WEST CHINA HOSPITAL
SICHUAN UNIVERSITY

Dual Zn^{2+}/Cu^{2+} Chelation-Engineered Nanotherapeutics for DNA-Mitochondrial Disruption in Triple-Negative Breast Cancer

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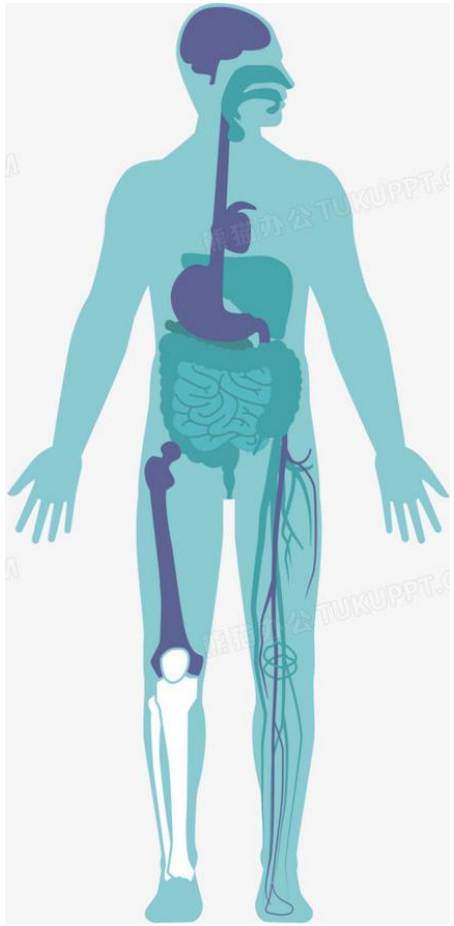
CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

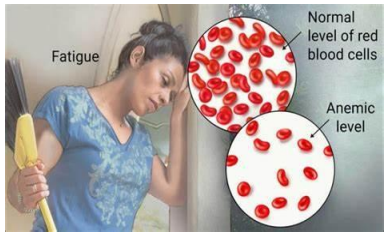
Metal Homeostasis & Pathological Implications



Trace elements
(< 0.01% body weight):

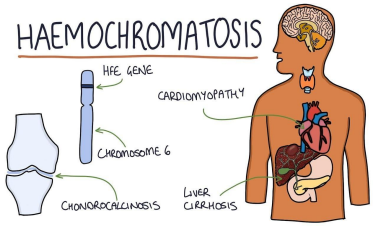
Fe	3-4 g
Zn	2-3 g
Cu	80-150 mg
I	15-20 mg
Se	13-20 mg
Mn	12-20 mg

Fe↓



iron-deficiency anemia

Fe↑

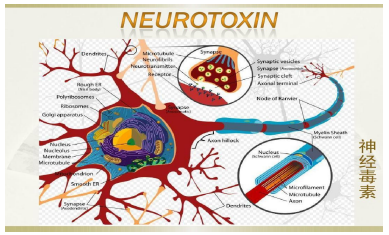


hemochromatosis

Zn↓

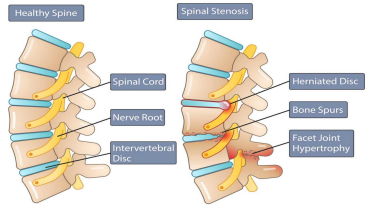
midgetism

Zn↑



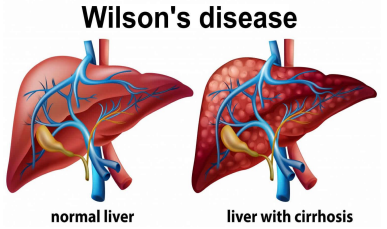
Neurological diseases

Cu↓



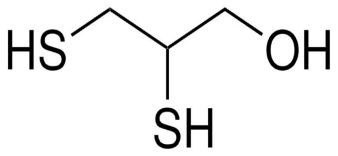
degeneration of posterior cord

Cu↑



Wilson’s Disease

Evolution of Metal Chelation Therapy



dimercaprol (BAL)

The birth of the antidote

1920-1950

Tetrathiomolybdate Inhibits Copper Trafficking Proteins Through Metal Cluster Formation

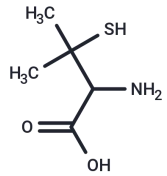
Hamsell M. Alvarez,[1*] Yi Xue,[1*] Chandler D. Robinson,[1] Mónica A. Canalizo-Hernández,[1] Rebecca G. Marvin,[1] Rebekah A. Kelly,[3] Alfonso Mondragón,[2] James E. Penner-Hahn,[3] Thomas V. O'Halloran[1,2†]

Anti-angiogenesis

1990-2020

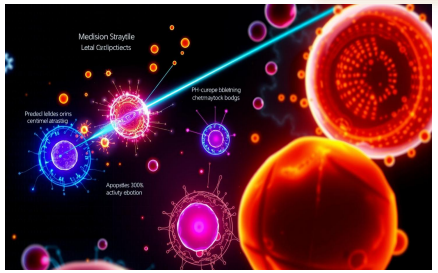
1950-1990

Treatment of Wilson's disease



Penicillamine

2020-now



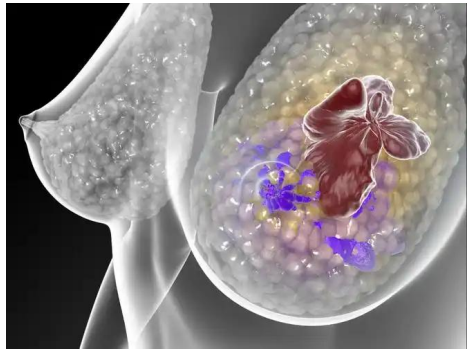
Nano-Chelators

Article | Published: 19 October 2020

Mitochondrial copper depletion suppresses triple-negative breast cancer in mice

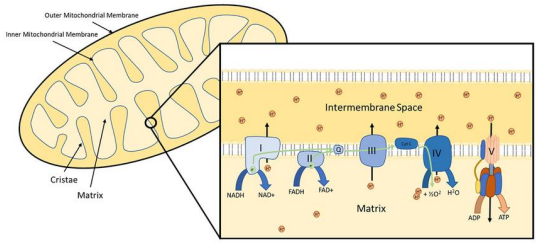
Liyang Cui, Arvin M. Gouw, Edward L. LaGory, Shenghao Guo, Nabeel Attarwala, Yao Tang, Ji Qi, Yun-Sheng Chen, Zhou Gao, Kerriann M. Casey, Arkadiy A. Bazhin, Min Chen, Leeann Hu, Jinghang Xie, Mingxi Fang, Cissy Zhang, Qihua Zhu, Zhiyuan Wang, Amato J. Giaccia, Sanjiv Sam Gambhir, Weiping Zhu, Dean W. Felsher, Mark D. Pegram, Elena A. Goun, ... Jianghong Rao ✉ + Show authors

Metabolic Vulnerabilities of Triple-Negative Breast Cancer



Triple-Negative Breast Cancer (TNBC, ER$^-$/PR$^-$/HER2$^-$)

- Ineffective to endocrine or HER2-targeted therapies
- Tumor heterogeneity
- Metastasis and chemoresistance



