# Supporting Information

## Nanomedicine-Assisted Combination Therapy of NSCLC: New Platinum-Based Anticancer Drug Synergizes the Therapeutic Efficacy of Ganetespib

Jyothi Kallu,[1] Tuhina Banerjee,[1] Shoukath Sulthana,[1] Saloni Darji,[1] Ryan Higginbotham,[1] Christina Fletcher,[1] Nikolay N. Gerasimchuk,[2] and Santimukul Santra[1,*]

1. Department of Chemistry, Pittsburg State University, 1701 S. Broadway Street, Pittsburg, Kansas 66762, United States.
2. Department of Chemistry, Missouri State University, 901 S. National Ave, Springfield, Missouri 65897, United States.

*Corresponding author: Santimukul Santra, Ph.D., Associate Professor. Department of Chemistry, Pittsburg State University, 1701 S. Broadway Street, Pittsburg, Kansas 66762, United States. Phone: 620-235-4861, Fax: 620-235-4003. Email: ssantra@pittstate.edu

## 1. Zeta potential of MNPs 1:

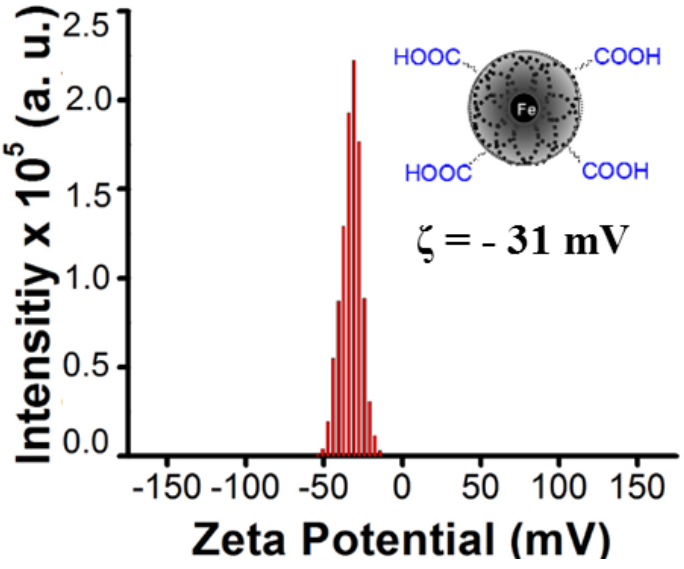
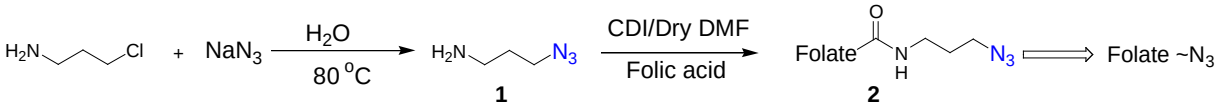



**Figure S1**: Zeta potential of MNP-COOH, **1**. Negative zeta potential indicates presents of carboxyl groups on the surface of MNPs.

## 2. Preparation of folate~$N_3$ using carbodiimide chemistry.

**Reference:** 1. Santra et. al., Mol Pharmaceutics. 2017; 14: 875–884.
2. Santra et. al., Small. 2009; 5: 1862-1868.




**Scheme S1.** Synthesis of azide functionalized folate (**2**) from chloropropyl amine

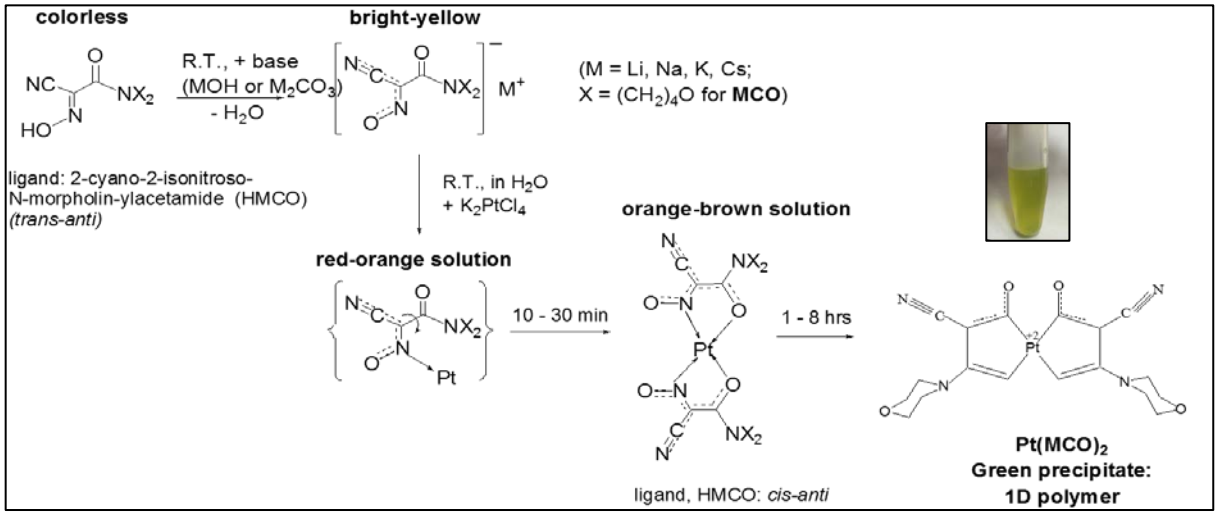
**Aminopropylazide synthesis:** Chloropropyl amine (7.0 g, 75.26 mmol) and sodium azide (14.23 g, 225.81 mmol) were added in a flask containing 40 mL of water and the reaction was performed at 80 ºC for 20 h. 2.1 g of KOH were added after concentrating the reaction mixture and the resulting solution was extracted from diethyl ether. After drying the mixture, it was purified using column chromatography. Yield: 5.0 g (65%). $^1$H NMR (300 MHz, $CDCl_3$, d ppm): 1.23 (bs, 2H), 1.79 (m, 2H), 2.85 (t, 2H), 3.41 (t, 2H). FT-IR (CHCl3): 3310, 2939, 2091, 1659, 1429, 1369, 1258, 1239, 1069, 1019, 821, 759 $cm^{-1}$.

**Azide-functionalized folic acid synthesis:** Folic acid (0.06 g, 0.15 mM) in DMF (2.5 mL), EDC (0.015 g, 0.15 mM) and NHS (0.009 g, 0.15 mM) in 500 µL MES buffer (pH =6.0) were added and the reaction mixture was incubated on a table mixer for 3 min. To this, ethylenediamine (0.008 g, 0.15 mM) in 0.3 mL of DMF was added drop-wise and the reaction was continued for 3 h at room temperature. The resulting product solution was then centrifuged and dissolved in 1 mL of DMF. Yield: 0.05 g (86%). The presence of a band at 2097 $cm^{-1}$ in the IR spectrum and a UV absorbance shoulder at 354 nm confirmed the formation of azide-functionalized folic acid. $^1$H NMR (300 MHz, DMSO-$d_6$): 1.59 (m, 2H), 1.71 (m, 2H), 1.87 (m, 2H), 2.17 (t, 2H), 2.81 (t, 2H), 4.20 (q, 1H), 4.19 (d, 2H), 6.59 (d, 2H), 7.60 (d, 2H), 8.61 (s, 1H). FT-IR (Neat): 3019, 2101, 1699, 1599, 1489, 1369, 1289, 1250, 1182, 1119, 1059, 951 $cm^{-1}$.

## 3. Synthesis and physical characterization of $Pt(MCO)_2$:

**References:**


1. Eddings D, et. al., Inorg Chem. 2004; 43: 3894-3909.
2. C. Cheadle, et al. *Dalton Transactions*, **2017**, 46 (39), pages 13562-13581.


**Scheme S2:** Synthesis and chemical structure of $Pt(MCO)_2$ drug.

## 4. Monitoring of the reaction progression during synthesis of $Pt(MCO)_2$.

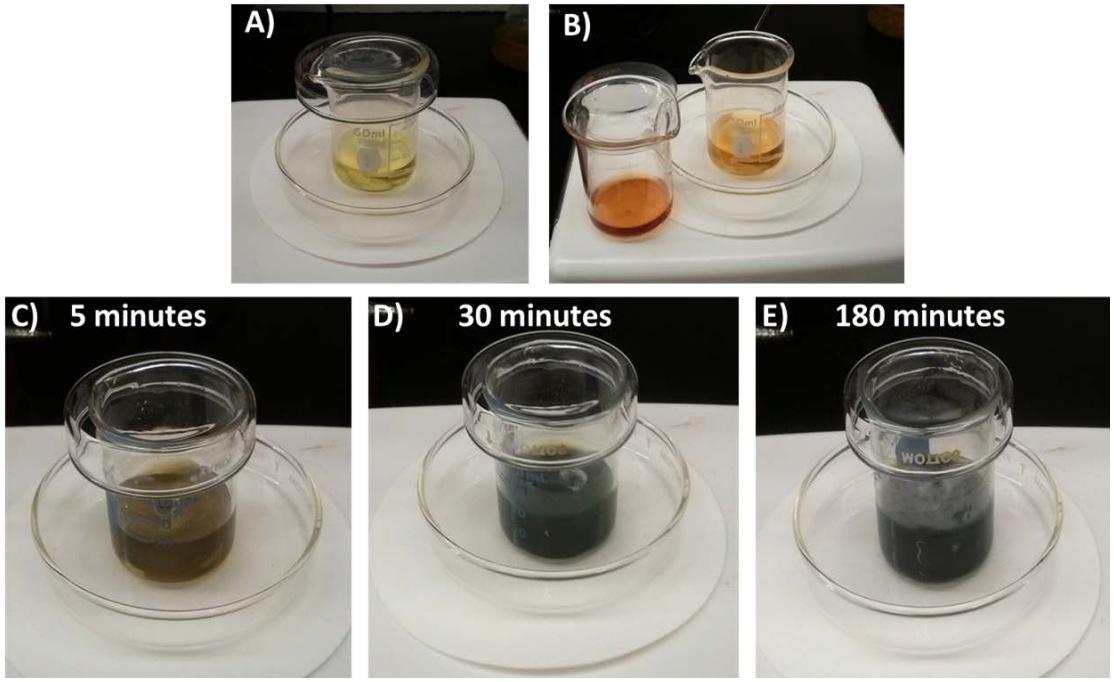



**Figure S2**: **A**) Initial Na(MCO) solution in water. **B**) A drop-wise addition of $K_2PtCl_4$ (left beaker) to the right (A) beaker. **C-E**) A photographic monitoring of the $Pt(MCO)_2$ preparation at ambient conditions and precipitation observed within 3 h. Obtained dark-green polymeric complex is fluorescent both in solid state and solutions. Excitation wavelength at 765 nm (**Figure S3**) and an intense fluorescence was observed in the range of 1000-1200 nm depending on sample's conditions.

## 5. Absorption spectra of $Pt(MCO)_2$:

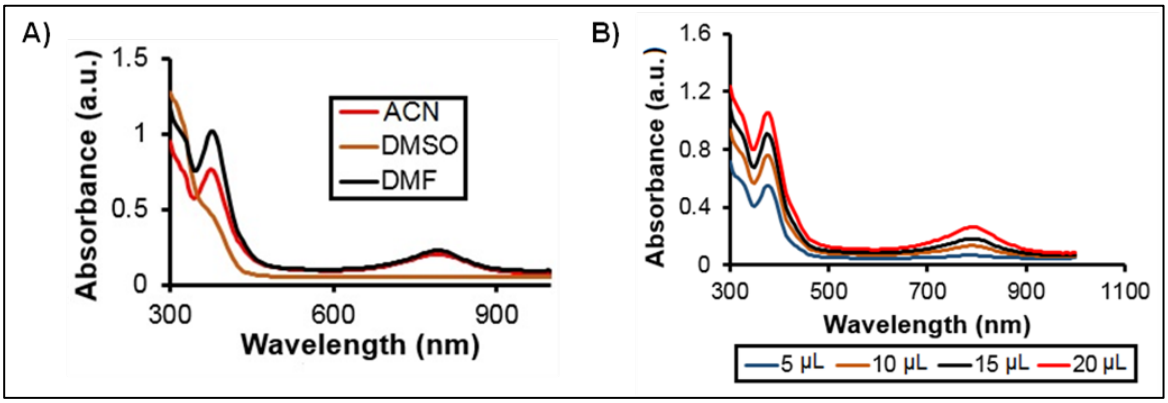



**Figure S3:** Absorbance spectra of $Pt(MCO)_2$-nanodrug in different solvent and in different concentrations (DMF). The instability of $Pt(MCO)_2$-nanodrug in DMSO may have caused for the absence of peak around 800 nm.

## 6. Characterization of functional MNPs upon synthesis:

| MNPs | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Size (nm) | 68±2 | 69±3 | 71±2 | 74±3 | 75±2 |
| Zeta (mV) | -31 | -32 | -22 | -29 | -30 |

**Table S1:** Overall diameter (size) and zeta potential of the synthesized functional MNPs (**1-5, Scheme 1**).

## 7. Time-dependent stability study of functional MNPs in term of size and T2 magnetic relaxation:

| MNPs | 2 | 4 | 5 | Time |
|---|---|---|---|---|
| DLS (nm) | 69±3 | 74±3 | 75±2 | 7 days |
| | 70±2 | 76±4 | 76±1 | 90 days |
| | 74±2 | 78±4 | 79±3 | 180 days |
| T2 (ms) | 130±2 | 133±2 | 142±2 | 7 days |
| | 130±3 | 135±1 | 143±3 | 90 days |
| | 132±3 | 139±3 | 147±2 | 180 days |

**Table S2:** Determination of the stability of the functional MNPs with time. It is expected that if MNPs are unstable there will be substantial change in diameter and the overall T2 MR value of the solution will be changed. Therefore, the long-term stability studies were carried out in term of the collection of size and T2 MR data.

