GOLD NANOPARTICLES AS CARRIERS OF CISPLATIN WITH A Ph SENSITIVE LINKER FOR INTRACELLULAR DRUG DELIVERY

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Summary

- The present invention relates to conjugates having colloidal stability in a medium comprising metallic nanoparticles coated with platinum containing compounds. It also relates to a process for their preparation and to pharmaceutical compositions containing them. The conjugates of the invention are used for the treatment of cancer.

- Platinum compounds play an important role in cancer chemotherapy. CisPt, the first generation of Platinum based chemotherapy drug, is one of the most common anticancer agents and has a wide spectrum of anticancer activity. However, drawbacks such as the poor selectivity between malignant and normal cells, leading to severe toxic effects and the presence of intrinsic or acquired resistance, so that the doses must be increased, importantly limit its efficacy.

- We have found that when a CisPt is conjugated to a metallic nanoparticle through a linker via coordination bonds, the resulting delivery system is capable of delivering 10 times more Platinum to the tumor without increasing the toxicity to normal tissues. As a result, tumor resistance to Pt compounds is reduced and side effects are diminished. In addition, the conjugates of the invention are highly soluble in comparison with the currently used free Platinum compounds, whose solubility is low.

WHY NANOPARTICLES FOR ONCOLOGY?

1.- Severity of the disease

2.- Hyperthermia (Berlin Frei University Hospital)

3.- Delivery to the tissues (leaky tumor vasculature)

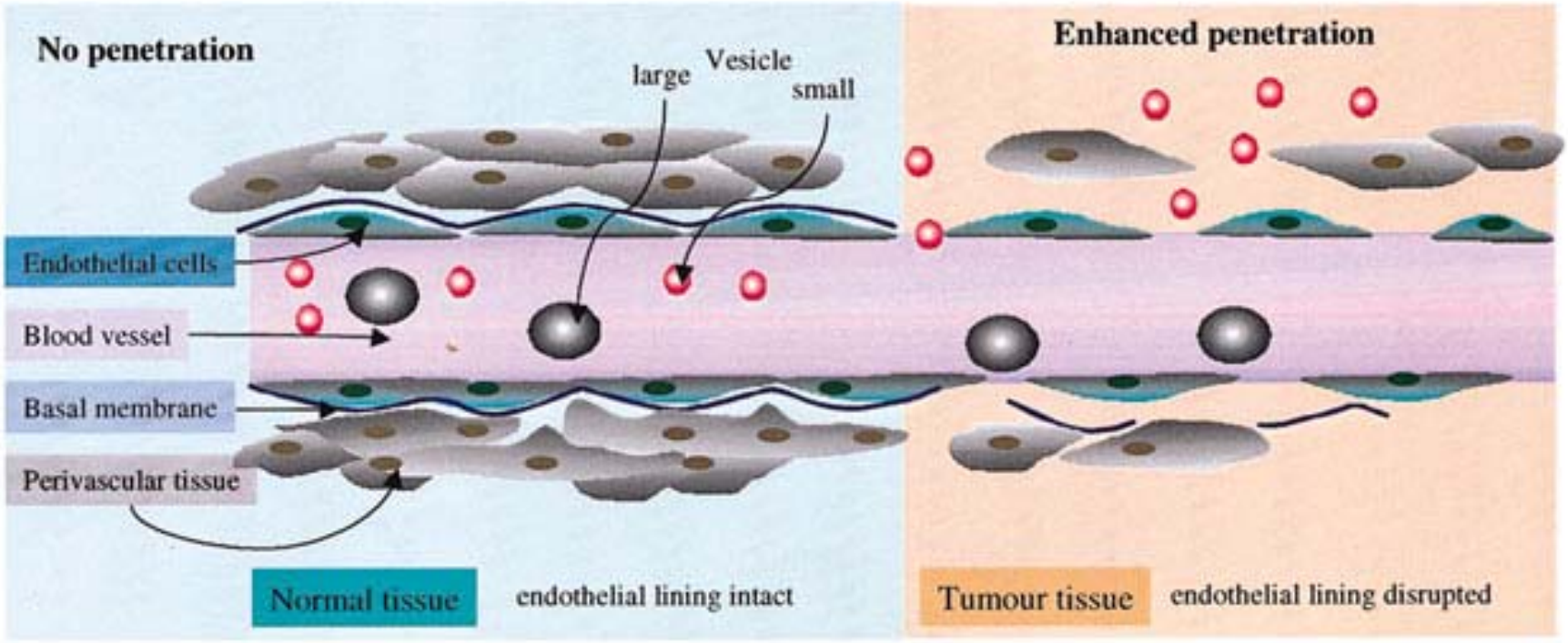
4.- Delivery to the cell (endocytosis)

5.- Loading Chemicals

6.- Multiple Conjugation (better targeting)