Metabolic Vulnerabilities

- Metabolic preference for OXPHOS
- Upregulation in mitochondrial copper enzyme (e.g., COX, SOD1)

Copper depletion represents a promising therapeutic strategy

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-27559-z OPEN

Check for updates

Copper depletion modulates mitochondrial oxidative phosphorylation to impair triple negative breast cancer metastasis

Divya Ramchandani[1], Mirela Berisa[2], Diamile A. Tavarez[1], Zhuoning Li[3], Matthew Miele[3], Yang Bai[1,4], Sharrell B. Lee[1], Yi Ban[1], Noah Dephoure[5], Ronald C. Hendrickson[3], Suzanne M. Cloonan[6,7], Dingcheng Gao[1,8,9], Justin R. Cross[2], Linda T. Vahdat[10]✉ & Vivek Mittal[1,8,9]✉

ICH GCP > US Clinical Trials Registry > Clinical Trial NCT06134375

A Study of Tetrathiomolybdate (TM) Plus Capecitabine

May 20, 2025 updated by: Linda.T.Vahdat, Dartmouth-Hitchcock Medical Center

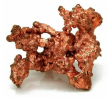
Novel Targeting of the Microenvironment to Decrease Metastatic Recurrence of High-Risk TNBC: A Randomized Phase II Study of Tetrathiomolybdate (TM) Plus Capecitabine in Patients With Breast Cancer at High Risk of Recurrence

There are two parts to this study. It is a phase 1b followed by a randomized phase 2 study to assess whether adding 3 years of adjuvant tetrathiomolybdate (TM) to standard 6 months treatment of adjuvant capecitabine and pembrolizumab in high risk for relapse triple negative breast cancer.

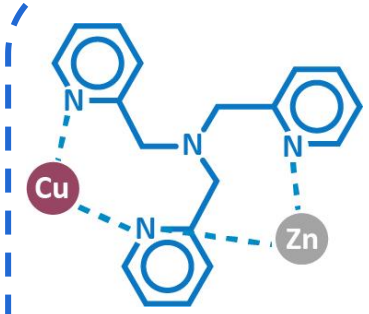
In the phase 1b part of the study, TM is added to adjuvant capecitabine and pembrolizumab in high risk for relapse triple negative breast cancer (RCB 2, 3, risk for relapse >60% at 5 years) after completion of neoadjuvant chemo-immunotherapy and surgery to establish the safety of the combination. This will be followed by a randomized phase 2 clinical trial of adjuvant TM and capecitabine vs capecitabine alone.

If pembrolizumab was administered in the neoadjuvant setting, it may be continued in the adjuvant setting per investigator discretion.

TPA: Dual Cu^{2+}/Zn^{2+} Chelator

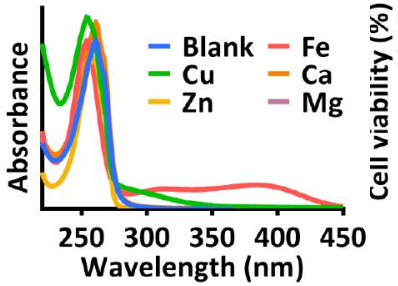
 Copper Ions (Cu^{2+})	 Zinc Ions (Zn^{2+})
Participates in mitochondrial energy metabolism	Stabilizes DNA, zinc finger protein-mediated gene regulation
Metabolic Impact	DNA Stability

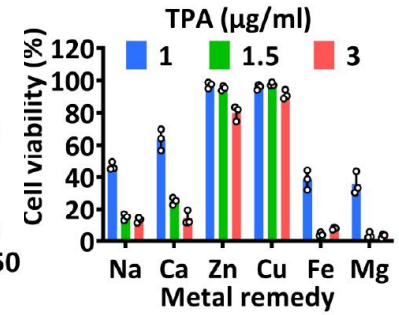
Ligand	Target ion	Cu^{2+} log K	Zn^{2+} log K	Solubility
TM	Cu^{2+}	15	＜1	hydrophilic
DP	Cu^{2+} ＞ Zn^{2+}	16.5	10.2	hydrophilic
TPA	Cu^{2+} ＞ Zn^{2+}	20.3	10.5	lipophilic
TPEN	Zn^{2+}＞ Cu^{2+}	20.4	15.4	lipophilic

