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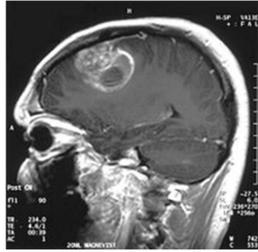
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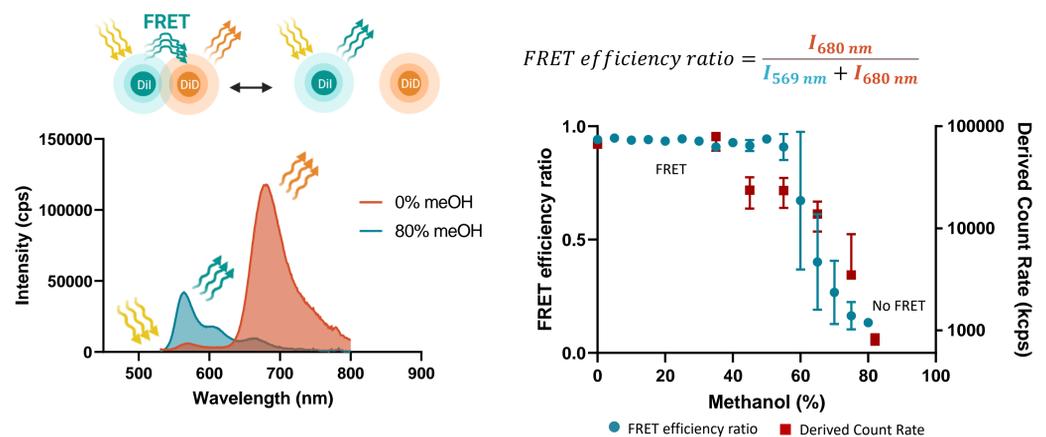
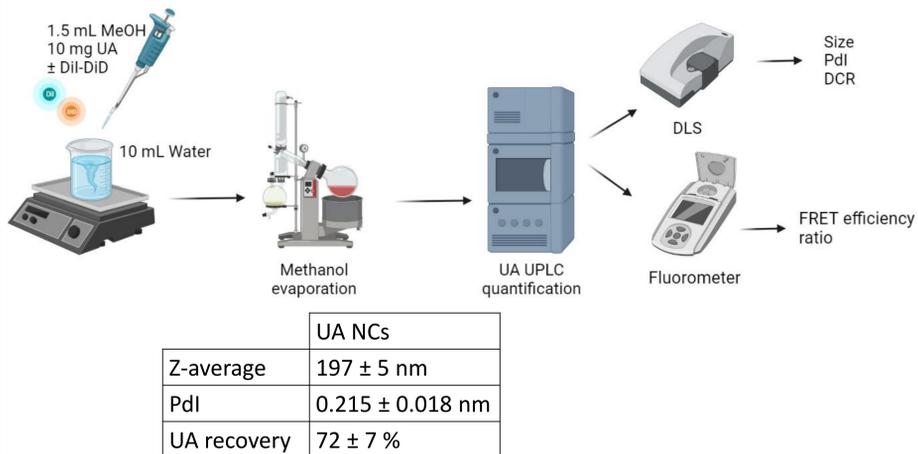
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Introduction



Glioblastoma (GBM) is the glioma with the highest grade (IV) according to the World Health Organization [1]. Despite it being a rather rare condition (6 cases for 100,000) [2], the survival prognosis is very low. The overall median survival is of only 15 months after treatment initiation [3]. The chemotherapy agent used in the gold standard treatment (Stupp protocol) is temozolomide (TMZ): an alkylating agent. TMZ adds methyl adducts on the ⁶O position of guanines [4,5]. The ⁶O-methylguanine-DNA-methyltransferase (MGMT) is a highly conserved protein involved in DNA repair by removing alkyl groups from the ⁶O position of guanines [6]. The mechanism of action of MGMT thus impairs the efficacy of a TMZ treatment and the outcome of the Stupp protocol is then dependent on the expression of MGMT. The median survival of patients with a methylated MGMT promoter (low MGMT expression) treated with TMZ is higher than for patients with a non-methylated MGMT promoter (high MGMT expression) [7,8]. The strategy used in this study is to use a MGMT inhibitor, ursolic acid (UA) to restore TMZ efficacy for patients with non-methylated MGMT promoter. UA has been formulated in nanocrystals (NCs) for which their destabilization and internalization has been observed using FRET (Fluorescence Resonance Energy Transfer) inducing dyes and the capacity of the UA NCs to inhibit the expression of MGMT and potentiate TMZ efficacy has been studied.