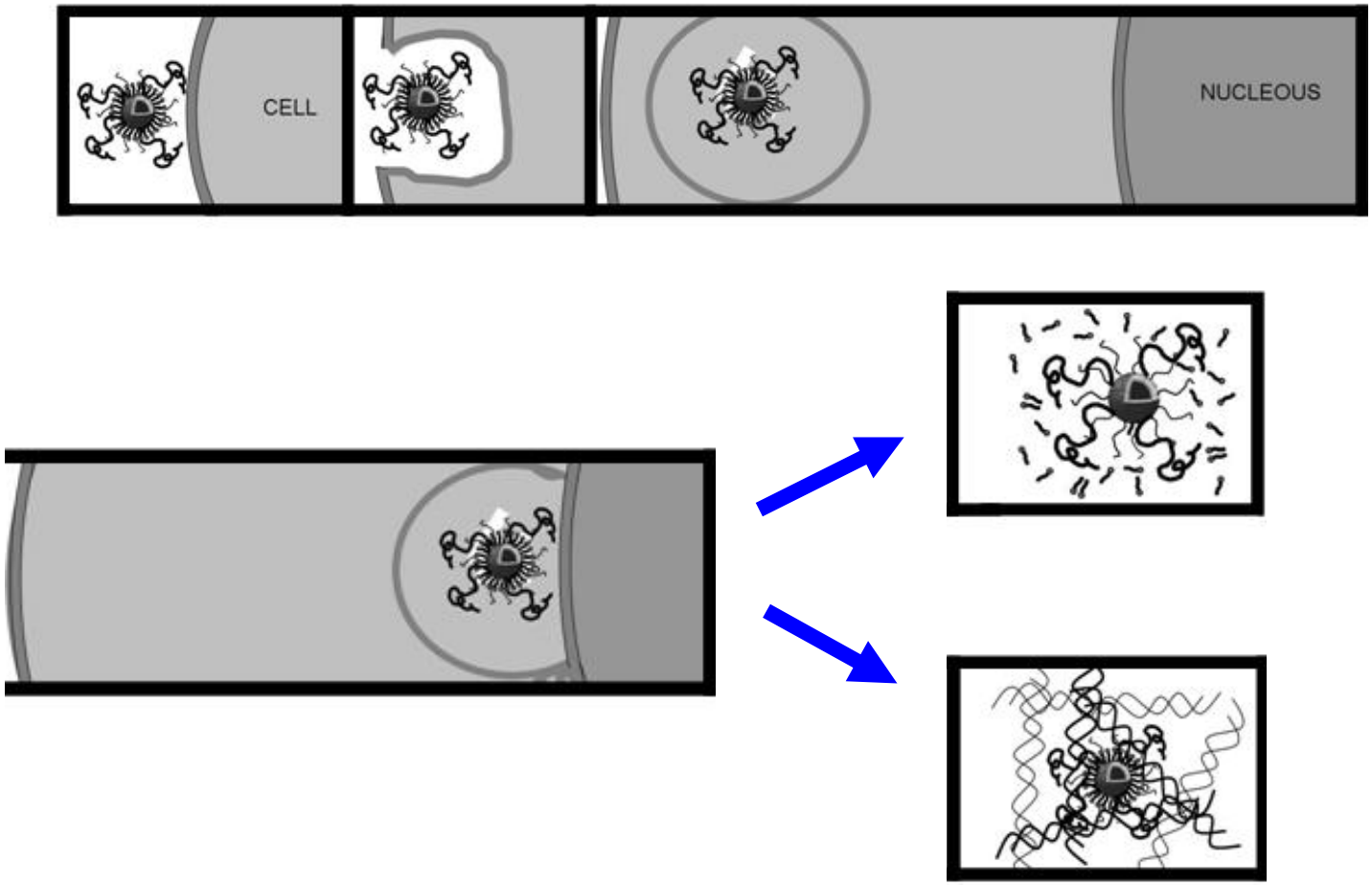
7.- Inorganic Contrast Agent

8.- Inorganic antenna for photo-ablation



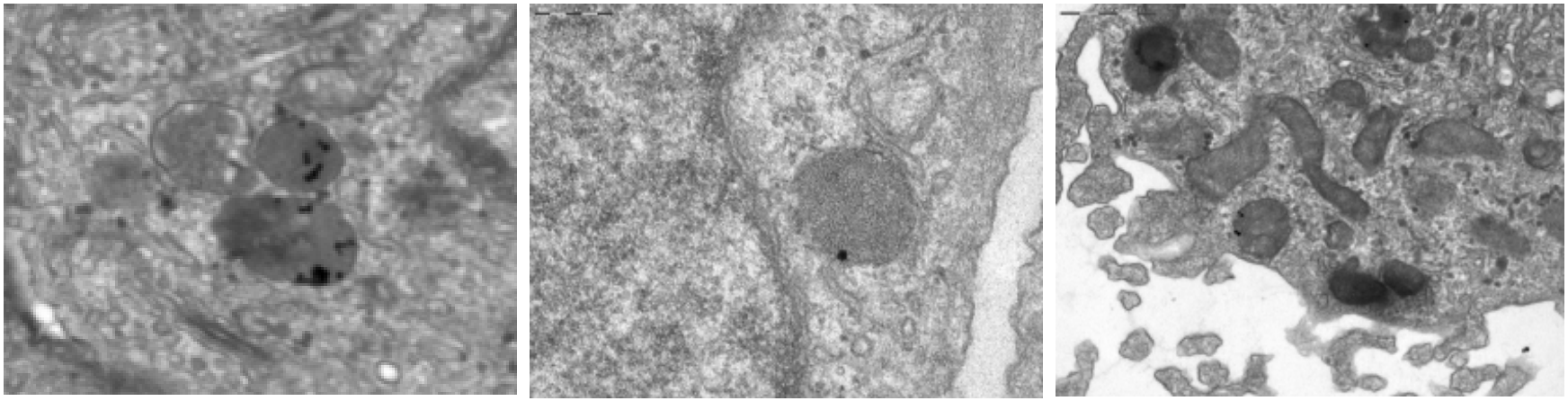
Jain, R. K. *Adv. Drug Deliv. Rev.* 46, 149–168 (2001).