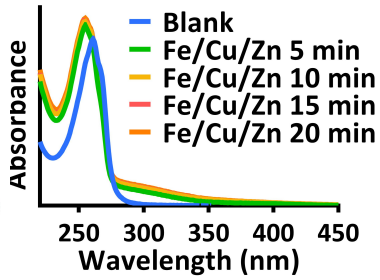


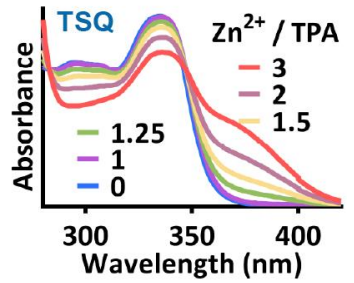
tris(2-pyridylmethyl)amine

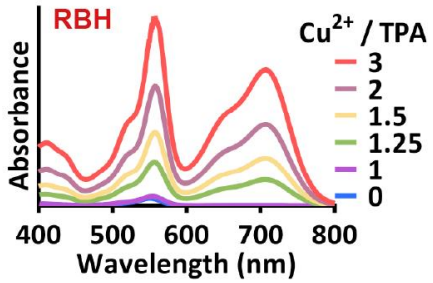
TPA









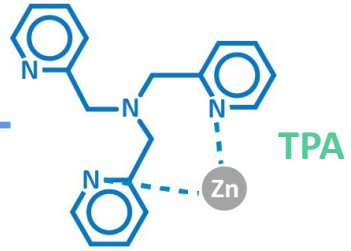


Chelating capacity: Cu^{2+} > Zn^{2+}

Cu^{2+}/ Zn^{2+} Coordination = 1 : 1

Zn^{2+} Chelation Impaired DNA Repair

Zn^{2+} chelation → DNA repair inhibition

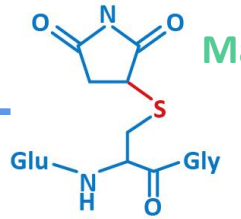


TPA

Closing Chromatin

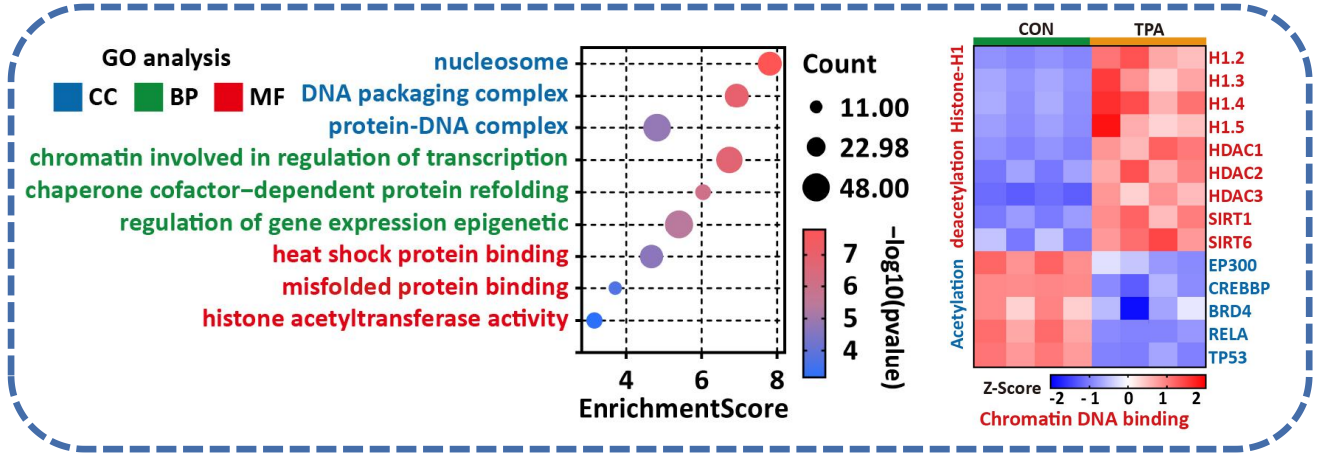
DNA damage

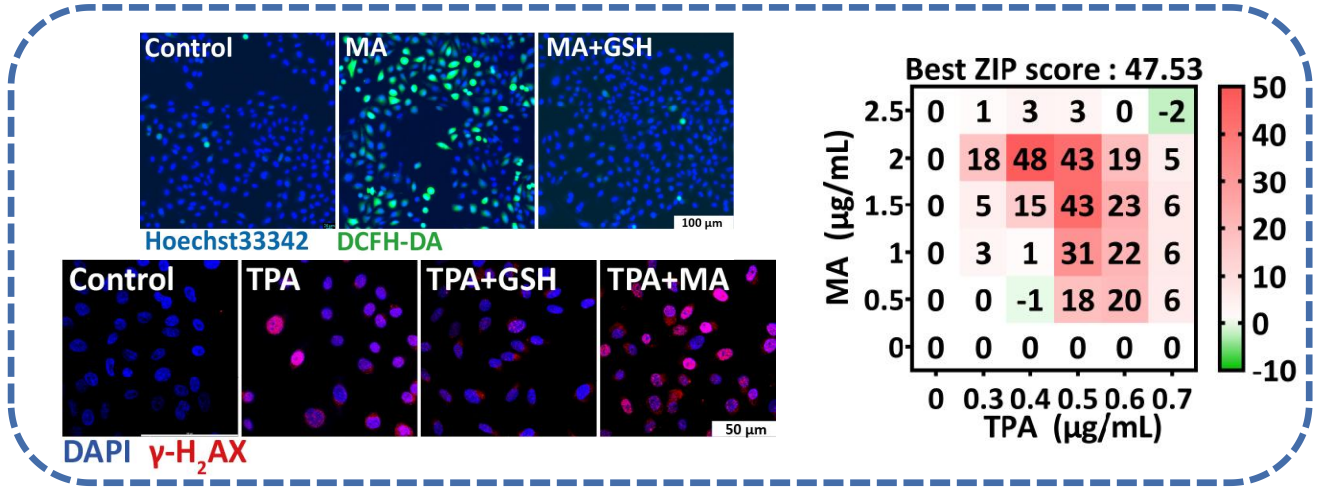
GSH comsuption



Maleimide (MA)