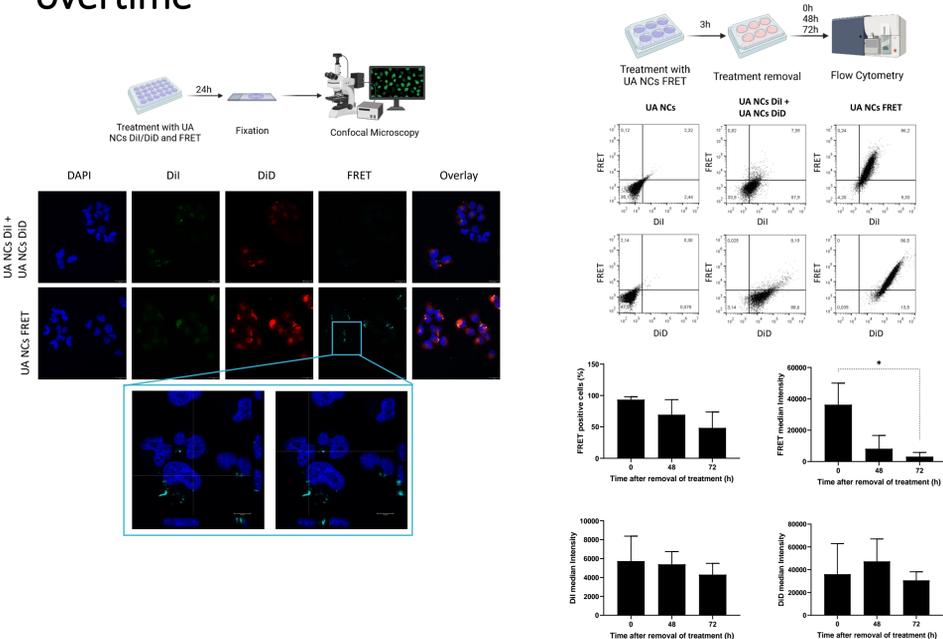
Ursolic acid nanocrystals integrity can be followed with FRET



→ UA NCs formulation was successful and NCs are approximately 200 nm wide and around 70 % of the initial UA mass was recovered

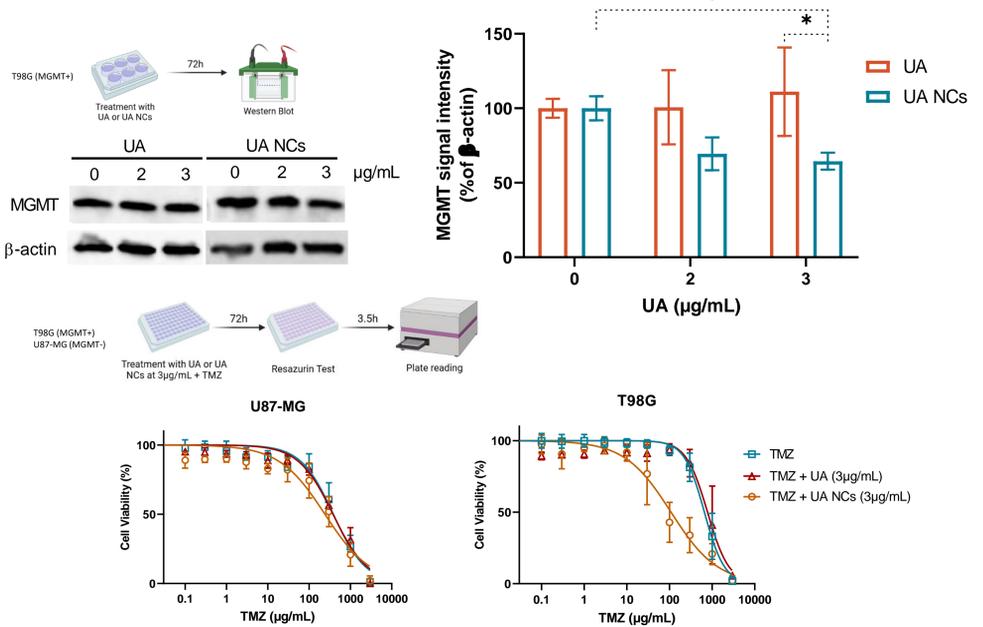
→ UA NCs are able to hold a FRET signal and this signal disappears when the NCs are solubilized. The FRET signal allows visualization of the integrity of the UA NCs.

Ursolic acid nanocrystals are internalized and degrade overtime



→ UA NCs are internalized in T98G cells and degrade over time as FRET signal disappears after approximately 72h of treatment

Ursolic acid nanocrystals resensitize temozolomide-resistant cells



→ UA NCs are better at reducing MGMT expression and thus potentiating the effect of temozolomide in MGMT expressing cells than unimolecular UA

Conclusion

UA has been formulated into 200 nm nanocrystals using an antisolvent crystallization method with a recovery of approximately 70% of the initial UA mass. FRET inducing dyes (DII and DiD) were successfully added to the UA NCs formulation. The measurement of this FRET signal allowed for the visualization of the UA NCs integrity. After 24 hours of contact with MGMT-positive cells, UA NCs were internalized and still intact, but were destabilized after around 72h. UA NCs were able to decrease the protein expression of MGMT and potentiate the efficacy of TMZ more than unimolecular UA.

References:

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Acknowledgements:

