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# Targeted Chemotherapy via Folic Acid Decorated Nanomedicines

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## Abstract

The development of nanomedicines decorated with ligands specifically recognized by cancer cells is a promising strategy to get a selective location of the antitumor drug at tumor cells, increasing its efficacy and reducing adverse effects. One of the most interesting ligands is folic acid, whose α-type-receptors are over expressed in numerous kinds of carcinomas. Several folic acid nanomedicines such as nanoparticles, micelles and liposomes have shown to increase the efficacy of conventional anticancer drugs in gynecological carcinomas, becoming in engaging therapeutics tools in these malignances.

**Keywords:** Folic acid; Nanomedicine; Tumor targeting; ovarian cancer; Breast cancer; Cervix cancer

## Introduction

A selective localization of antineoplasic drugs at tumor cells level is highly desirable in chemotherapeutic treatments, to get a reduction of drug adverse effects and an improvement of therapeutic efficacy. The use, as carriers of antitumor drugs of nanomedicines (micelles, liposomes, dendrimers and nanoparticles among others) that are decorated with ligands that are selectively recognized by receptors over expressed in the membrane of cancer cells, is one of the most promising strategies to get a targeted chemotherapy [1,2]. In this sense, there are numerous molecules that are currently under investigation such as different carbohydrates, folic acid, biotin, transferrin, epidermal growth factor, antibodies, viral proteins or aptamers [3,4].

Folic acid is one of the most promising ligands due to: (i) the overexpression of folate receptor-α (FR-α) in numerous kinds of tumors including ovarian, breast, kidneys, lung, uterus, and colon carcinomas; showing folic acid a high binding affinity for these receptors ($K_d \sim 10^{10} M^{-1}$); (ii) its low immunogenicity, (iii) it is easy modify and (iv) its low cost [5,6].

This paper focuses on the use of folic acid decorated nanomedicines loaded with conventional anticancer drugs as targeted chemotherapy strategy in gynaecological cancers.

## Breast Cancer

Paclitaxel (PTX) is a common chemotherapeutic agent used in breast cancer treatments. Several authors have

shown that nanosystems loaded with placlitaxel enhance tumor cell sensitivity via folic acid targeting, increasing the cellular uptake of the drug. In this sense, cyclodextrin nanoparticles and liposomes decorated with folic acid and loaded with PTX significantly increased *in vitro* drug efficacy on ZR75-1 [6] and MCF-7 and MDA-MB-231 cells (FR-αpositive) respectively, decreasing $IC_{50}$ values. In the case of liposomes the $IC_{50}$ of folate decorated formulations were 2,2 and 11.5 times lower than non-decorated ones for MCF7 and MDA-MB-231 cells respectively. The more significant enhancement in MDA-MB-231 cells has been attributed to the major overexpression of FR-α [7]. Finally, folic acid functionalized micelles also improved the inhibition of MCF-7 cell proliferation, comparing to other PTX formulations. While the $IC_{50}$ of this cells after 72 hours of incubation for free PTX and non-targeted micelles were 14.01 and 11.78nM respectively, targeted micelles exhibited a significantly lower value of 6.61nM [8] (Table1). Folic acid conjugation also increased the uptake of lipids nanoparticles co-loaded with docetaxel (PTX analogue) and curcurmin in MCF-7 cells, improving anticancer efficacy. *In vivo* experiments in rats also demonstrated a less docetaxel accumulation in heart and kidney than conventional formulations, resulting in a toxicity diminution [9].

## Ovarian Cancer

Folic acid targeting has also shown to improve the efficacy of taxanes and other antineplasic drugs in ovarian cancer. Paclitaxel and cisplatin loaded nanogels functionalized with folic acid have reported an increase of the *in vitro* anticancer activity in A2780 cells (FR-α positive), comparing to non-functionalized formulations and being this improvement attributed to folic acid association. *In vivo* experiments in tumor xenograft mouse models also proved that these folate conjugated formulations, after intraperitoneal administration, were more effective [10]. Folic acid conjugated liposomes also increased the cytotoxic effect of carboplatin in IGROV1 cells, decreasing the $IC_{50}$ value from 40 to 13.1μM in free and encapsulated drug respectively. Finally, this effect has also been demonstrated *in vivo* in mouse models, showing an increase of the survival rate [11] (Table1).

| Carcinoma | Nanocarrier | Drug | Cell line | $IC_{50}$ | Reference |
|---|---|---|---|---|---|
| Breast | Cyclodextrin nanoparticles | Paclitaxel | ZR75-1 T-47D | NA | [6] |
| | Liposomes | Paclitaxel | MCF-7 | Free PTX=660.7 nM Liposomes= 214.1 nM FA-Liposomes=97.6 nM | [7] |
| | | | MDA-MB-231 | Free PTX=689.3 nM Liposomes= 183.1 nM FA-Liposomes=15.7 nM | |
| | Micelles | Paclitaxel | MCF-7 | Free PTX= 14.01nM Micelles=11.78nM FA-micelles= 6.61nM | [8] |
| | Lipids nanoparticles | Docetaxel Cucurmin | MCF-7 | NA | [9] |
| Ovarian | Nanogels | Paclitaxel Cisplatin | A2780 | Nanogel= 3.0 μM FA-nanogel= 1.4 μM | [10] |
| | Liposomes | Carboplatin | IGROV-1 | Free Carboplatin=40μM FA-Liposomes=13.1 μM | [11] |
| | Micelles | Paclitaxel | Hela | NA | [12] |
| Cervix | Gelatin nanoparticles | Cisplatin | Hela | Free cisplatin=38.4 μM Nanoparticles= 16.8 μM FA-Nanoparticles= 14.9 μM | [13] |

Table1: Effect of folic acid decorated (FA) nanomedicines in breast, ovarian and cervix carcinomas.
NA: non available.

## Cervix Cancer

Folic acid conjugated nanomedicines has also reported to increase the efficacy of paclitaxel and cisplatin in cervix cancer cells facilitating the intracellular uptake. *In vitro* studies in Hela cells (FR-α positive) have demonstrated that paclitaxel micelles [12] and gelatin nanoparticles loaded with cisplatin [13] and decorated with folic acid improve the inhibition of cell proliferation, increasing therapeutic efficacy. This inhibition improvement of folate decorated micelles of PTX was not observed in A459 lung adenocarcinoma cells (FR-α negative), showing a similar efficacy than non-targeted formulations and indicating that folic acid conjugation is the responsible of the enhancement of anticancer efficacy [13] (Table1).

## Conclusions

Folic acid decorated nanomedicines have shown to increase the efficacy of several conventional anticancer drugs, such as taxanes and platinum based treatments, in breast, ovarian and cervix tumors, malignances that overexpress folic acid receptors. This improvement is due to a major uptake by cancer cells, getting a more selective location at the tumor mass; increasing antitumor efficacy and decreasing their adverse effects. In spite of the promising therapeutic of these folate-nanocarriers, the most of these systems have only been tested *in vitro*, and further research is necessary to investigate their effect using in vivo models.

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