CELL DISTRIBUTION

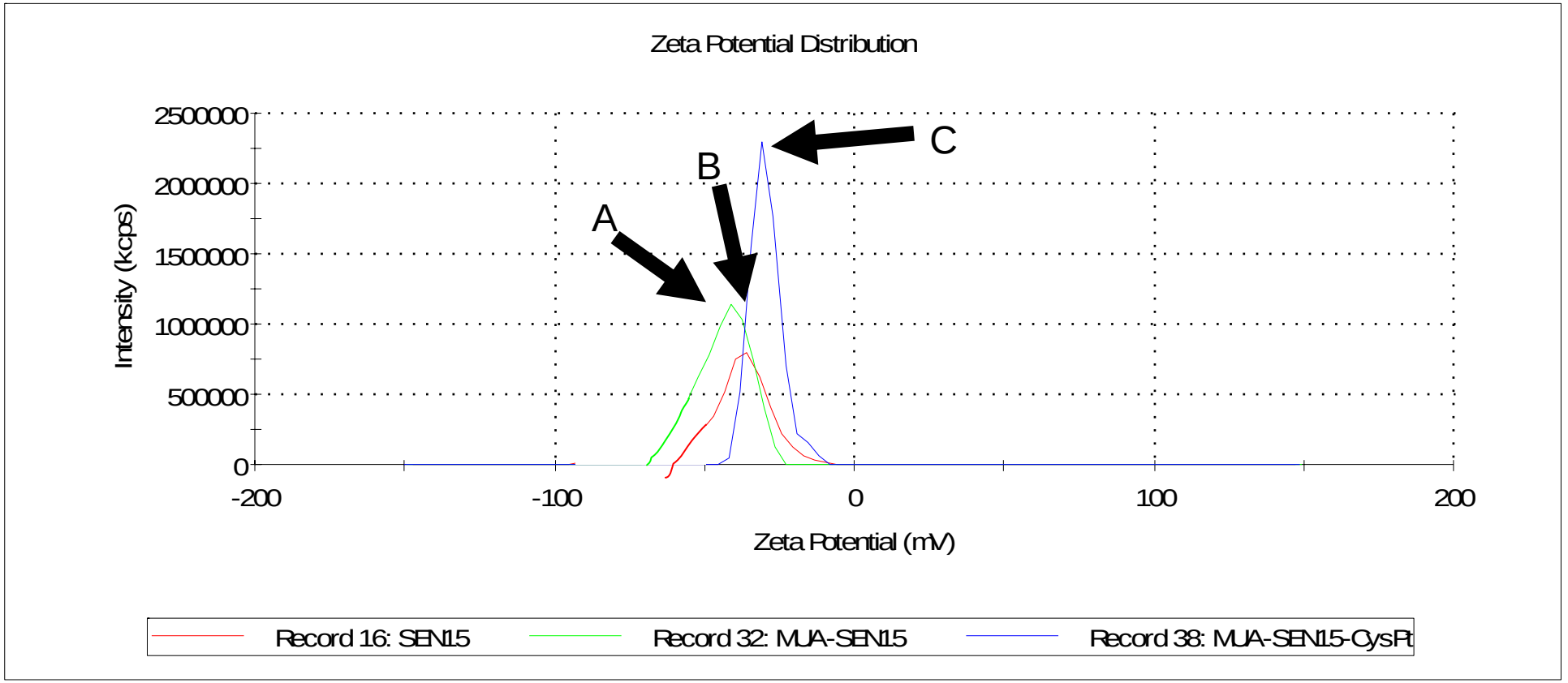


GOLD NP CONJUGATED TO CISPLATIN

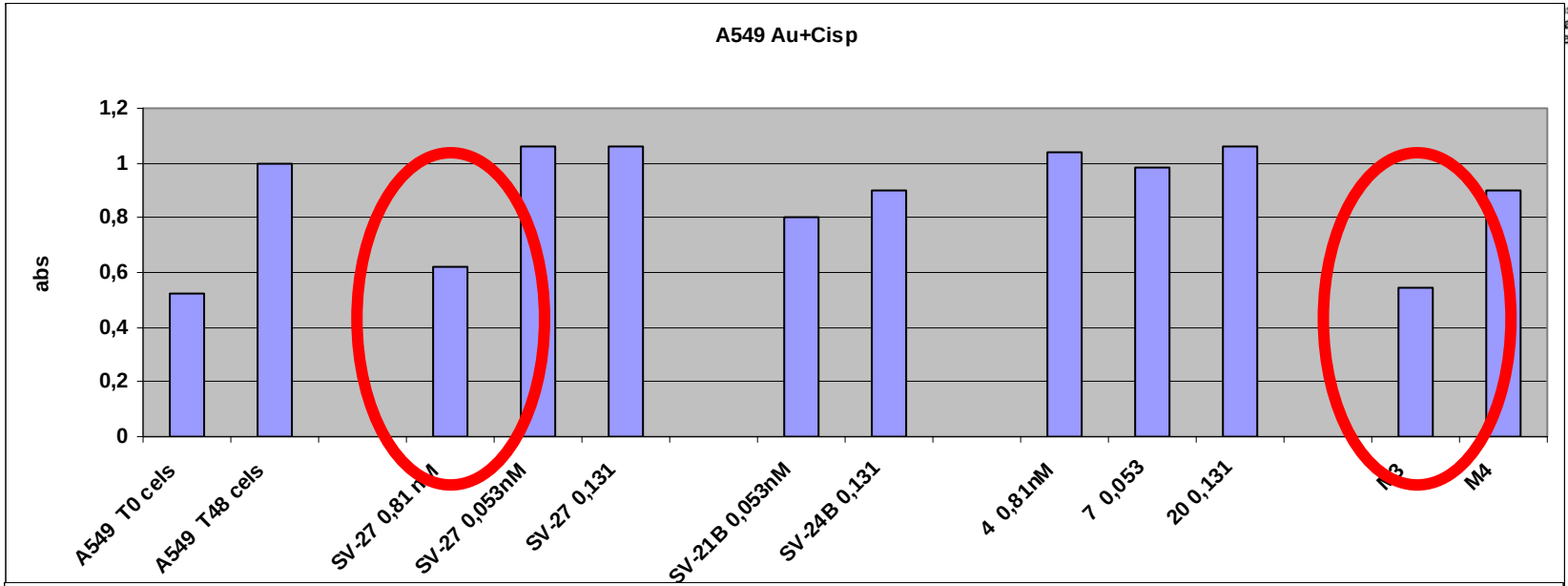