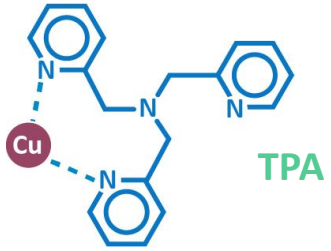
ROS sensitive





Cu^{2+} Depletion Amplifies Mitochondrial Dysfunction

Cu^{2+} chelation → mitochondrial respiration inhibition

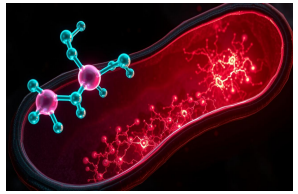


TPA

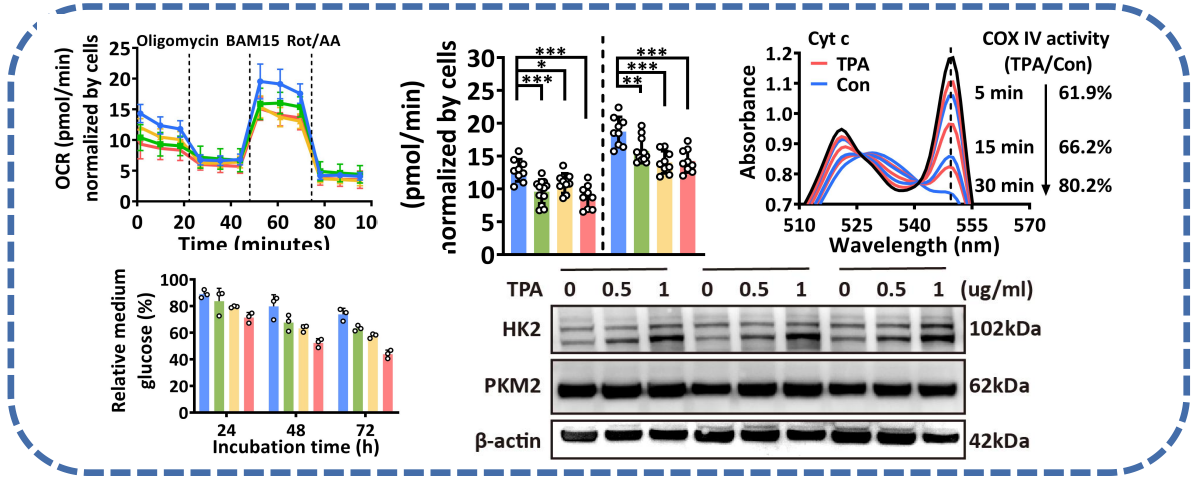
Relieve hypoxia

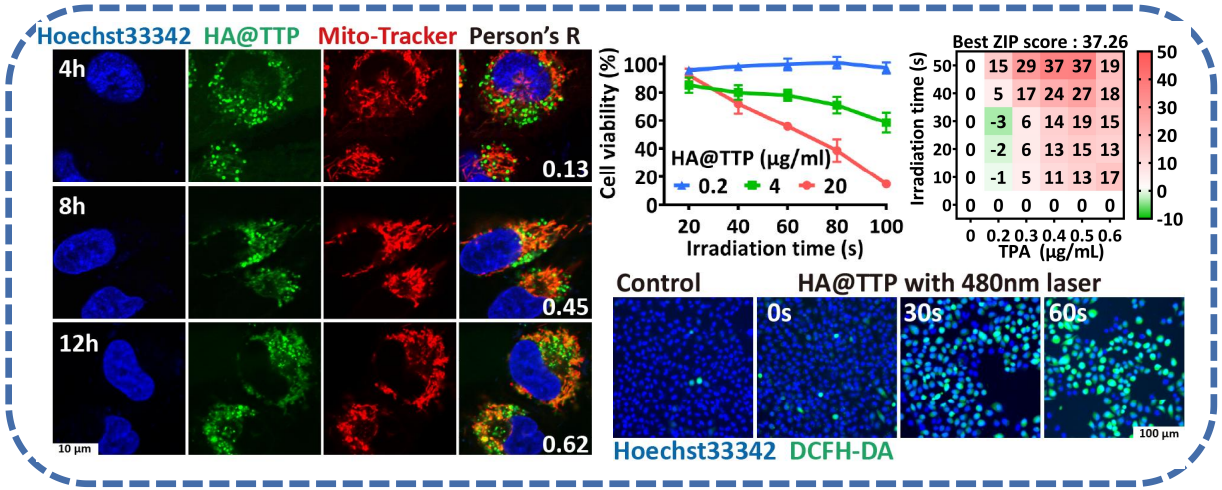
Mitochondrial damage

Mitochondrial-Targeting PDT

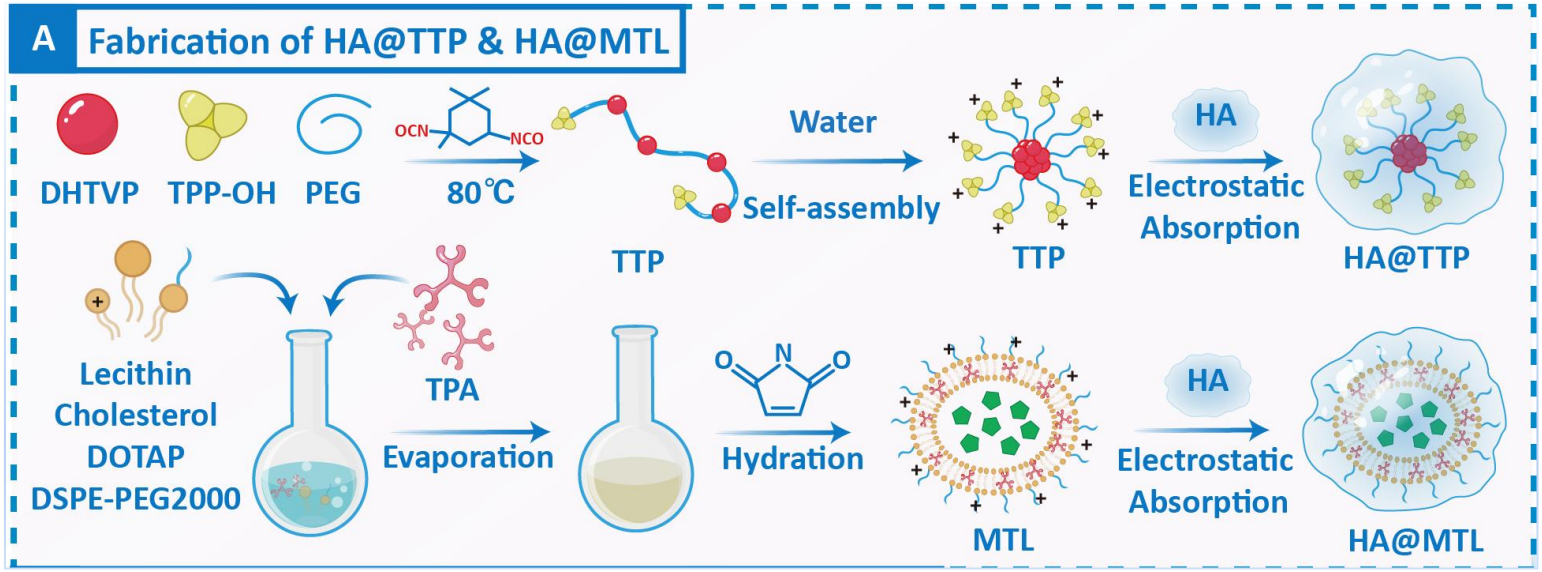


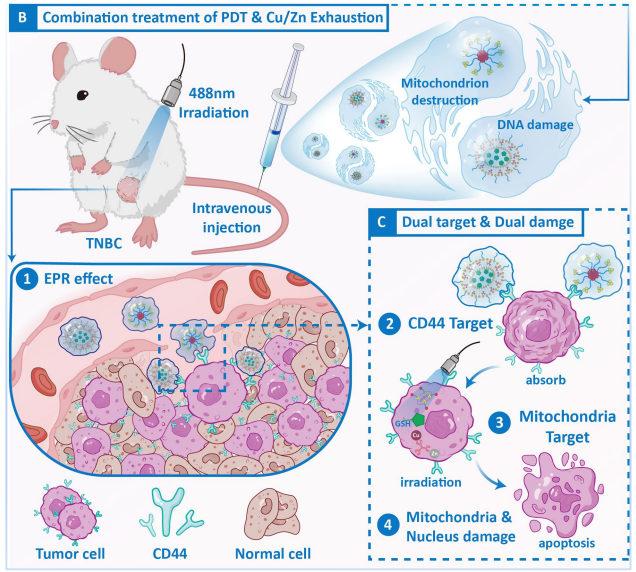
ROS



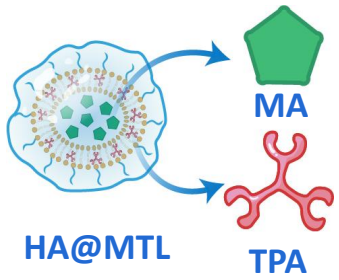


Nano-Engineered Tumor-Specific Delivery

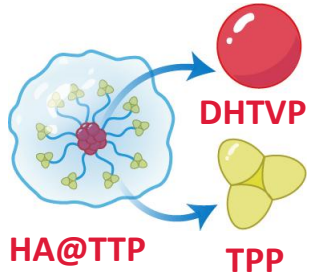




MA/TPA co-loaed Liposome (MTL)



