

Glioblastoma treated with Pt/TiO₂ -1% Functionalized Bionanocatalyst

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ABSTRACT

This research paper presents the clinical case of a 25-year-old male patient diagnosed with glioblastoma. This work is presented as a brief report because it is one of the first clinical cases in which a bionanocatalyst has been used for therapeutic purposes. Unlike studies published up to 2025, which focused on developing nanoparticles for the controlled release of chemotherapy (especially alkylating agents) or on combining temozolomide (TMZ) with other drugs, this work proposes a selective alternative that allows for the destruction of the tumor mass through the catalytic cleavage of DNA bonds without inducing toxicity.

The NPt bionanocatalyst is notable for its high biocompatibility (LD₅₀ = 17 mg/ mL). It consists of 1% platinum, the active metal, supported on titanium dioxide via a sol-gel synthesis that achieves complete dispersion of the platinum within the titanium dioxide, followed by functionalization. Thanks to the functionalized molecules on its surface, the catalyst targets only cancer cells, not healthy cells, as its mechanism of action involves the entry of the nanoparticle through receptor-mediated endocytosis. After the bionanocatalyst is released from the cell vacuole into the cytoplasm, some molecules target the mitochondria and attack mitochondrial DNA, while others target the nucleus to break the bonds of nuclear DNA.

Keywords : GB ; Platinum nanoparticles ; titania, sol-gel ; LD₅₀ ; MRI; SEM; MET

INTRODUCTION

Glioblastoma is the most aggressive and lethal primary tumor of the central nervous system (CNS) in adults, occurring predominantly in the supratentorial region, most frequently affecting the frontal, temporal, and parietal lobes.^[1] Epidemiologically, this type of neoplasm represents 14.5% of all CNS tumors and almost half (48.6%) of all malignant tumors detected.^[2] According to the World Health Organization (WHO), in 2021, the term **glioblastoma (GB)** was defined exclusively for wild-type (non-mutated) IDH tumors, which are classified as the most aggressive grade IV subtype.^[3]

Biologically, GB is characterized by excessive cell growth, high invasiveness, and a strong affinity for carbohydrates, lipids, peptides, nucleotides, and genes, which allows it to regenerate after treatment. Furthermore, it exhibits resistance to rejection by virtually any conventional treatment.^[4] Despite efforts in clinical and biotechnological research, progress has been limited, as patients undergoing conventional treatment (surgery, radiotherapy, chemotherapy) have a survival rate of less than 6 months.^[1,5]

The heterogeneity of glioblastoma (GB) and its ability to infiltrate any part of the brain presents a challenge for its treatment. To understand the complexity of these tumors, desorption electrospray ionization mass spectrometry (DESI-MS) was used to spatially profile the chemical composition of 36 tumors.^[6] Although it initially allowed for an understanding of the cerebral heterogeneity among histological grades, it also suggested negligible variation. Recent studies have highlighted the complexity of lipid profiles in high-grade gliomas. Their analysis consisted of examining the liposomes of 99 GB samples. The authors analyzed 582 lipid species from 75 tumors and compared them in detail with seven normal brain tissues. The results revealed considerable differences in more than 500 of these species, confirming that the composition Lipid levels differ according to the isocitrate dehydrogenase (IDH) status and the molecular subtype of the tumor.^[4,7]

CLINICAL CASE

A 25-year-old male patient, with no comorbidities, presented to the emergency department of the National Institute of Neurology and Neurosurgery (INNN) with a four-month history of holocranial headache, refractory to analgesics and opioids, accompanied by nausea, inattention, irritability, and bradypsychia. The condition progressed with right hemiparesis and hypoesthesia, motor aphasia, and amnesia, culminating in a focal seizure with secondary generalization. Neurological examination confirmed right pyramidal syndrome, bradylalia, and altered mental status.

Brain magnetic resonance imaging (MRI) in T2 and FLAIR sequences revealed a large, hyperintense, infiltrative intra-axial lesion in the left hemisphere, with severe vasogenic edema, absence of calcifications, and a marked mass effect that shifted the midline. A stereotactic biopsy and histopathological examination demonstrated proliferation of atypical glial cells, pleomorphism, high mitotic activity, necrosis, and microvascular proliferation. Positive immunohistochemistry for GFAP and an elevated Ki-67 index confirmed the diagnosis of glioblastoma (WHO Grade 4).

Treatment was initiated with dexamethasone, anticonvulsants, and combination therapy with surgical resection, followed by the standard Stupp protocol (radiotherapy 60 Gy administered in 30 fractions over 6 weeks and temozolomide (TMZ)), supplemented with intravenous bevacizumab. Two months later, the patient was readmitted due to tumor recurrence associated with obstructive hydrocephalus; an emergency decompressive craniotomy with placement of a ventriculoperitoneal shunt was performed.

