Titanocene-Gold Derivatives as Chemotherapeutics for Renal Cancer

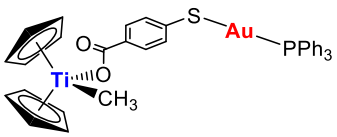
40-80% of cancer patients receive Cisplatin and corresponding derivatives, alone or in combination as the treatment of choice, despite the compounds' high toxicity and side effect profile, acquired or intrinsic resistance, and limited spectrum activity. Because of this, there has been continued interest in exploring other metal and heterometallic complexes, to develop improved anticancer therapeutics that preserve the efficacy of these complexes while moderating their limitations.

Gold complexes have shown promise in cancer chemotherapy, with several compounds having overcome cisplatin resistance of specific cancer cells, furthering their appeal. Early-transition metal complexes, particularly titanocene-based complexes, are another class of compounds being explored for cancer chemotherapy. These compounds have shown significant renal tumor growth inhibition.

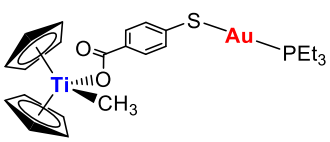
The increased interest in research around metallodrugs is especially promising for renal cancer, which has limited chemotherapeutic options. Conventional or clear cell renal cancers do not typically respond well to traditional chemotherapeutics. Recently novel metallodrugs have been successfully explored as potential cancer chemotherapeutics, including recent clinical trials with gold and ruthenium derivatives.

Technology

Dr. Joe W. Ramos, professor and deputy director at the University of Hawai'i Cancer Center, and his colleague, Dr. Maria Contel, professor at the City University of New York, have developed novel heterometallic, titanocene-gold, compounds that have demonstrated impressive *in vitro* and *in vivo* activity against renal cancer (human Caki-1 xenografts in mice) while displaying a mode of action different from that of cisplatin. The hypothesis was that combining two metals with distinct biological activities in a single molecule would improve the pharmacological profile of the generated compound.



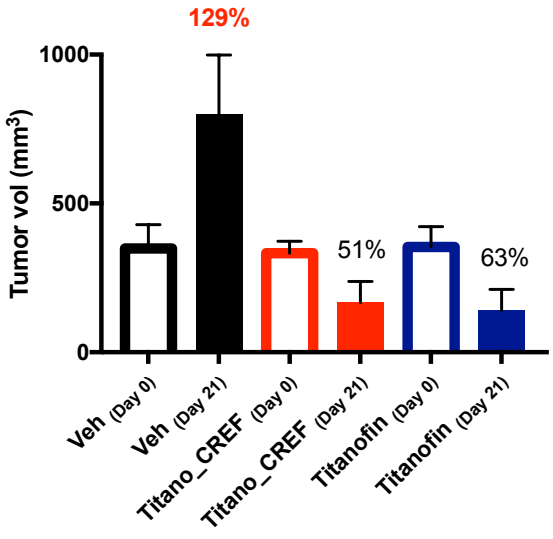
Titano-CREF



Titanofin

Lead bimetallic titanocene-gold complexes developed and patented.

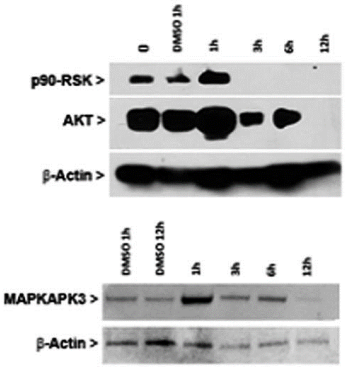
Two lead bimetallic compounds **Titano-CREF** and **Titanofin**, have both resulted in very effective tumor reduction with minimal to no side effects (in mice with subcutaneous Caki-1, renal, tumors) compared to control mice. Titano-CREF (elimination half-life ($t_{1/2}$) = 32.38 h) was evaluated in two different trials (3 mg/kg every 48 hours for 28 days and 5 mg/kg every 72 hours for 21 days) with impressive results for tumor reduction (67 and 51% respectively). Titanofin (elimination half-life ($t_{1/2}$) = 47.16 h) was extremely efficient as well with a tumor reduction of 63% (10 mg/kg every 72 hours for 21 days). These compounds performed much better than previously described titanium derivatives which only exerted tumor growth inhibition.