HeLa

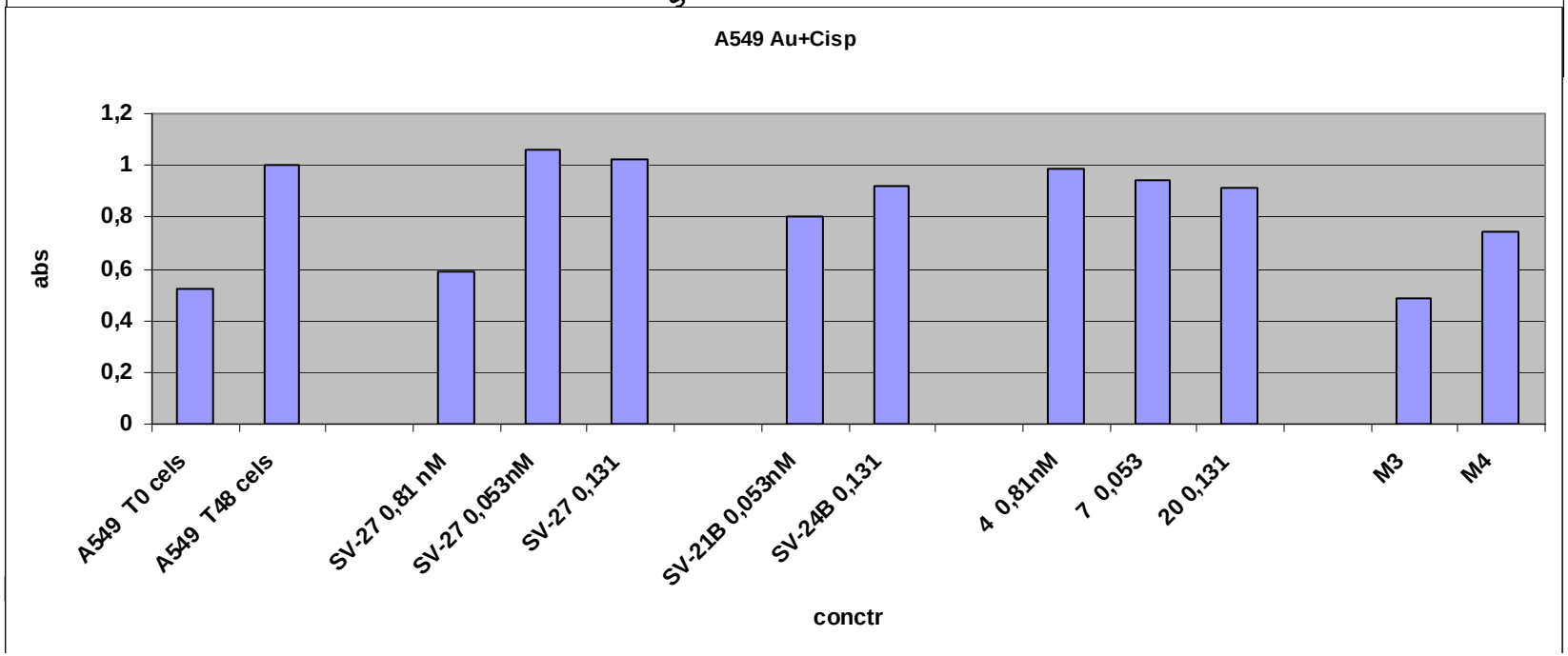


CONTROLLING SURFACE CHARGE

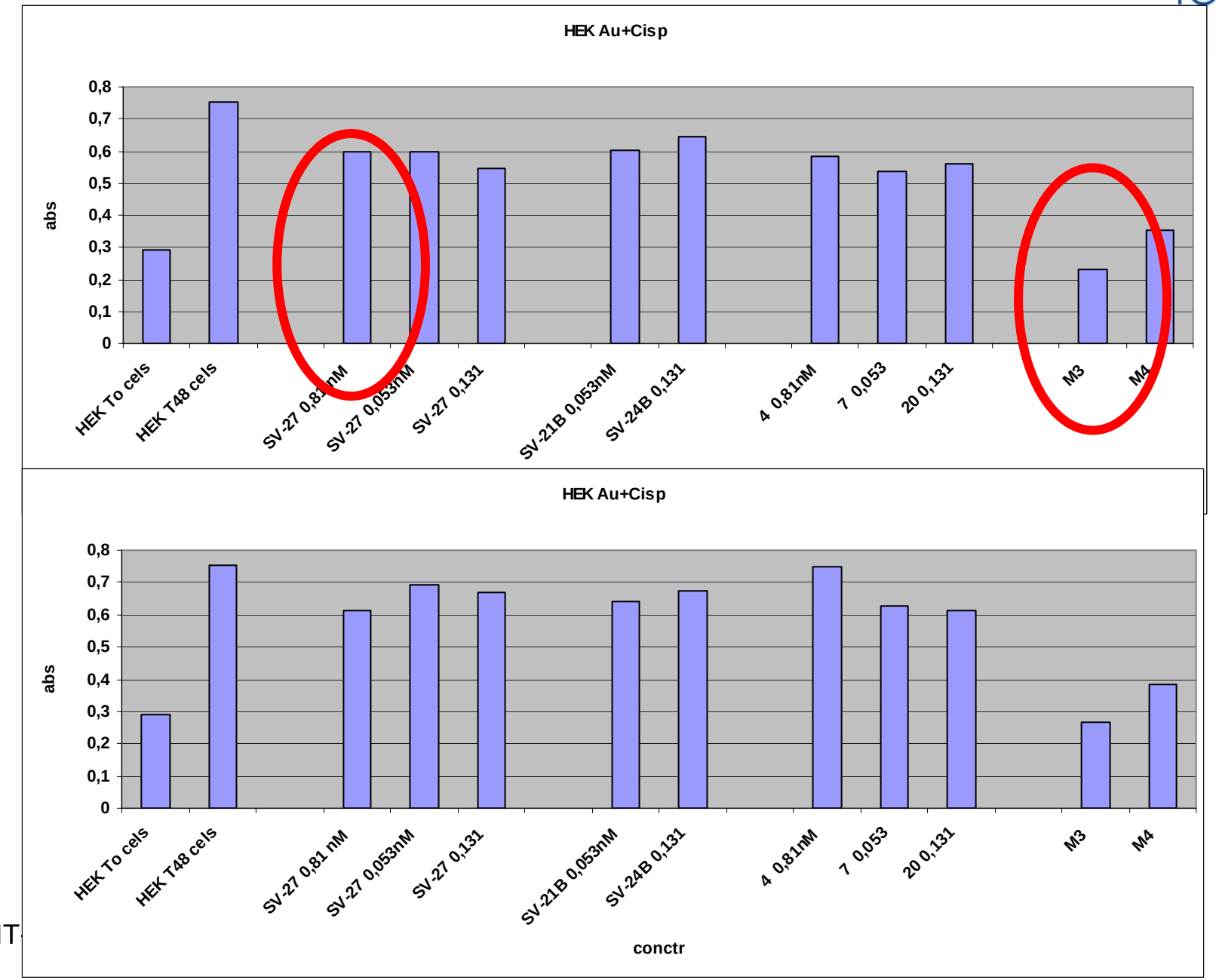


