Glioblastoma (GB) is the most aggressive primary tumor of the central nervous system, with a 5-year survival rate of approximately 5.7%. GB is characterized by resistance to conventional radio- and chemotherapy and by diffuse invasiveness that precludes complete surgical resection. Furthermore, its localization beyond the blood brain barrier (BBB) limits drug penetration, making GB a cancer of unmet need that urgently requires new therapeutic interventions to improve patient survival. Recent data indicate that GB treatment might be improved by innovative strategies of drug delivery able to ensure high concentration of therapeutic drugs at the site of the tumor. This would indeed allow to reach and eliminate infiltrating cells, while lowering systemic and organ toxicity. A number of studies demonstrated the requirement of Hedgehog-GLI (HH) pathway in GB growth, stem-like cell (GSC) self-renewal, invasion and chemoresistance. Importantly, inhibition of HH signaling decreases expression of O6-methylguanine DNA methyltransferase (MGMT) and restores sensitivity to temozolomide (TMZ), the standard of care for GB.

The objective of this project is to develop a novel drug delivery approach against GB, using a locoregional treatment with a biocompatible gel containing entrapped TMZ combined with two different types of anti-cancer drugs targeting the GLI transcription factors, the final effectors of the HH pathway.

In detail the following activities are forecasted

- Nuclear magnetic resonance (NMR) 1H- and 13C- will be used for structural characterization and to check the good success of the chemical purity and coupling reaction.
- Structure and presence of organic backbone and various functional groups also in the final nanocarriers will be confirmed with a FT-IR analysis and CHN-elemental analysis.
- All the nano-microcarriers will be largely investigated especially in size, stability in buffered solutions, and stability in time: DLS (dynamic light scattering) will be used to determine size together with the PDI (polydispersity index).
- Morphology of nanoparticles will be explore using combined techniques like AFM (atomic force microscopy) and SEM (scanning electron microscopy) including an EDS (Energy-dispersive X-ray spectroscopy) probe to check the atomic composition, part of this will be carried out in collaboration.
- Uv-Vis (ultraviolet-visible spectrophotometric) analysis will be performed to check the absorption spectra and maximum wavelength of the biomolecules. This technique coupled with colorimetric analytical tests can be also applied to biomolecules determination in the nanocarriers after coupling reaction.
- TGA (termo-gravimetric analysis) or DSC (differential scanning calorimetry) will be used to investigate the final composition of the metal-loaded nanoparticles in terms of ratio between metal phase and polymer one.