Anticancer prodrugs, the new way of using nanoparticles

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INTRODUCTION

- ✧ Cancer is a disease with a high mortality rate which breast cancer is considered the second one.
- ✧ There isn't a single-cure treatment due to the hallmarks of cancer.
- ✧ Treatments that are already on market have a lot of side effects causing damage to non-tumoral cells, cellular apoptosis.

→ New approach: *Prodrugs encapsulated in nanoparticles*

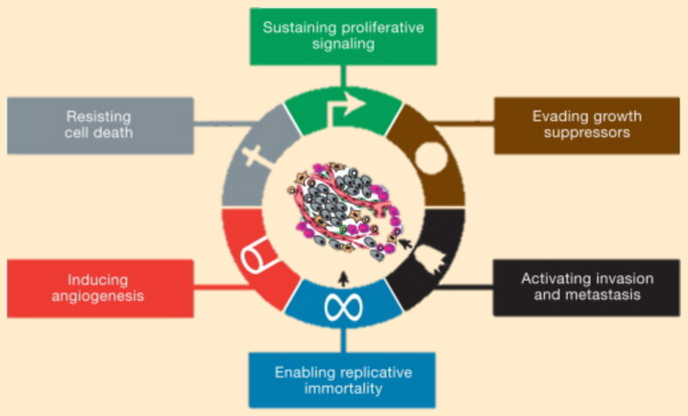


Figure 1. The hallmarks of cancer [1].

BREAST CANCER

Common characteristics

- ✧ Decrease of the pH → release of lactate.
- ✧ Higher temperature → faster metabolisms.
- ✧ EPR effect
  - → major permeability → Angiogenesis to decrease hypoxia.

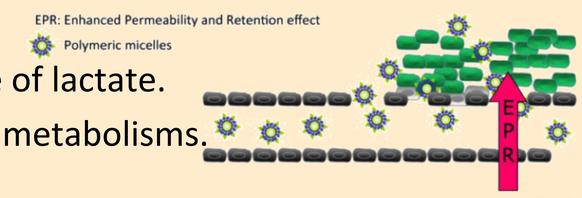


Figure 2. Changes in the surroundings leading to EPR effect[2].

Particular characteristics

- ✧ BRCA → tumor suppressor gene is mutated
- ✧ Her2/neu receptor → over-expressed

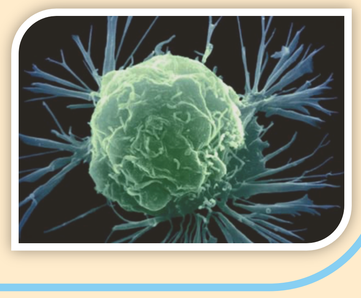


Figure 3. Morphology of breast cancer cell[3].

NANOBIOPARTICLES

Definition

It is a particle between 30 and 200nm in size for medical applications which is used to transport and release a drug.

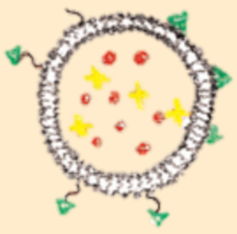


Figure 4. Scheme of a nanoparticle [4].

Objectives

To improve:
- ✧ Biodistribution
- ✧ Pharmakinetics

Components

- ✧ Liposomes
- ✧ PEG
- ✧ Target ligand
- ✧ (Pro)Drug

Advantages

Delivery	Surface	Loading	Release
✓Specific target ✓Transport into bilayers	✓No potential ✓No aggregation ✓ Minimize opsinization	✓ Incorporation method ✓ Absorption method	✓ Solubility ✓ Long-term action

CONCLUSIONS

Prodrugs encapsulated in nanoparticle are good for:
- ✧ Target-specific → EPR effect in the vessels of tumors surroundings.
  - → Interaction to Her2/neu of breast cancer cells.
- ✧ Activate the prodrug close to the tumor → acidic pH.
- ✧ Avoid toxic side effects to "normal" cells.
- ✧ Encapsulate hydrophobic and hydrophilic (pro)drugs.

To accomplish that, the nanoparticle has to be:
- ✧ Liposome covered with PEG to avoid opsinization.
- ✧ It can have a big size → max. 200 nm → EPR effect.
- ✧ Ligand of Her2/neu attached to surface of the NP.

PRODRUGS

Definition

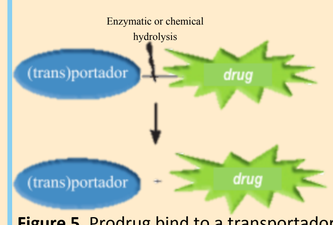
It is the precursor of a drug, administrated within an inactive form but through metabolic processes will be converted into the pharmacological molecule.