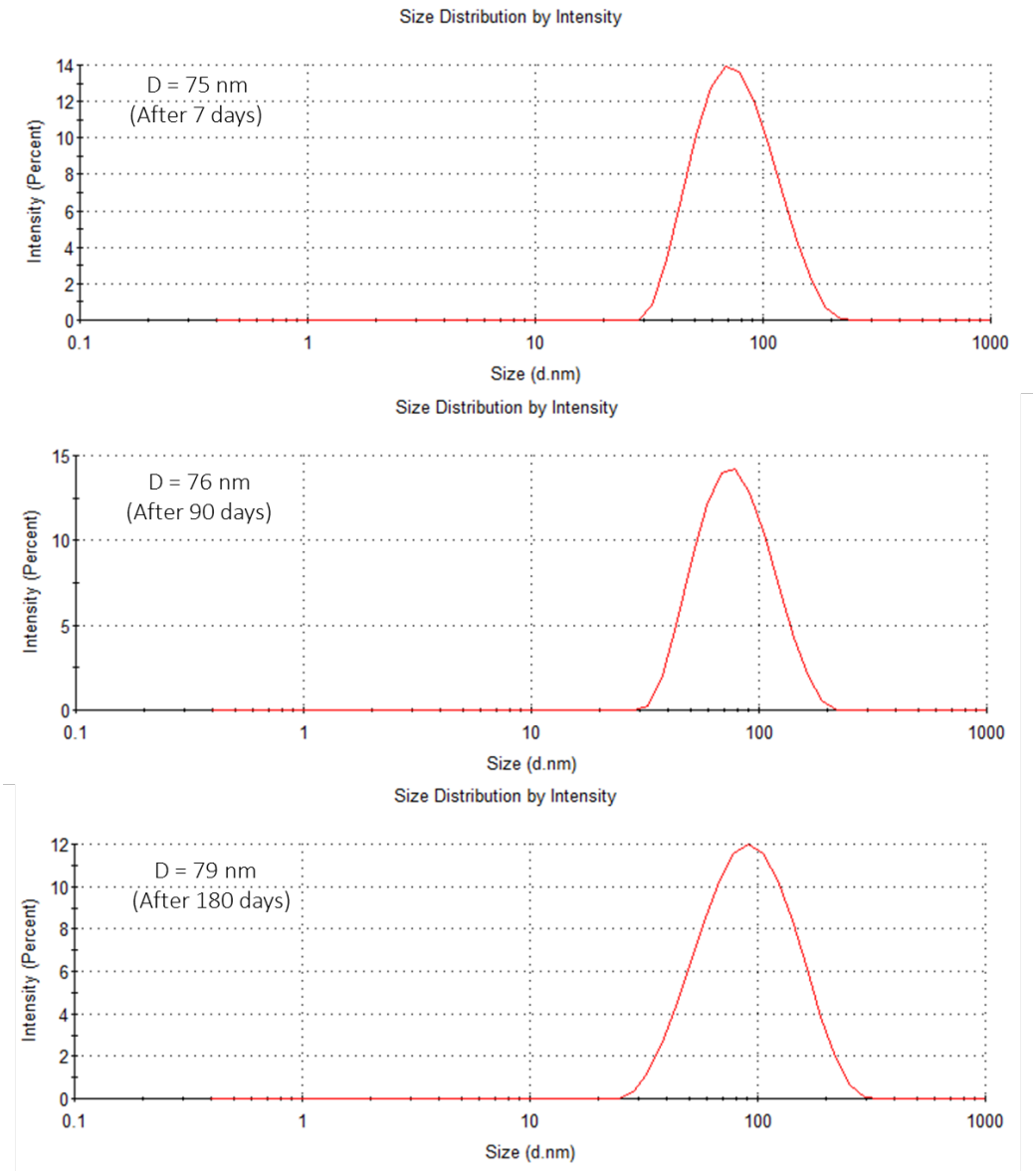



**Figure S4:** Time-dependent size measurement of MNPs (**5b**).