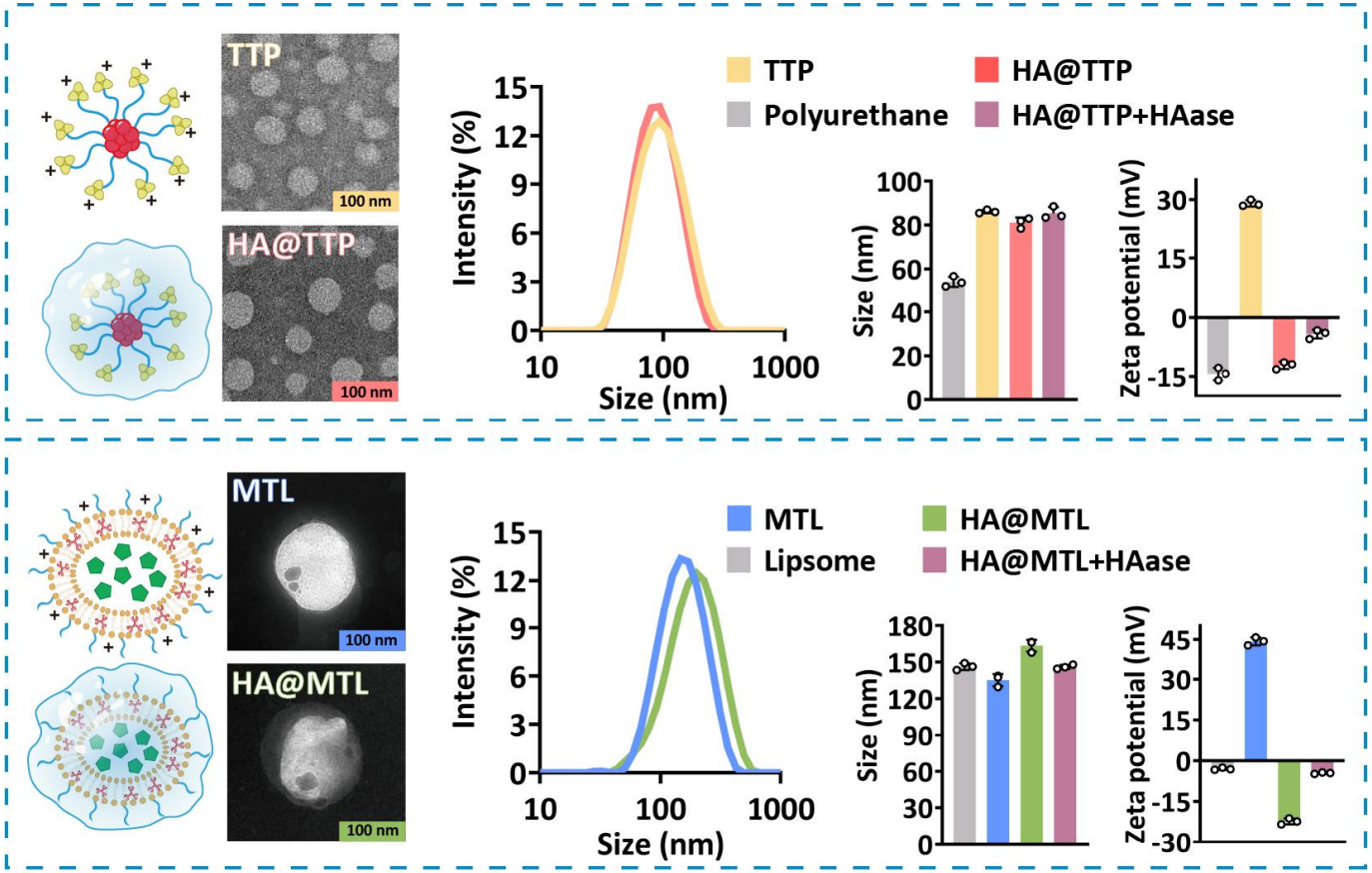
TPP-targeting and TVP-conjugated Polymer (TTP)



DNA damage → Apoptpsis ← Mitochondrial damage

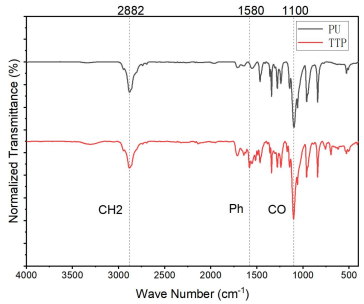
Physicochemical Characterization of HA@MTL & HA@TTP

Particle size and Zeta potential

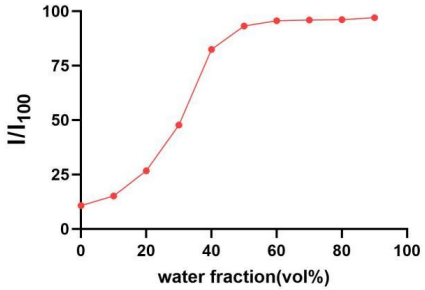


HA@TTP

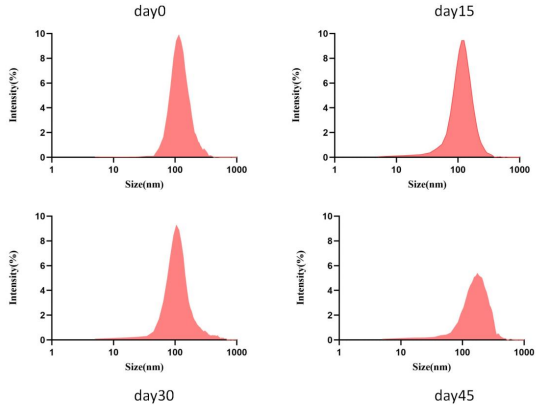
FT-IR



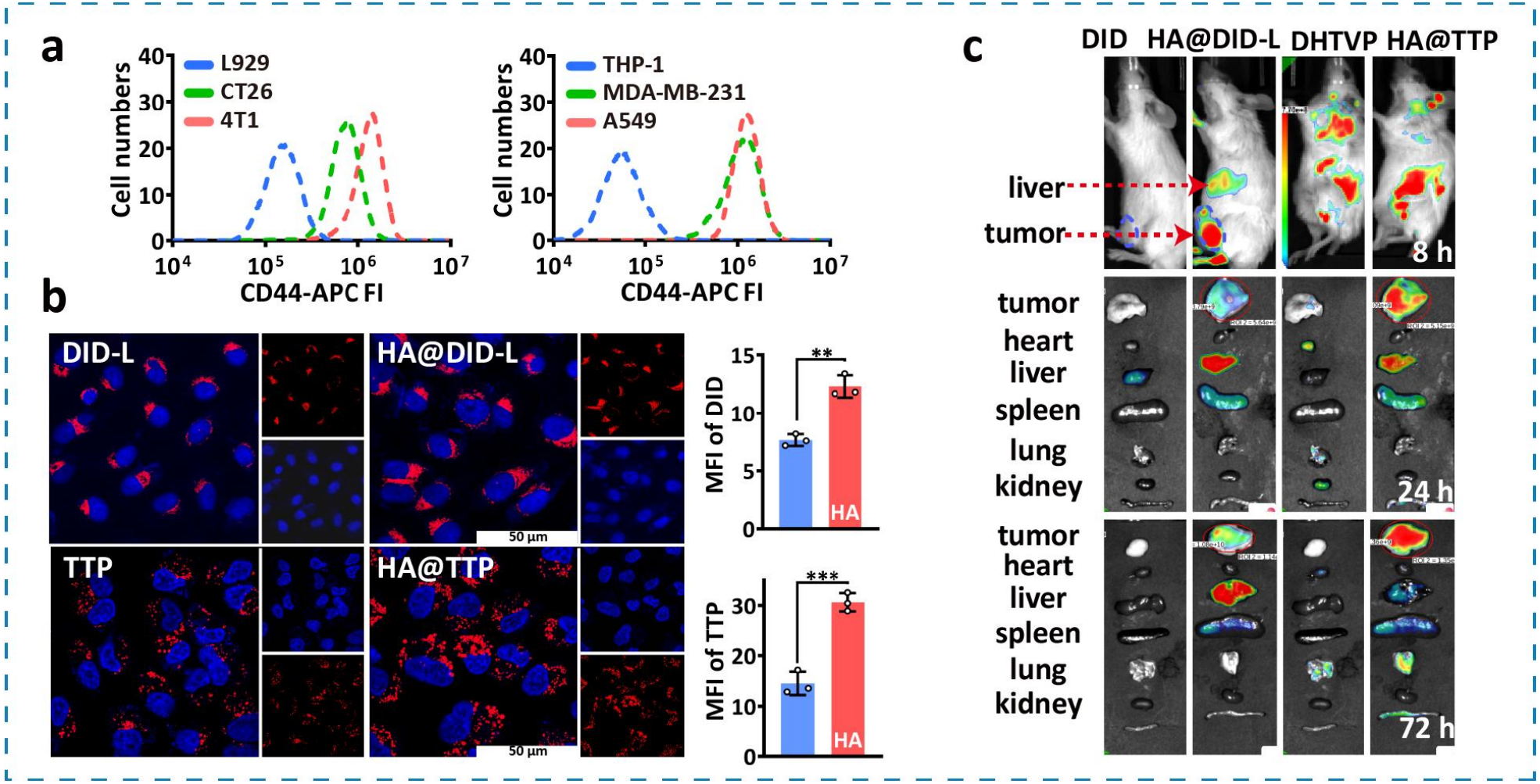
Aggregation-Induced Emission (AIE)



