

Potential And Challenges Of Titanium Nitride Nanoparticles For Glioblastoma Photothermal Therapy

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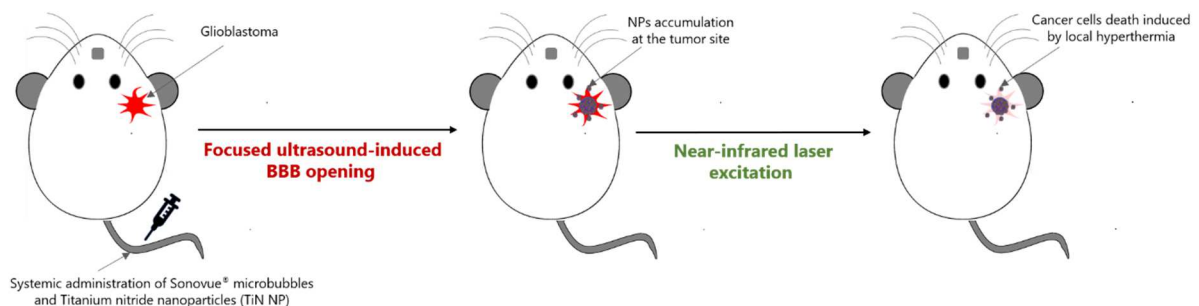
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Introduction: Glioblastoma (GBM) is the most common and aggressive brain tumor in adults. Despite aggressive standard of care treatment, the prognosis for GBM patients is poor and finding a long-term beneficial treatment is an unsolved medical need¹. Recently, some studies have reported that photothermal therapy induced by metal nanoparticles could represent a promising approach to treat various types of cancer, including GBM². This strategy consists in inducing rapid temperature elevations in the tumor tissues while minimizing thermal diffusion in the surrounding tissues, to selectively kill cancer cells.

Aim: In this work, our aim is to evaluate if Titanium Nitride Nanoparticles (TiN NP) can be systemically administered, accumulate in the brain at the tumor site through ultrasound-mediated (US) blood-brain barrier (BBB) opening and induce local hyperthermia under near-infrared (NIR) laser excitation to reduce tumor growth *in vitro* and *in vivo*.



Methods & results: Ultrapure 30 nm TiN NP (transmission electron microscopy analysis) were synthesized by laser ablation in aqueous medium, and they presented low cytotoxicity and excellent cellular uptake *in vitro*. Following near-infrared (NIR) laser excitation, TiN NP showed photothermal cytotoxic efficacy on U87-MG spheroids³. *In vivo*, TiN NP presented good blood stability after systemic administration in healthy mice (drug quantification by inductively coupled plasma mass spectrometry). Single spot localized US opening led to a significant increase in Ti concentration in the selected brain region after systemic administration of TiN NP. Efficacy studies on a subcutaneous U87-MG GBM tumor model showed that intratumorally administered TiN NP followed by 10 min NIR irradiation induced local heating (determined by photoacoustic monitoring). However, no delay in tumor growth was observed in these conditions.

Conclusion: GBM photothermal therapy via systemically delivered TiN NP relies on the combination of several techniques that needs to be singularly optimized before combination: US-mediated BBB opening to accumulate TiN NP into the tumor, NIR-laser irradiation to increase the temperature locally and kill tumor cells, photoacoustic thermometry to monitor the temperature variations *in situ*.

Although TiN NP showed to be promising tools for photothermal therapy *in vitro*, further studies are ongoing to find the optimal conditions to confirm this innovative photothermal therapy approach *in vivo*.

¹ Stupp *et al. Lancet Oncol* (2009) 10(5): 459-66

² Madsten *et al. Ann Biomed Eng* (2012) 40(2): 507–515

³ Popov *et al. Sci Rep* (2019) In press

Learning objectives:

- Development of a unique platform for US BBB opening, photothermal therapy and photoacoustic thermal monitoring
- Optimization of the TiN NP formulation and experimental setup to address *in vivo* challenges
- Define the limiting steps of the project and optimize them separately before combining them