2G, which demonstrated long lasting immune response (7 months) in mice study.

In conclusion, novel complexes demonstrated high efficacy across cell lines derived from various types of MPM and seven complexes exhibited higher efficacy against MPM tumor compared to standard-of-care cisplatin-premetrexed regimen. Meanwhile, liver and kidney toxicity was not observed in experimental mice.