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# Ferrocifen loaded Nanoparticles: Targeting MDR tumors via the Thioredoxin Reductase Pathway

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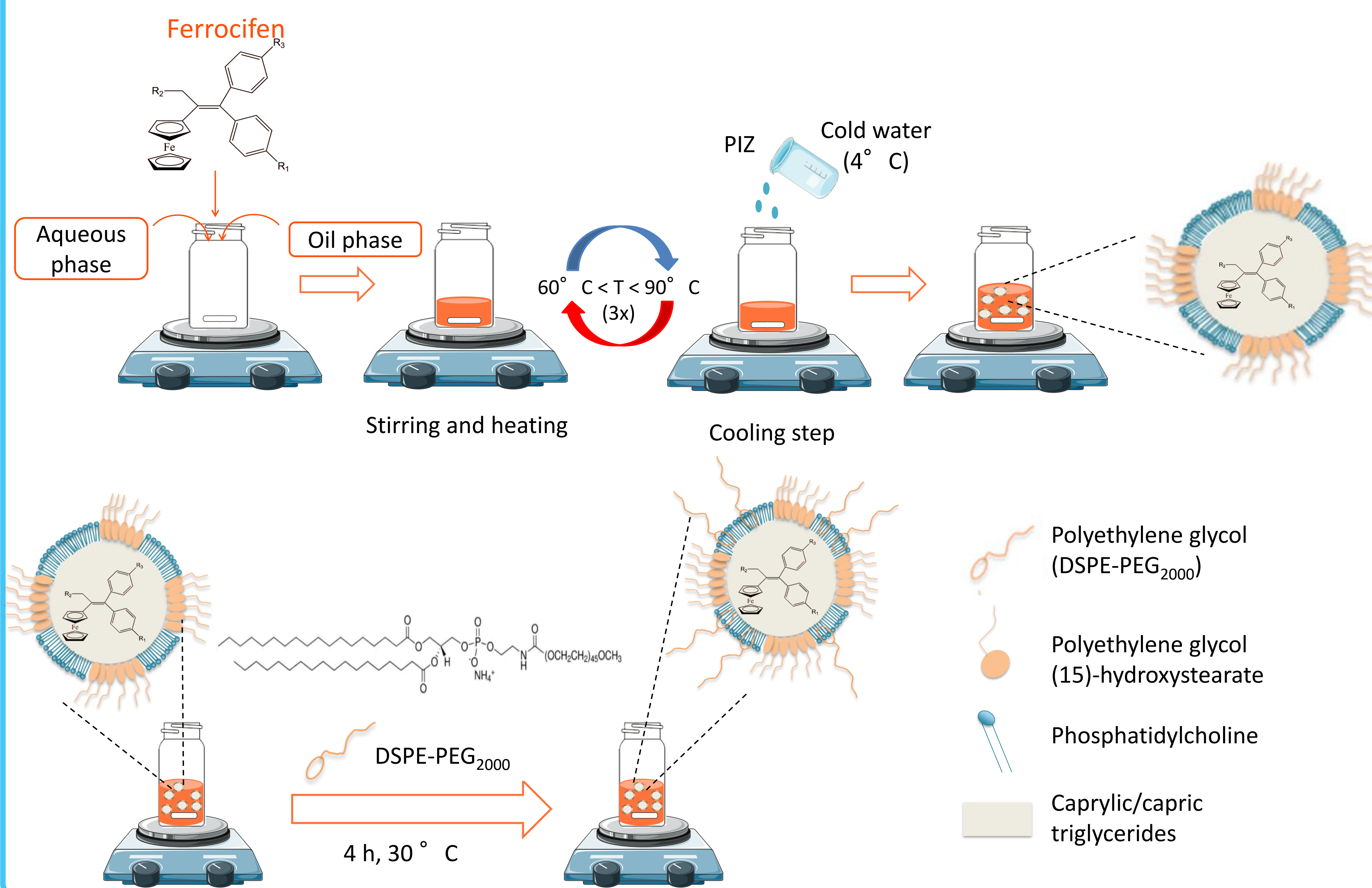
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## Introduction

Regardless of the leaps being achieved in the field of cancer treatment, 90% of the failures of chemotherapy arise from the multidrug resistance aspect gained by the tumors<sup>1</sup>. Aiming to overcome these limitations, ferrocifens, a family of molecules obtained chemically by combination of one ferrocene with hydroxytamoxifen derivatives<sup>2</sup>, encapsulated in lipid nanocapsules, could offer an innovative and promising approach to combat this resistance. Moreover, the functionalization of the obtained nanoparticles with polyethylene glycol would imbue them with stealth properties<sup>3</sup>, increasing their half-life and blood circulation time, while utilizing the enhanced permeability and retention effect (EPR) to improve the internalization into cancer cells<sup>4</sup>.