CISPLATIN DERIVED NP AND HUMAN EPITELIAL LUNG CANCER CELLS A549

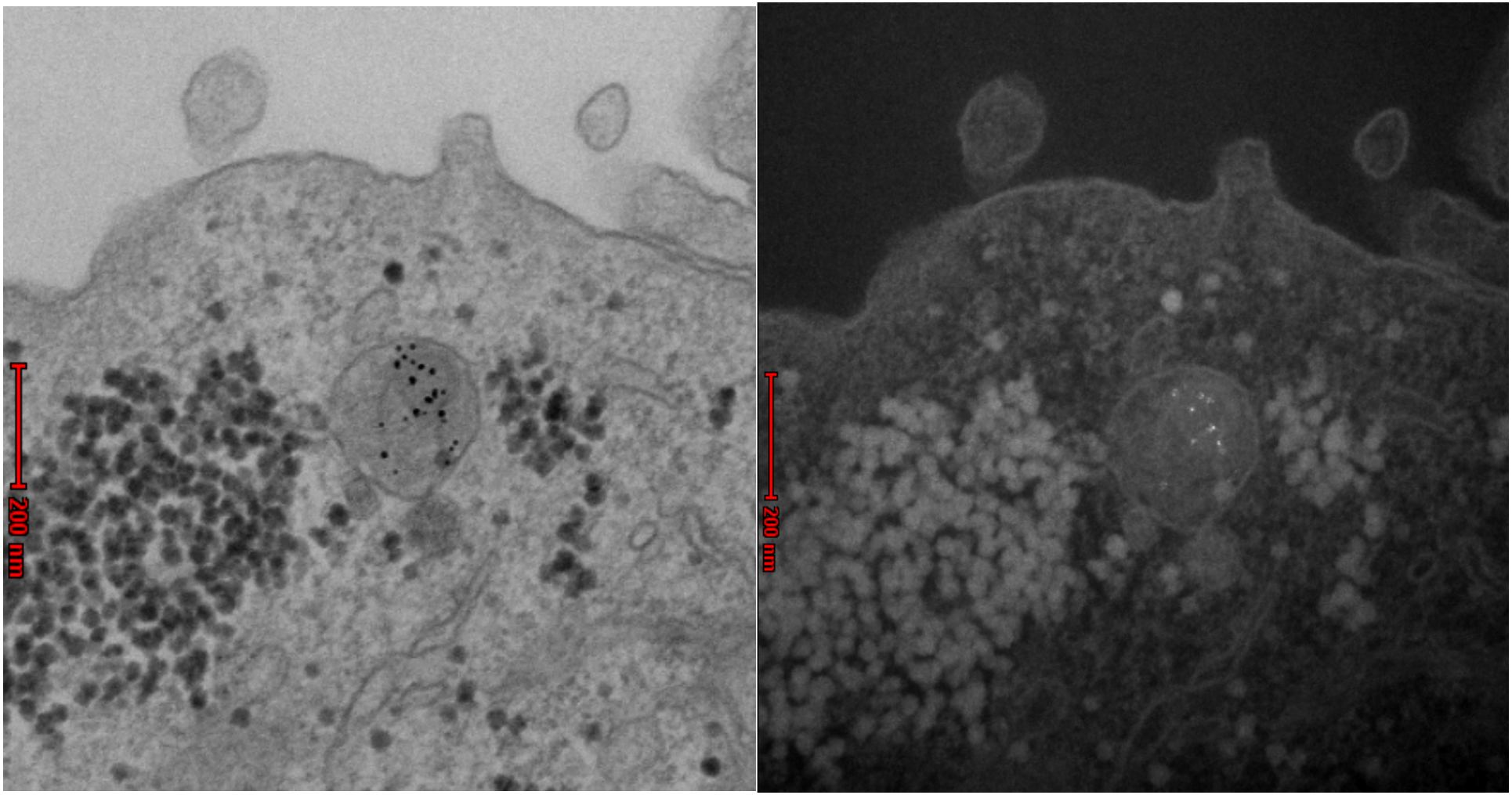




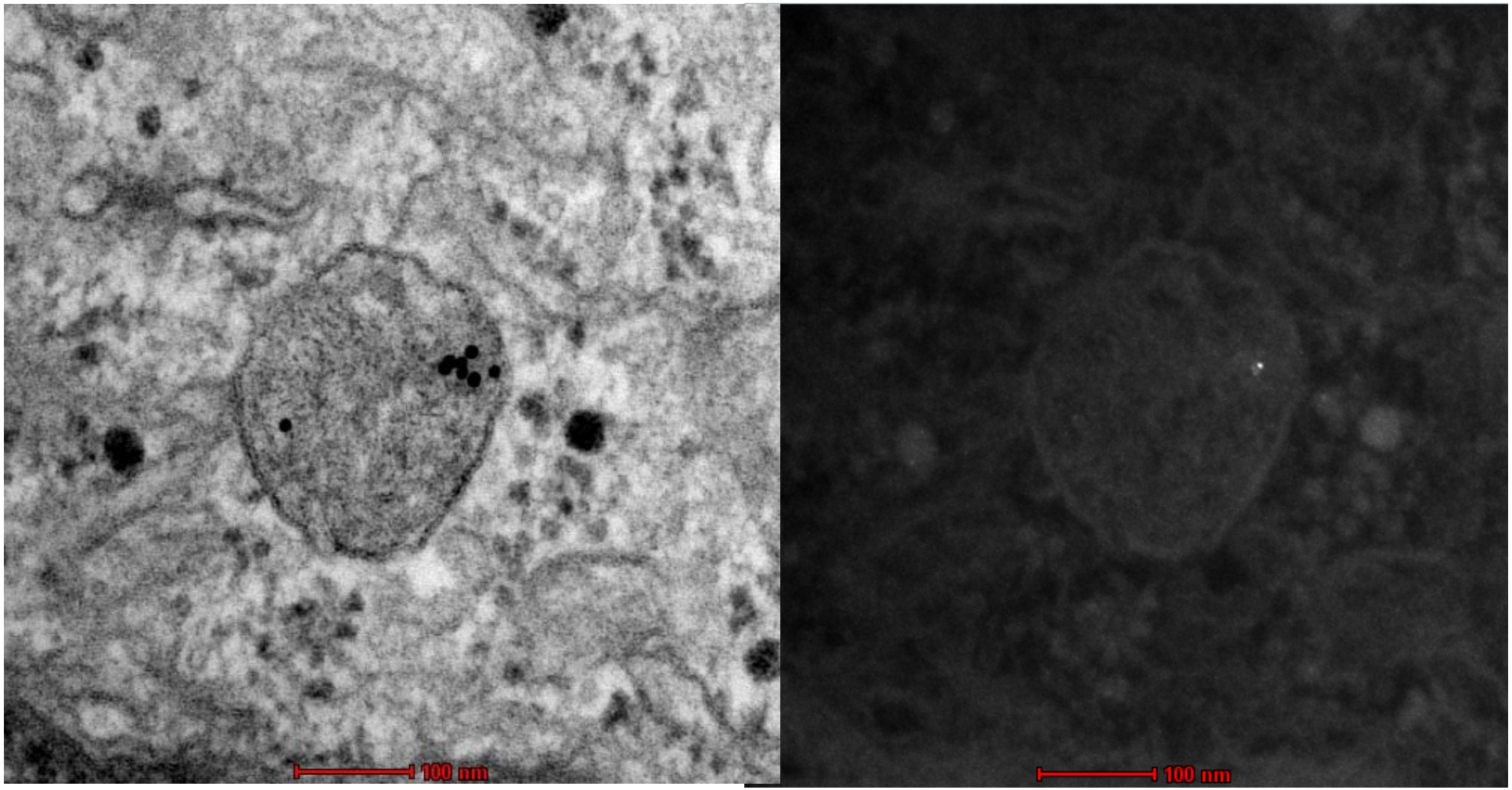
