78. Gold(III) Metformin and Phenformin Prodrugs

(Northwestern University)

Asset Overview

Product Type	Others
Disease Area	Oncology
Indication	Tiple-negative breast cancer (TNBC)
Current Stage	Lead Optimization
Target	Energy production in cancer cells
MoA	Metformin and phenformin target energy production in cancer cells by inhibiting Complex I of the mitochondrial respiratory chain, activating 5′-adenosine monophosphate-activated protein kinase (AMPK) and lowering body insulin levels by altering insulin/insulin-like growth factor-I (I/IGF) pathway.
Brief Description	• Northwestern inventors designed a new series of Au^{III} complexes, featuring both energy-disrupting metformin or phenformin ligands and multitarget Au^{III} species. • In vitro evidence demonstrated that metabolic changes caused by 3met initiated attempts of cancer cells to protect themselves by metabolic reprogramming, UPR and mitophagy. These defense processes were successfully prevented by shutdown of mitochondrial respiration and impairment of autophagic flux, leading to the inhibition of protein degradation and apoptotic cell death. • High degree of selectivity of the novel complexes to cancer cells over healthy cells were observed. Lead drug candidate 3met halted the growth of aggressive breast tumors in a mammary fat pad breast cancer model and activated the immune response, indicating the potential benefits of this drug candidate for TNBC patients with high risk of metastasis and relapse.
Intellectual Property	WO2021194420A1
Publication	Interfering with Metabolic Profile of Triple-Negative Breast Cancers Using Rationally Designed Metformin Prodrugs. Angew Chem Int Ed Engl. (2021)
Inventors	Irina Balyasnikova, Wee Han Ang, Maria Babak

Highlights

- A first in class therapeutic of Au(III)-based metformin complexes
- Synergistic action with metformin
- Anticancer activity of metformin at nanomolar concentration range
- Anticancer activity of metformin prodrug increased more than 6500X in comparison with uncoordinated metformin

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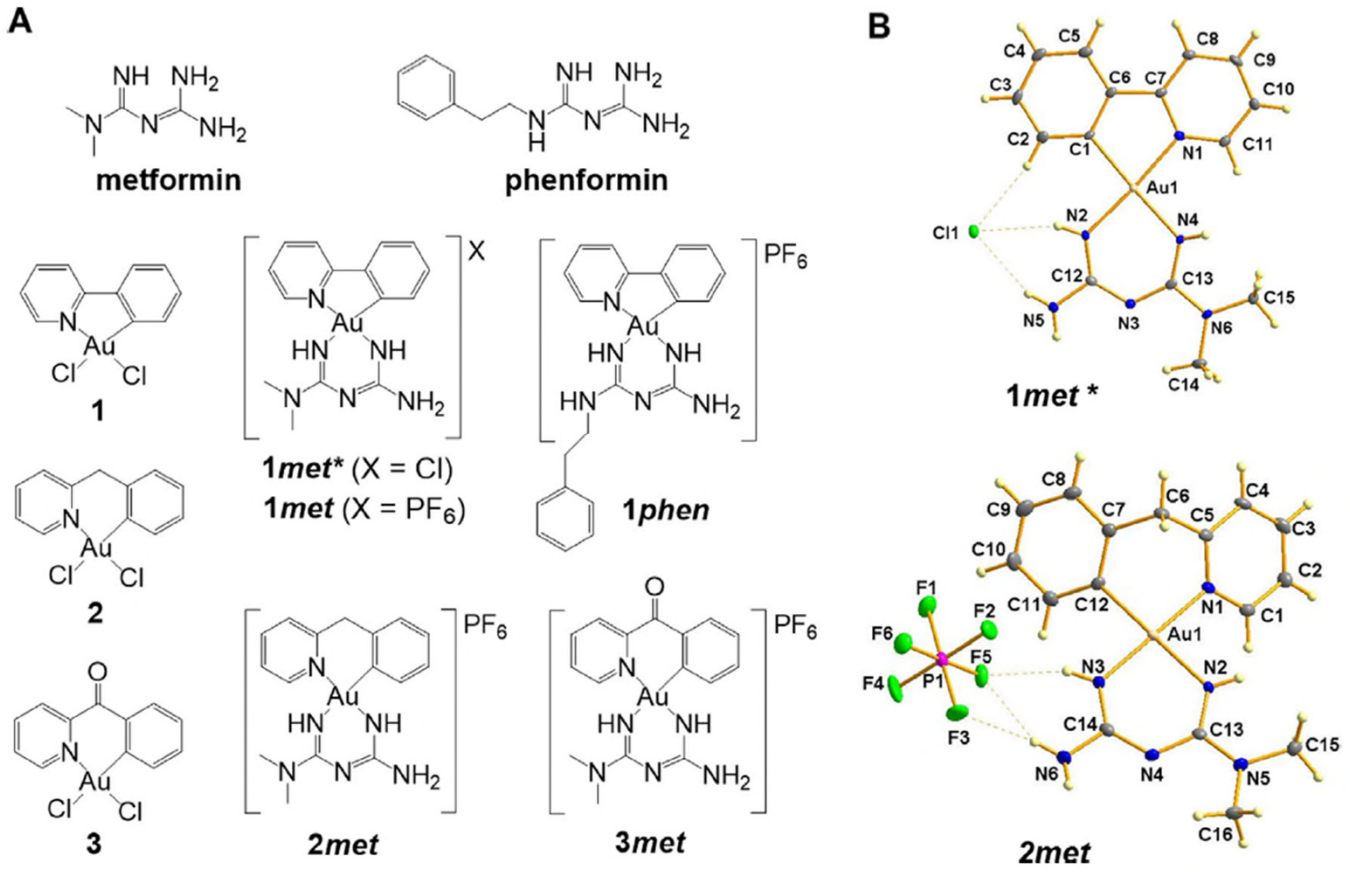
Key Data

Cyclometalated Au^{III} complexs of interest



A) Chemical structures of metformin, phenformin and Au^{III} complexes used in this study.
B) ORTEP representation of 1met and 2met; non-H atoms are represented as thermal ellipsoids at 50% probability. Solvent molecules were omitted for clarity.