Ferrocifen has been hypothesized to act via targeting the thioredoxin reductase (TrxR), a system responsible for thiol redox homeostasis and overexpressed in cancer cells, leading to an increased resistance<sup>5,6</sup>. This action might stem from TrxR displaying a selenocysteine residue at its C-terminal active site, which can be targeted by metal complexes. This project, along-side producing ferrocifen loaded nanoparticles, aims to verify and establish the mode of action of this active substance on TrxR, using different genetic and molecular experimental techniques.

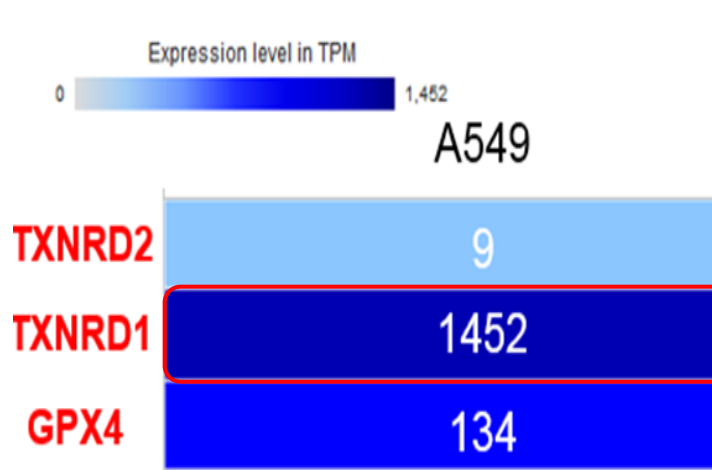
## 1. Formulation and characterization of the Lipid Nanocapsules (LNCs)



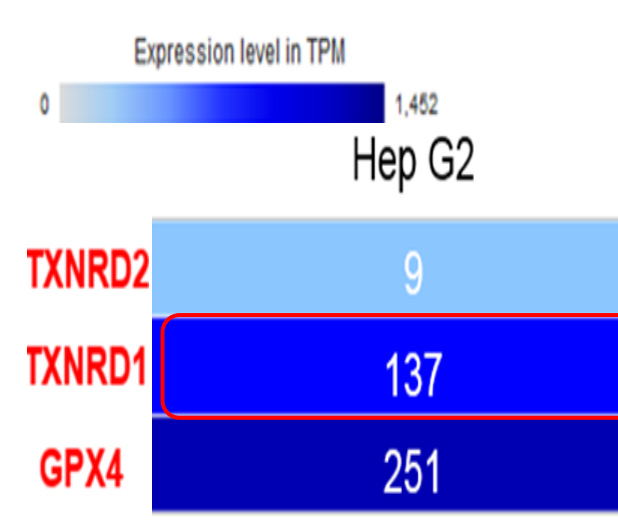
	Diameter (nm)	PDI	Zeta Potential (mV)
Blank LNC	53.2 ± 0.3	0.09 ± 0.01	-2.8 ± 0.5
Blank LNC-PEG	57.4 ± 0.3	0.09 ± 0.02	-20.3 ± 2.8
P15 LNC	51.0 ± 0.2	0.05 ± 0.01	16.2 ± 1.5
P15 LNC-PEG	55.5 ± 0.2	0.07 ± 0.01	-5.5 ± 0.7
P53 LNC	50.0 ± 0.3	0.02 ± 0.01	-0.5 ± 0.7
P53 LNC-PEG	56.0 ± 0.7	0.02 ± 0.01	-26.3 ± 0.5
P722 LNC	49.0 ± 0.1	0.06 ± 0.01	-2.5 ± 0.7
P722 LNC-PEG	52.4 ± 0.2	0.07 ± 0.09	-17.0 ± 0.8