CISPLATIN DERIVED NP AND HUMAN KIDNEY EMBRYONIC CELLS HEKC



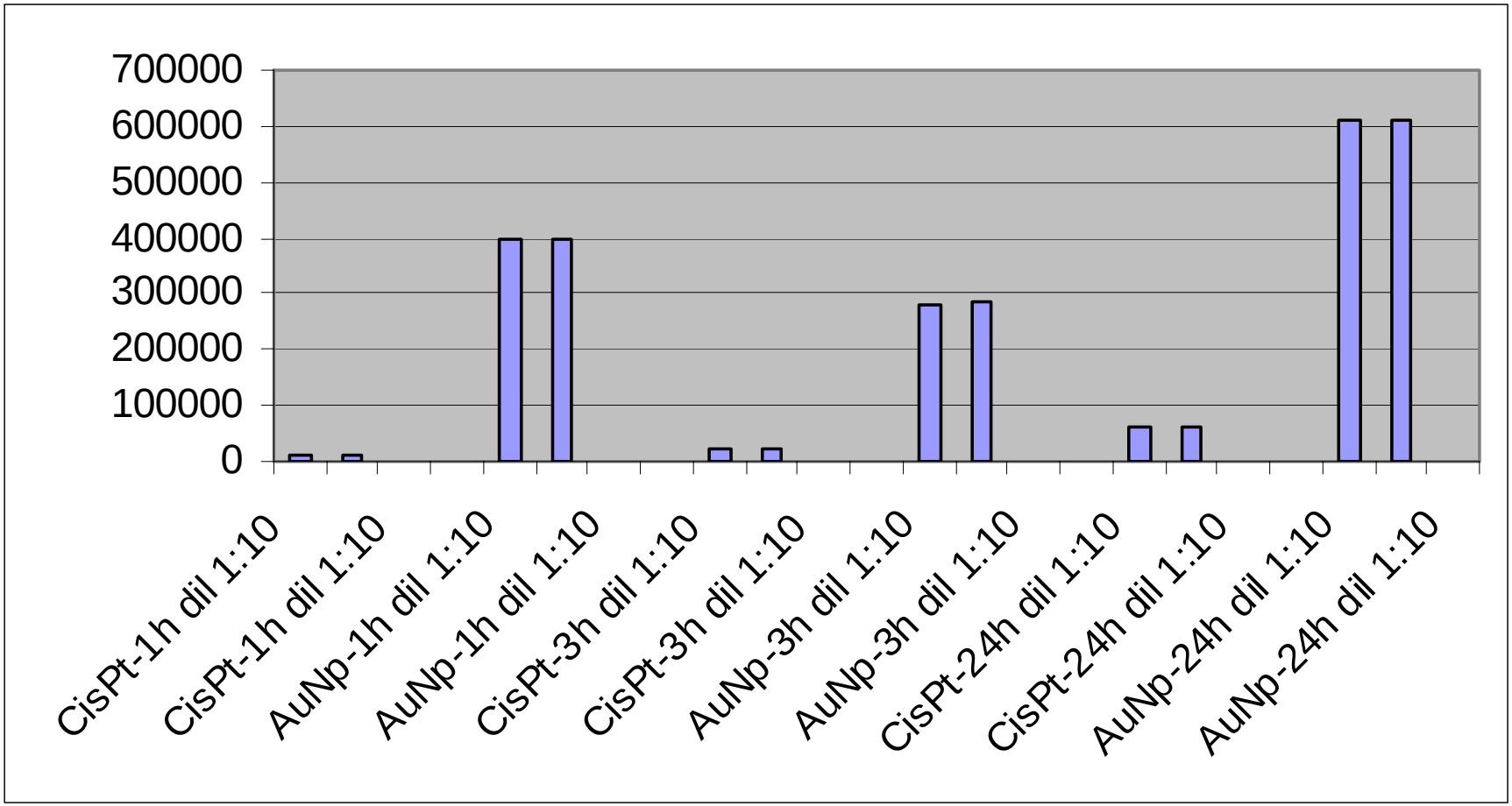
NP INTERNALIZATION IN HeLa (Dark Field)