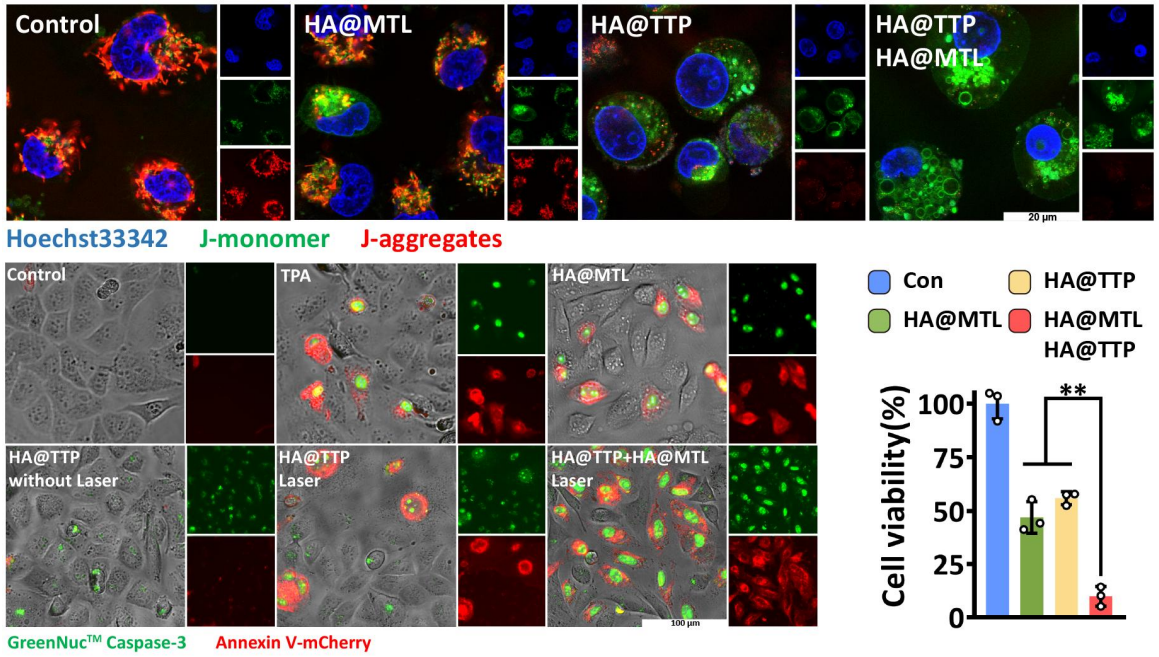
Stability

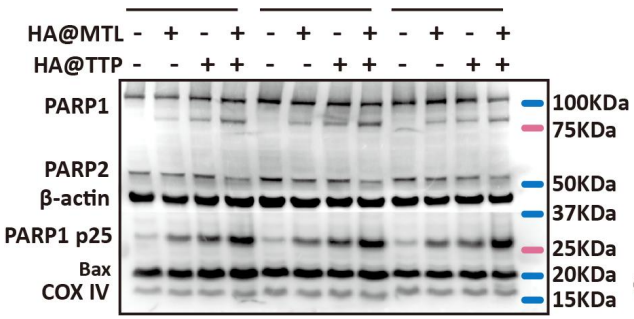


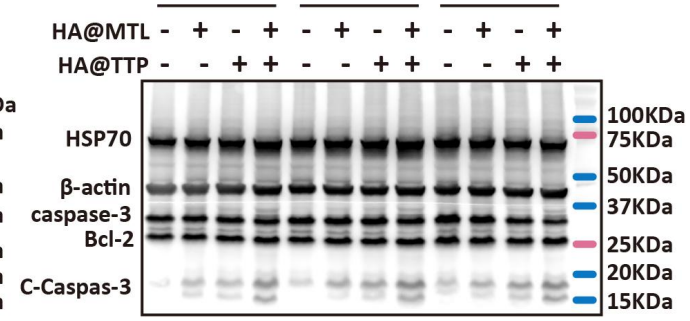
HA Coating Facilitated Tumor Uptake of Nanoformulations