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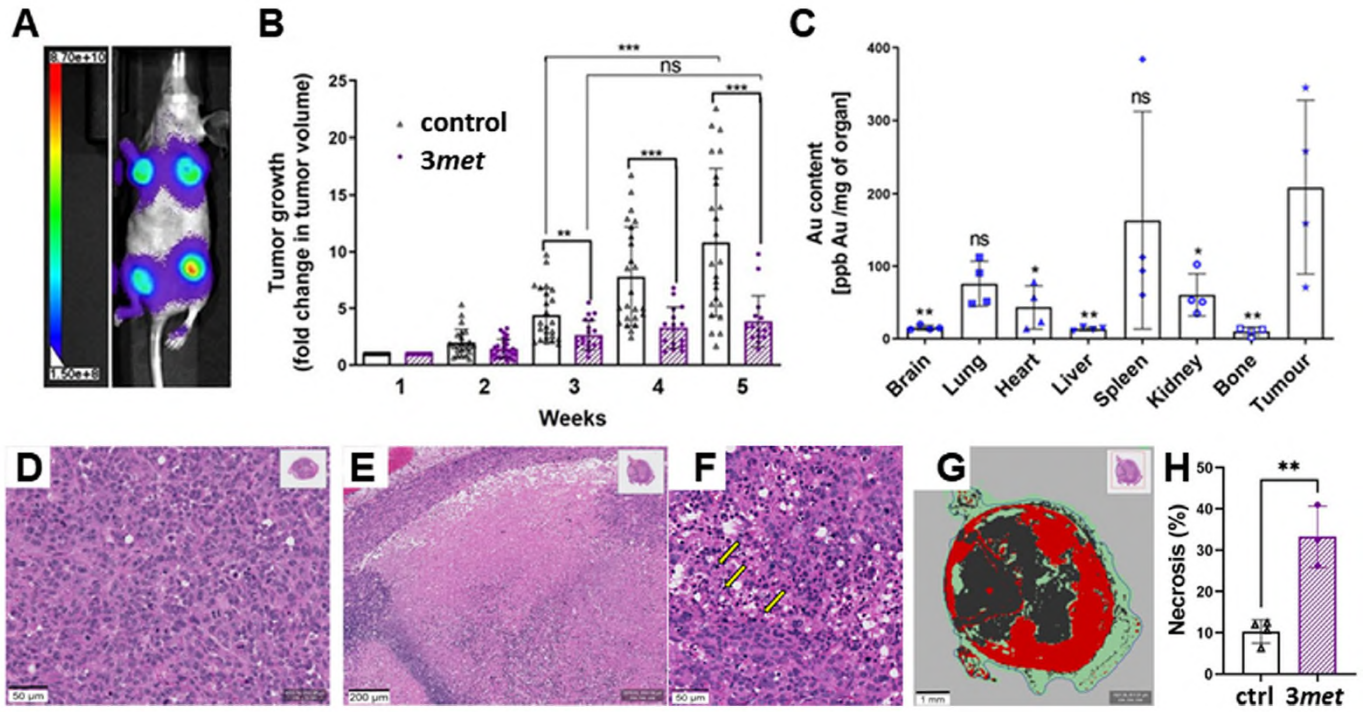
Effects of 3met on aggressive breast tumor growth in vivo



A) Bioluminescent live image of xenografted luciferase-expressing MDA-MB231 cells orthotopically implanted into two mammary fat pads near pectoral and inguinal nipples. Post-implantation week 5.
B) Growth of MDA MB-231 tumors from week 1 (before treatment) presented as a fold change in tumor volume. Starting from week 2 tumors became palpable and their volume was measured by calliper weekly. Mice (n=7) were treated with 3met at 15 mg /kg^{-1} or respective vehicle (DMSO in sterile saline) via i.p. route every other day on weeks 3, 4 and 5.
C) Au accumulation in mouse organs obtained from 3met-treated mice at the endpoint and quantified by ICP-MS.
D) Representative H&E-stained tumor tissue of a vehicle-treated mouse, demonstrating grade 3 breast carcinoma with high rate of mitosis.
E, F) Representative H&E-stained tumor tissues of a 3met-treated mouse, demonstrating (E) wide area of necrosis and strong lymphohistiocytic tumor infiltration and (F) lymphohistiocytic infiltration (depicted with yellow arrows).
G) Algorithm for quantification of tumor tissues using QuPath software (random trees pixel classifier, red color is tumor, black is necrosis and green is stroma).
H) Quantification of necrosis in H&E-stained tumor tissues of vehicle- and 3met-treated mice using algorithm presented in (F). Statistical analysis was performed by one-way ANOVA test with (B) Bonferroni or (C) Dunnett post hoc analysis (vs. tumor) or (B, H) unpaired T test using GraphPad Prism 9 software (GraphPad Software Inc., CA) with $p<0.05$ considered as significant (* $p<0.05$, ** $p<0.01$, *** $p<0.001$, ns: not significant).