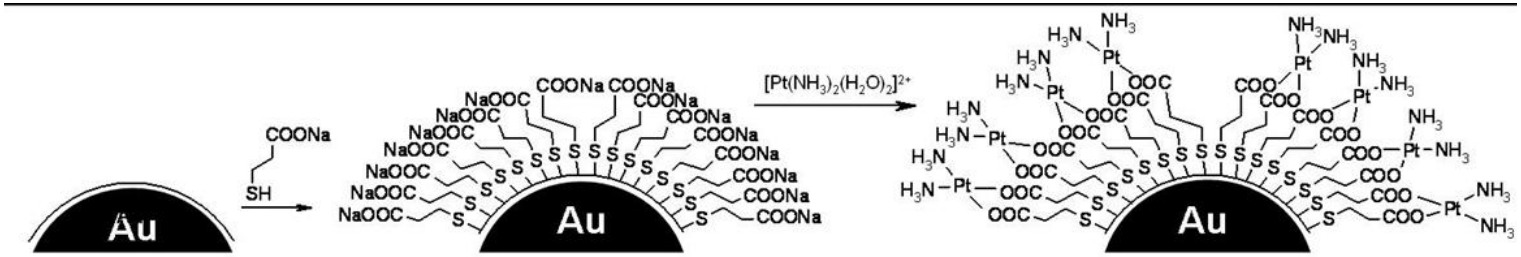


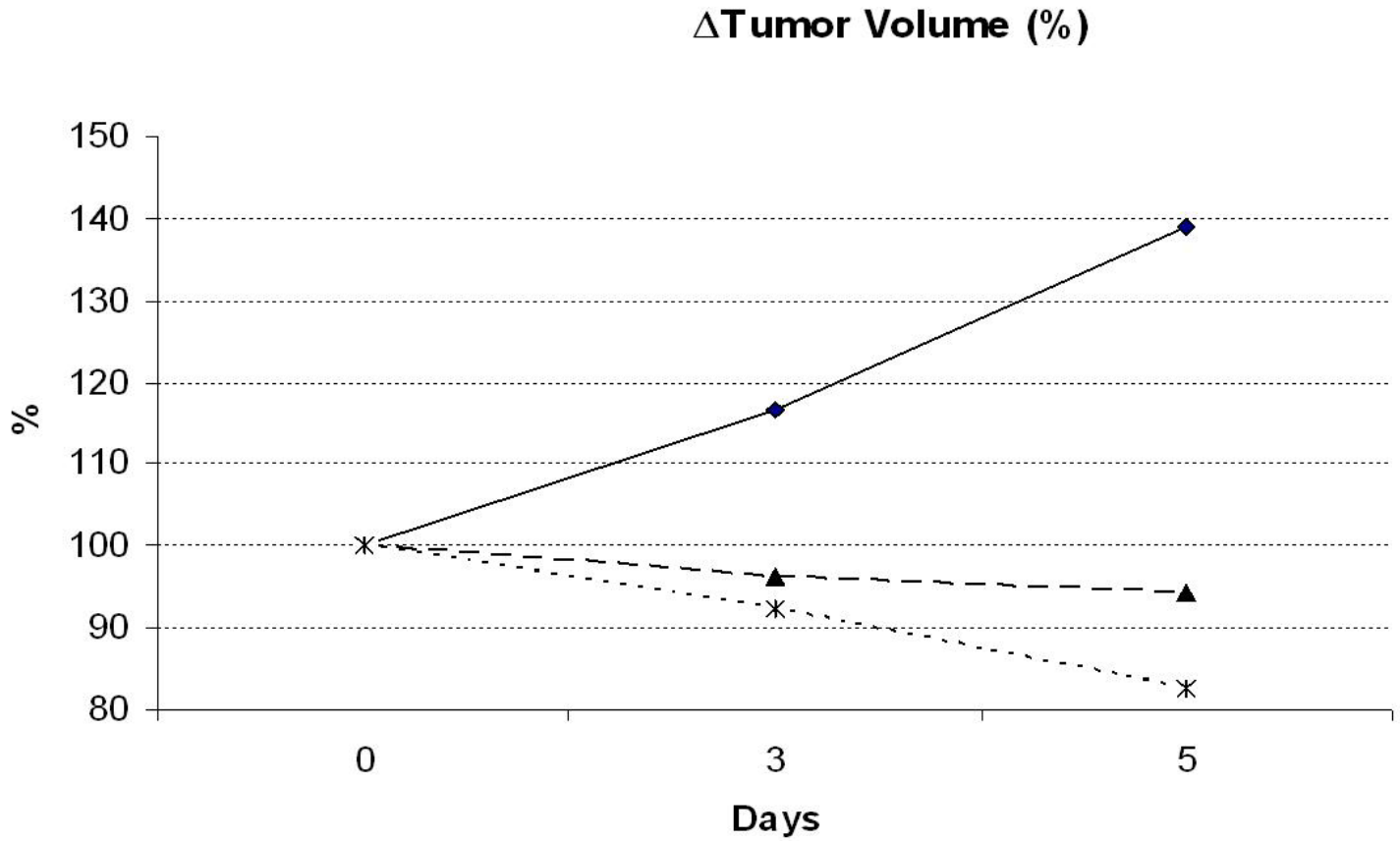
NP INTERNALIZATION IN HeLa (Dark Field)