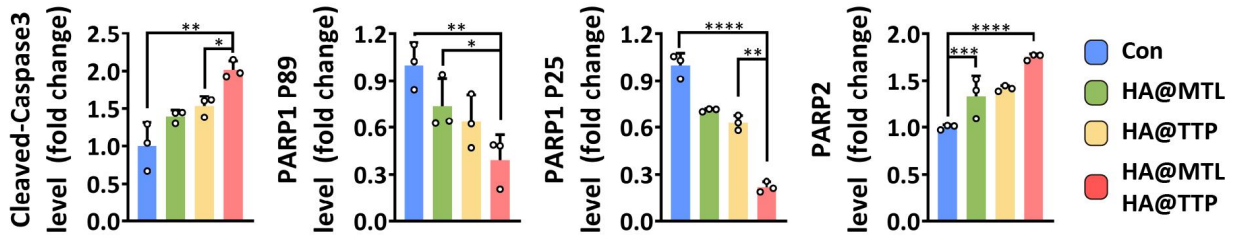


Nano-TPA Combined with PDT Induced TNBC Cell Death



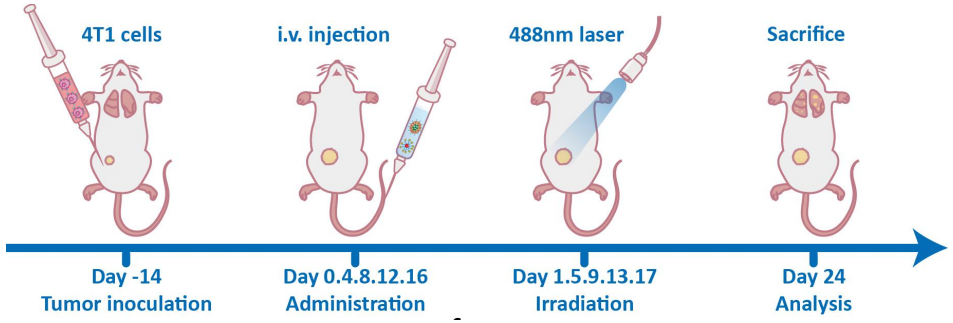




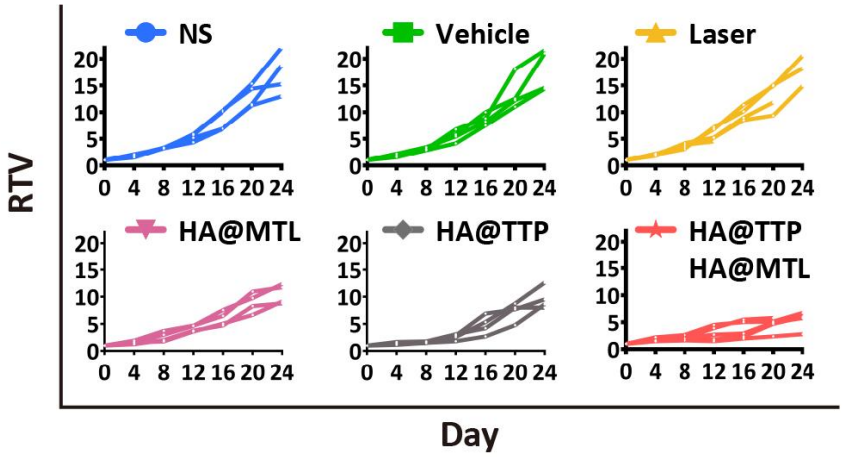


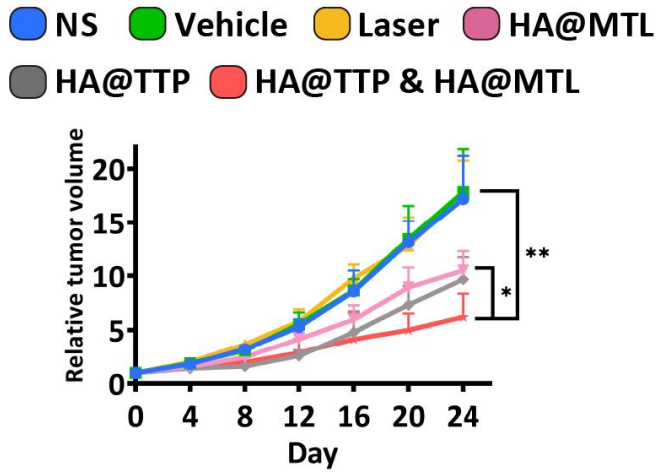
Nano-TPA combined with PDT efficiently induced TNBC cell death through apoptosis

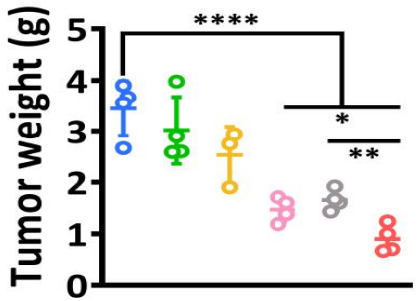
Nano-TPA Combined with PDT Inhibited TNBC Tumor Growth