## 2. Cytotoxicity studies via MTT

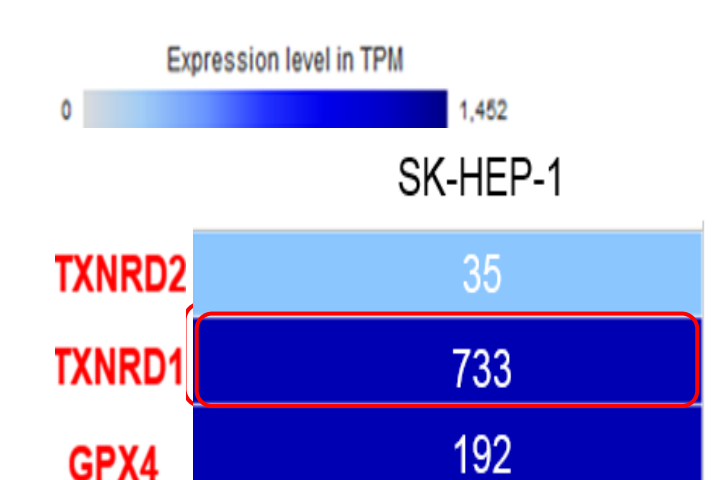
A549	IC <sub>50</sub> in μM							
	Auranofin	P15	P53	P722	Blank LNC-PEG	P15 LNC-PEG	P53 LNC-PEG	P722 LNC-PEG
4h	18	17	106	187	75	0.03	509	49
24h	7.3	6.7	10	184	10	47	17	6.2
48h	2.9	4.3	7.7	485	4.8	0.75	9	0.79
72h	3.6	1.69	1.55	189	6.95	0.76	4.3	0.3



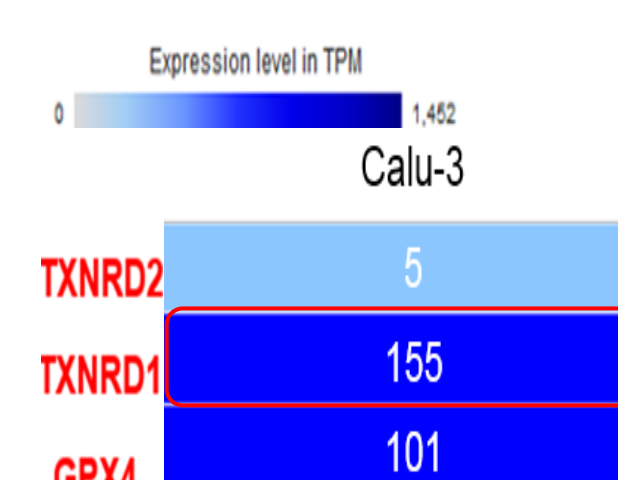
Hep G2	IC <sub>50</sub> in μM							
	Auranofin	P15	P53	P722	Blank LNC-PEG	P15 LNC-PEG	P53 LNC-PEG	P722 LNC-PEG
4h	8.8	18	97	89	85	126	1188	94
24h	3.18	1.86	9.1	72	12	14	13	20
48h	1.7	1.6	12	9.1	10	10	15	28
72h	6.4	1.8	9	4.8	10.7	6.3	6.9	28



SK-HEP-1	IC <sub>50</sub> in μM							
	Auranofin	P15	P53	P722	Blank LNC-PEG	P15 LNC-PEG	P53 LNC-PEG	P722 LNC-PEG
4h	4	21	182	93	19	97	108	103
24h	1.59	6.17	17	19	7.63	11	22	28
48h	1.54	13	14	19	6.34	11	22	29
72h	1.55	12	1.23	15	2.2	7.5	31	17



Calu-3	IC <sub>50</sub> in μM							
	Auranofin	P15	P53	P722	Blank LNC-PEG	P15 LNC-PEG	P53 LNC-PEG	P722 LNC-PEG
4h	12	19	93	93	122	183	79.86	14
24h	2.4	20	6.6	12.4	70	68.83	92	0.2
48h	1.7	6.6	0.7	3.8	20	11	14	6
72h	2.3	5.9	6.2	3.6	9.8	9.5	8.7	3.6



## Conclusion

- P722 LNC-PEG is the best acting ferrocifen formulation with the lowest IC<sub>50</sub> at 72 hours.
- Encapsulation of P722 in LNCs enhances its action starting from earlier time points.
- P722 LNC-PEG has a 630-fold increased activity after encapsulation into LNC
- P722 LNC-PEG has a 55-fold increased activity on HIGH compared to MEDIUM TrxR1 cell lines (A549 vs SKHEP-1).
- P722 LNC-PEG have an 63-fold increases activity on HIGH compared to LOW TrxR1 cell lines (A549 vs HepG2).

## Perspectives

- Annexin V / PI apoptosis studies via FACS
- Ferroptosis studies via MTT
- Lipid peroxidation studies via FACS
- Western blot to determine the expression of keys proteins
- QRT-PCR to determine the expression levels of keys genes
- In vivo* studies on PDX murine models
- Ex vivo* studies on tissues / organs extracted from PDX models

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