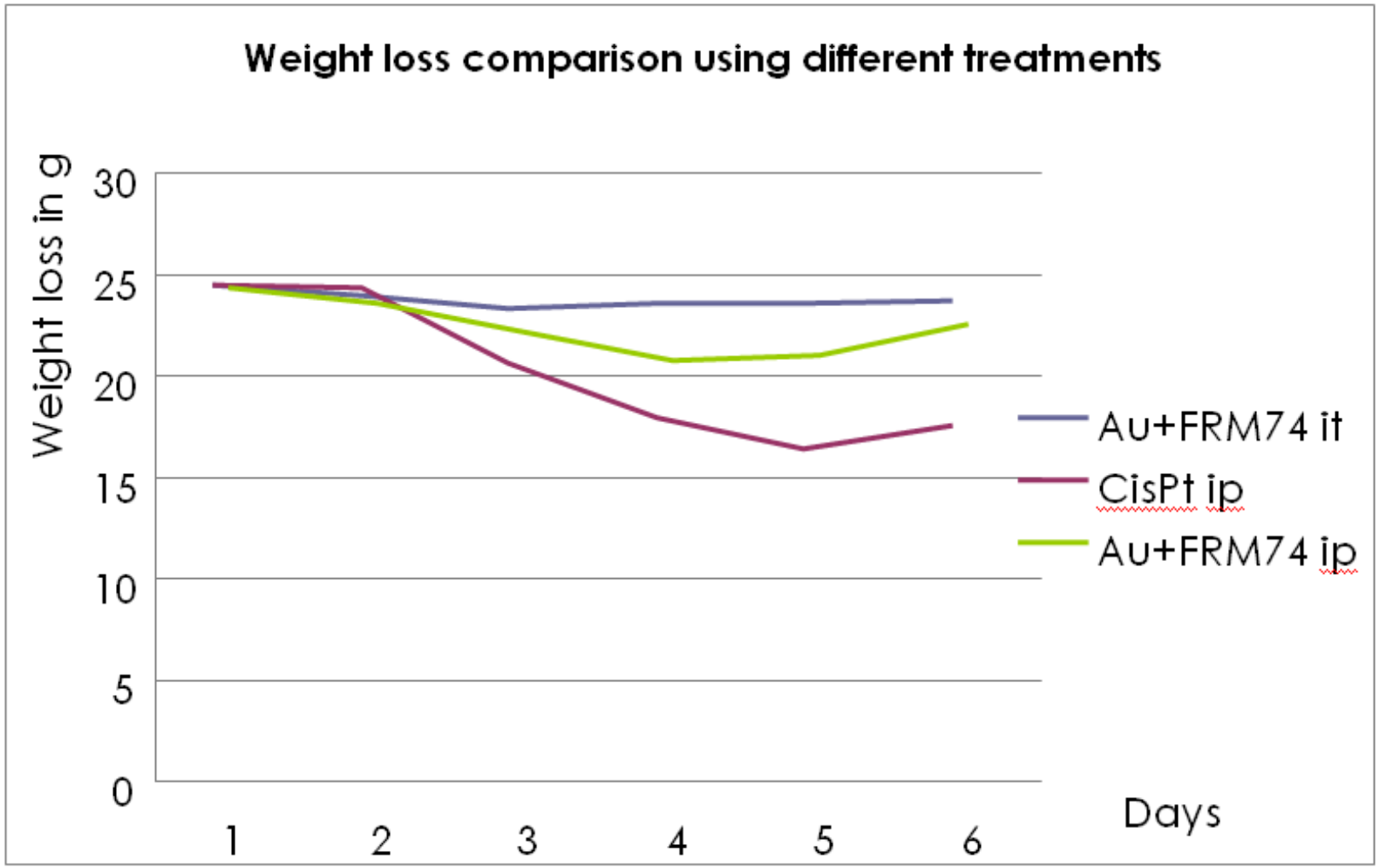


CisPt Intracellular content. 1, 3 and 24 h after treatment with free CisPt and CisPtAuNP conjugate.




Au
SH
COONa
NaOOC
S
Au
$[Pt(NH_3)_2(H_2O)_2]^{2+}$
H_3N
Pt
OOC
COO
NH_3
Au


ΔTumor Volume (%)
150
140
130
120
110
100
90
80
%
0
3
5
Days


Weight loss comparison using different treatments
Weight loss in g
30
25
20
15
10
5
0
1
2
3
4
5
6
Days
Au+FRM74 it
CisPt ip
Au+FRM74 ip

Conclusions

- We have reported the synthesis in aqueous solution of AuNP-CisPt conjugates that are stable in physiological conditions, which once it arrives to the cell it is passively endocytosed (after accumulation in the tumor as all the particulate antineoplastic drugs). In the endosome a pH drop leads to the release of the CisPt which it is free to go to the nucleus to do its job.

- The cytotoxicity studies suggested that CisPt is more toxic when is carried by AuNPs to the cell.

- This first approximation in the design of a new drug delivery system to lower the secondary effects of the actual administered drug has been successful.

- This invention opens a promising area of research towards the development of new chemotherapeutic agents that will allow lowering the doses obtaining the same beneficial effects.

Thank you for your attention !!!

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