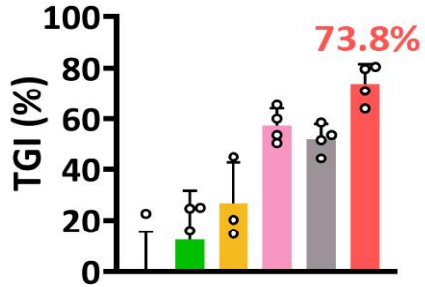


I.V. every four day for a total of 5 doses

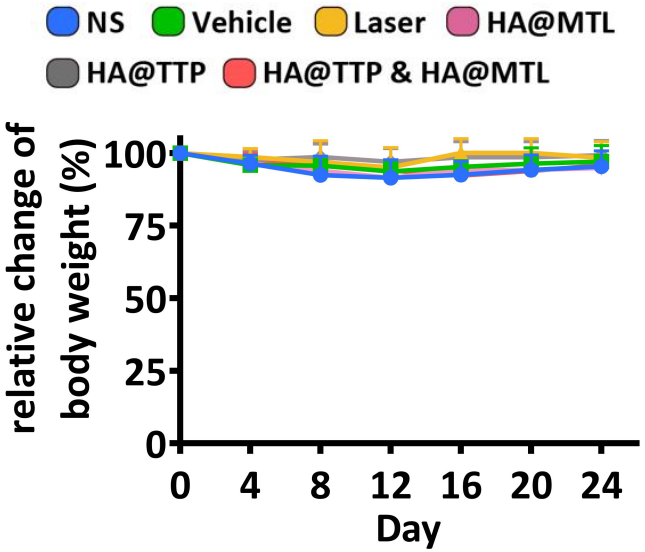


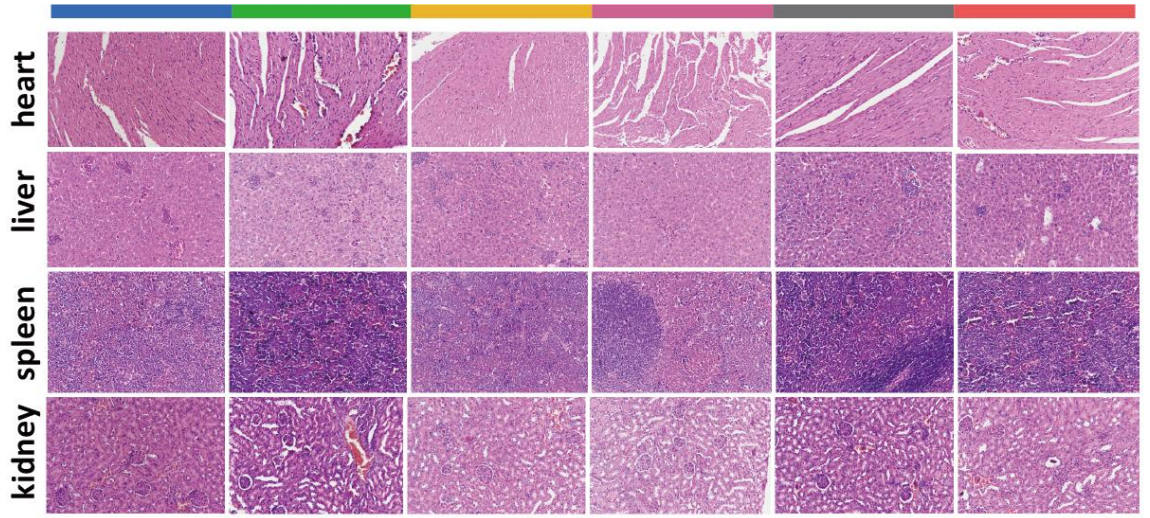


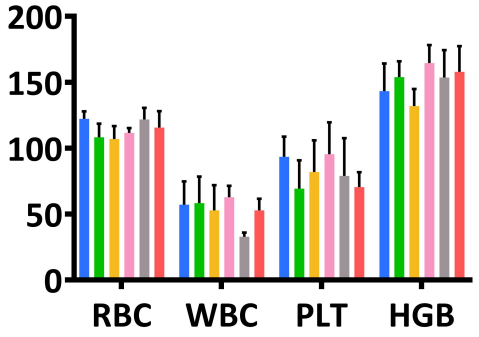


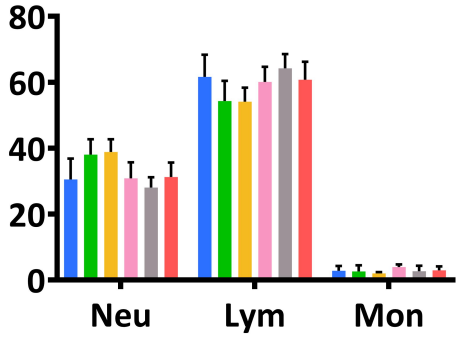


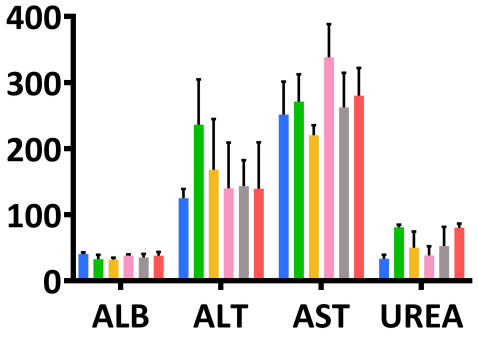
Biosafety Profile



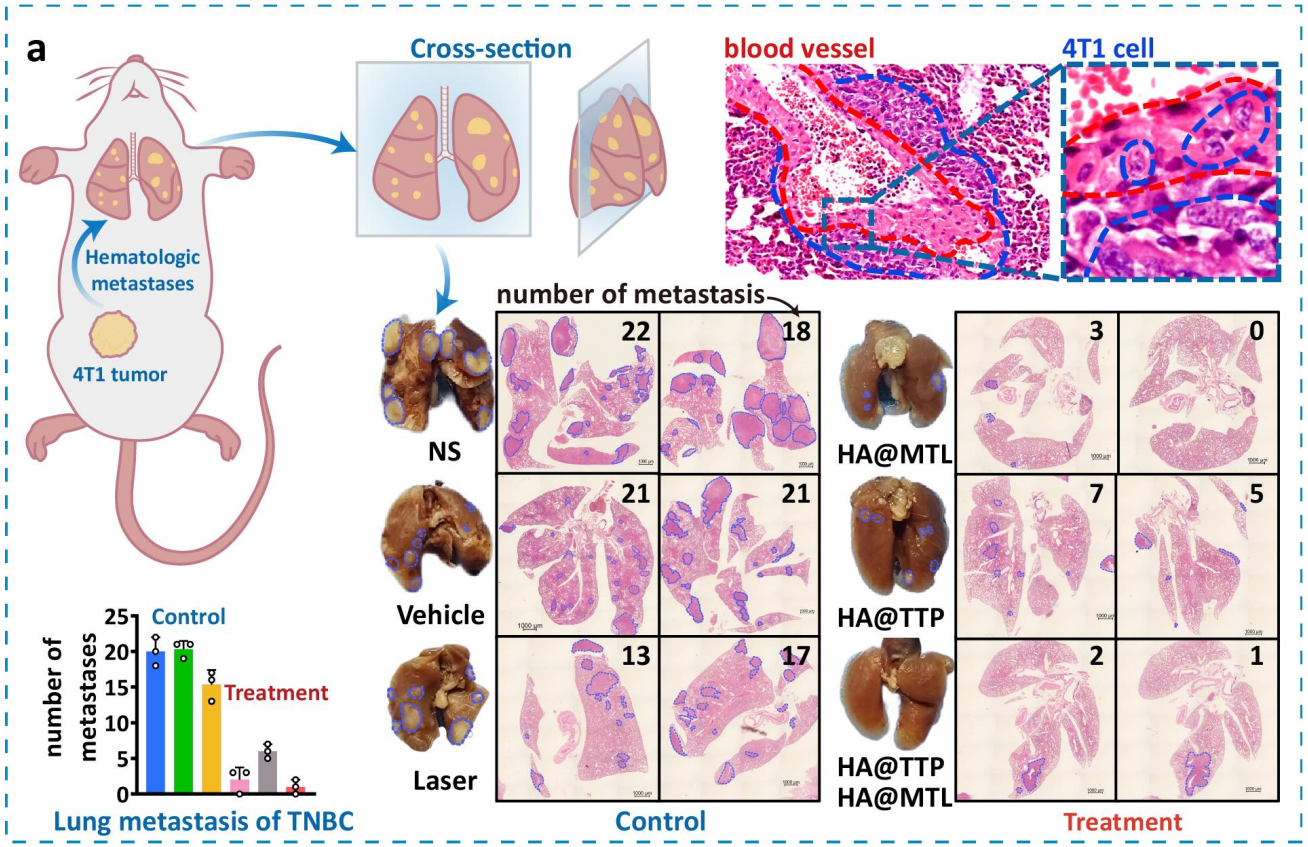


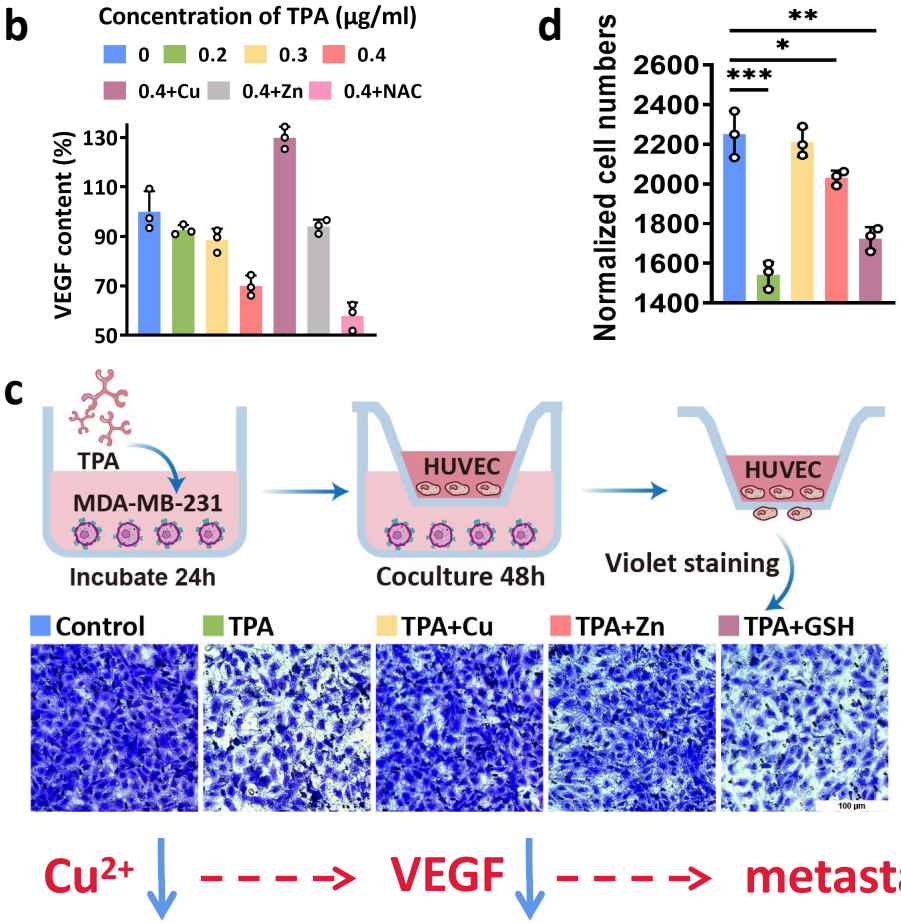






Nano-TPA Combined with PDT Inhibited TNBC Metastasis





Summary

1. Targeted nano-delivery of dual Zn^{2+}/Cu^{2+} chelator TPA disrupted DNA repair and mitochondrial metabolism in TNBC.

2. Nano-TPA in conjugation with PDT achieved potent tumor suppression and metastasis inhibition *in vitro* and *in vivo*.

3. This platform is potentially adaptable to radiotherapy/DNA-damaging chemo combinations.

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THANKS