Advantages

- ✓ ↑ Solubility
- ✓ ↑ Absorption
- ✓ ↓ Metabolism
- ✓ Tissue specific

Classification

Binded to transporters



The lipophilic drug will be released for a better uptake and distribution.

Figure 5. Prodrug bind to a transportador [5].

Bioprecursors

Their activation is due to oxidation or reduction, among other situations.

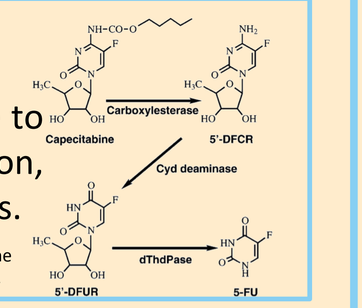


Figure 6. Activation of the capecitabine to 5-FU [6].

Molecular mechanism of prodrugs

They are different type of anticancer prodrugs:
- ✧ Antimetabolite → stop synthesis of DNA or blocking mRNA function.
- ✧ Antimitotic → Gemcitabine and Capecitabine
  - → Inhibit the depolymerization of microtubule in cell division
  - → Paclitaxel

Paclitaxel

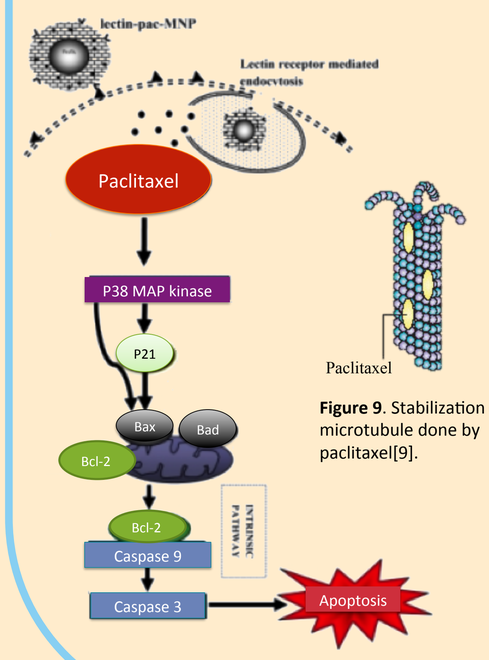


Figure 9. Stabilization of microtubule done by paclitaxel[9].

Figure 8. Molecular mechanism of paclitaxel [8].

Gemcitabine

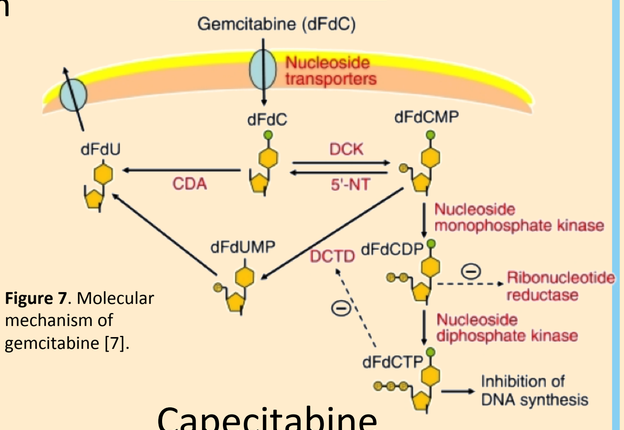


Figure 7. Molecular mechanism of gemcitabine [7].

Capecitabine

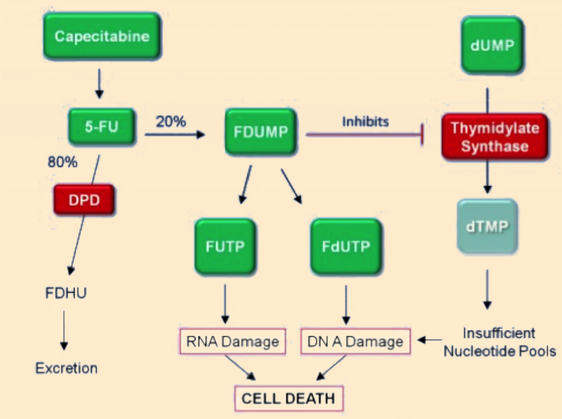


Figure 10. Molecular mechanism of capecitabine in the cell [10].

IMAGES REFERENCES

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