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# MULTIFUNCTIONAL NANOPARTICLES TO FIGHT HORMONE-RESISTANT PROSTATE CANCER

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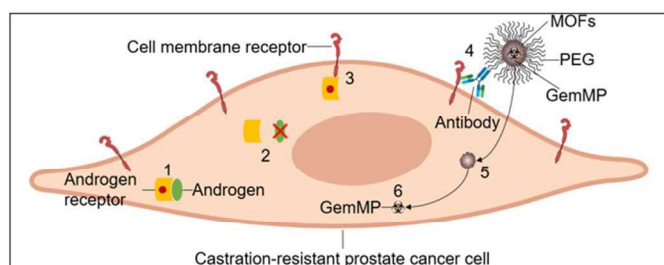
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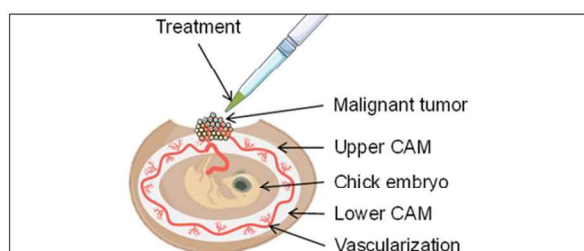
Androgen deprivation therapy, the standard treatment of prostate cancer, leads to the development of castration-resistant prostate cancer (CRPC) [1]. This can be partially explained by the overexpression of a specific cell membrane receptor [2]. Therefore, we aim to target this receptor to develop nanomedicines to combat CRPC. Our approach involves using Metal-Organic Frameworks (MOFs), known for their biodegradability and porous structure, allowing them to encapsulate a wide variety of drugs [3]. The goal of this work is to encapsulate gemcitabine-5'-monophosphate (GemMP), a potent but rapidly metabolized anticancer drug, within MOFs, to protect the drug, then coat the MOFs with a CRPC-specific targeting unit (fig.1). First, we coated the MOFs with PEG-based shells to enhance their stability and ability to evade the immune system. We proved that PEG stabilized and protected the MOFs in various solvents. We also showed that PEG@MOFs were five times less internalized than MOFs in immune cells. Similarly, MOFs internalization in cancer cells decreased two-fold with the PEG. Despite this, GemMP@PEG@MOFs were as efficient as GemMP@MOFs for cell viability impairment *in vitro*. Finally, we showed that both formulations promoted more than a two-fold decrease of tumor growth, which was not achieved with the free drug in the *in ovo* model (fig.2). Altogether, these results are evidence of the higher potential of encapsulated GemMP as a chemotherapeutic. The development of the CRPC-specific targeting unit should further help overcoming cancer resistance.

## References

[1] C. Parker et al. (2020), « Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up », *Ann. Oncol.* ; [2] T. Chandrasekar et al. (2015), « Mechanisms of resistance in castration-resistant prostate cancer (CRPC) », *Transl. Androl. Urol.* ; [3] P. Horcajada et al. (2010), « Porous metal-organic-framework nanoscale carriers as a potential platform for drug delivery and imaging », *Nat. Mater.*



**Figure 1. Graphical abstract.** 1. Androgen-dependent growth; 2. Androgen deprivation; 3. Growth in androgen-deprived conditions; 4. CRPC-targeting coated MOFs; 5. MOFs internalization in CRPC cells; 6. Drug release in cancer cells



**Figure 2. Schematic representation of *in ovo* experiment.** A window was opened in the eggshell to unravel the upper chorioallantoic membrane (CAM), a transparent and richly vascularized tissue growing around the chick embryo. Cancer cells are deposited to form a vascularized tumor within a few days. Treatments are administered after the tumor was formed.