Titano-CREF and Titanofin were administered via i.p. injection to NOD.CB17-Prkdc SCID/J mice bearing subcutaneous Caki-1 tumors at a dose of 5 mg/kg (Titano-CREF) or 10 mg/kg (Titanofin) every 72 hours over 21 days.

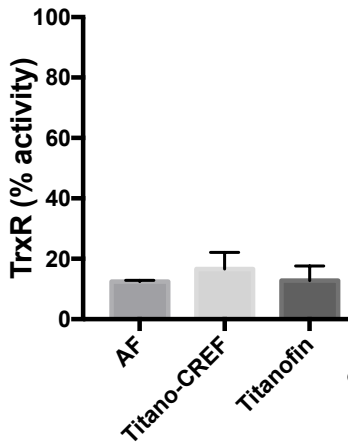
Preliminary mechanistic studies indicate that these compounds exert a mode of action different to that of cisplatin and more correlated to the mode of action displayed by other gold(I) derivatives containing lipophilic ligands such as phosphanes and N-heterocyclic carbenes. The compounds did not show interaction with plasmid DNA.

It was demonstrated that Titano-CREF acts on the p90-RSK / AKT / MAPKAPK3 pathway involved in cell growth, cell motility, cell survival and cell proliferation.



Decreased expression of p90-RSK, AKT, and MAPKAPK-3 in Caki-1 cells in response to Titano-CREF. Cells were incubated with either Titano-CREF or 0.1% DMSO for the indicated times, followed by cell lysis and Western blot analysis. Blots were probed with anti-β-actin antibody as a control for protein loading.

More recent studies have shown that the compounds display relevant inhibition of migration and invasion, while also inhibiting molecular pathways associated with these processes. The molecular targets most inhibited are IL-6 and MMP-9, which are involved in tumor metastasis and angiogenesis, and to a much lesser degree the angiogenic factor VEGF. They also inhibit the mitochondrial protein TrxR that is overexpressed in cancer cells and is critical in apoptosis evasion.



Decreased activity of Thioredoxin reductase in Caki-1 cells in response to Auranofin, Titano-CREF and Titanofin Compounds (IC_{50} concentrations) after 24 h of treatment. Percent of control is shown.

The level of inhibition is comparable to that of Auranofin (Ridaura®) an anti-arthritic and anti-rheumatoid drug known to be an excellent TrRx inhibitor. In addition, both Titano-CREF and Titanofin inhibit cyclooxygenase-2.

The properties of the compounds are promising for a variety of cancers, but are extremely relevant for certain types of kidney cancer that are known to be highly metastatic.

Additional studies are ongoing to further elucidate the MOA, optimize dose, and further analyze toxicity.

Applications:

- Treatment of renal cancer
- Second generation compounds may be useful in the treatment of:
  - Prostate cancer
  - Ovarian cancer

Advantages:

- Showed a 50-70% tumor reduction in human renal cancer Caki-1 xenografts
- Mode of action different than that of cisplatin and related compounds
- Strong anti-migratory and anti-invasiveness properties
- Inhibition of biomolecules associated with tumor migration, metastasis and resistance to cisplatin *in vitro* (MMP-9, IL-6, TrRx and to a lesser extent VEGF)
- Cyclooxygenase-2 inhibitors
- Relevant for certain types of kidney cancers that have high metastatic risk
- Promising safety profile - *in vivo* studies show very little toxicity or side effects

Additional Information:

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Publication(s): Fernandez-Gallardo et al, Chemical Science 2015
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