Given the tumor's progression to an inoperable stage, a new alternative was chosen using a platinum/titanium dioxide bionanocatalyst. This proposal was supported by preclinical phases and previous clinical use at the INNN and the Children's Hospital of Mexico (with approximately 50 patients treated), where the bionanocatalyst induces the selective catalytic cleavage of CC, CN, and CO bonds in mitochondrial and nuclear DNA within the tumor.

The first surgical intervention for the application of nanoparticles was performed by craniotomy, where a tumor resection was performed to subsequently perform the local infiltration of NPt in the brain bed with a perilesional safety margin of 2 cm to prevent cell proliferation .

HISTOLOGY

Gliomas are subdivided into astrocytoma, oligodendroglioma, or glioblastoma based on two molecular markers: isocitrate dehydrogenase (IDH) and 1p/19q codeletion . Tumors with IDH mutations exhibit elevated levels of 2-hydroxyglutarate (2-HG) and reduced production of nicotinamide adenine dinucleotide phosphate, which can lead to increased histone methylation and DNA hypermethylation . Elevated 2-HG levels can also result in local immune responses and glioma-induced epilepsy.^[8]

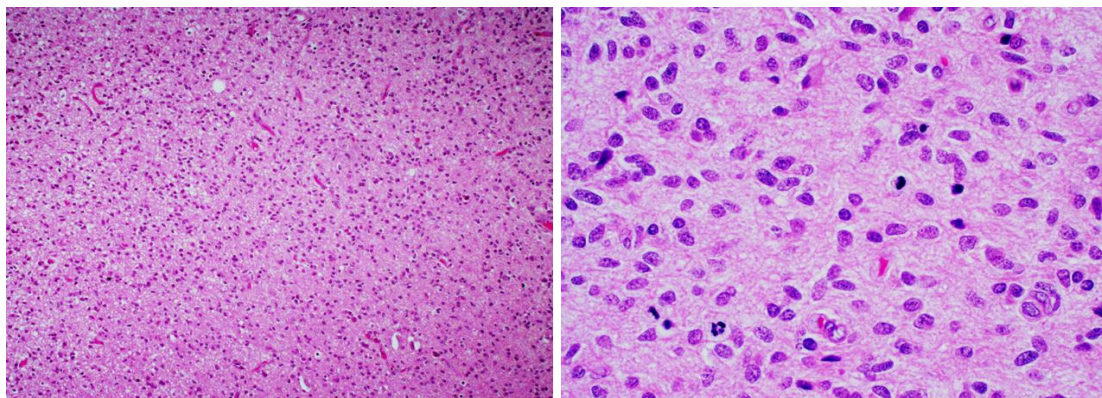


Figure 1: Hematoxylin and eosin staining of a 25-year-old patient with a clinical diagnosis of high-grade malignant glial tumor: glioblastoma.

Microscopic examination revealed that the tumor is a malignant glial neoplasm, a cancer that originates in the supporting cells of the central nervous system, known as glial cells. It exhibited a particular characteristic: high cellularity, indicating a large number of tumor cells in the same area and reflecting accelerated growth of the neoplastic tissue.

The cells also exhibited marked pleomorphism (variability in size and shape). These alterations demonstrate that the cells have lost their normal morphology and reflect genetic instability, a characteristic of malignant tumors. The WHO uses high mitotic activity as a parameter to classify CNS tumors as high-grade. This means that a large number of cells were undergoing mitosis, and the more this process is observed, the faster the tumor grows.

Areas of tumor necrosis were identified; these are regions where cells die because tumor growth was so rapid that the supply of oxygen and nutrients became insufficient. Ellison et al. (2020) explain that the simultaneous presence of necrosis and high mitotic activity reflects rapid cell proliferation, which is generally associated with a worse prognosis and a higher probability of recurrence after treatment.^[9,10]

Magnetic Resonance Imaging

In **Figure 2A**, the magnetic resonance imaging (MRI) scan reveals a coronal T2-weighted section showing a hyperintense intra-axial lesion in the left temporal lobe with poorly defined margins and infiltration of the adjacent brain parenchyma. Significant perilesional vasogenic edema is observed, with necrotic areas, possible

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cysts, and hemorrhage. Figure 2B shows an axial T2-weighted sequence, where a marked mass effect is evident, with compression of the ipsilateral lateral ventricle, distortion of the ventricular anatomy, and contralateral midline shift, as well as blurring of the cortical sulci—findings suggestive of secondary intracranial hypertension.

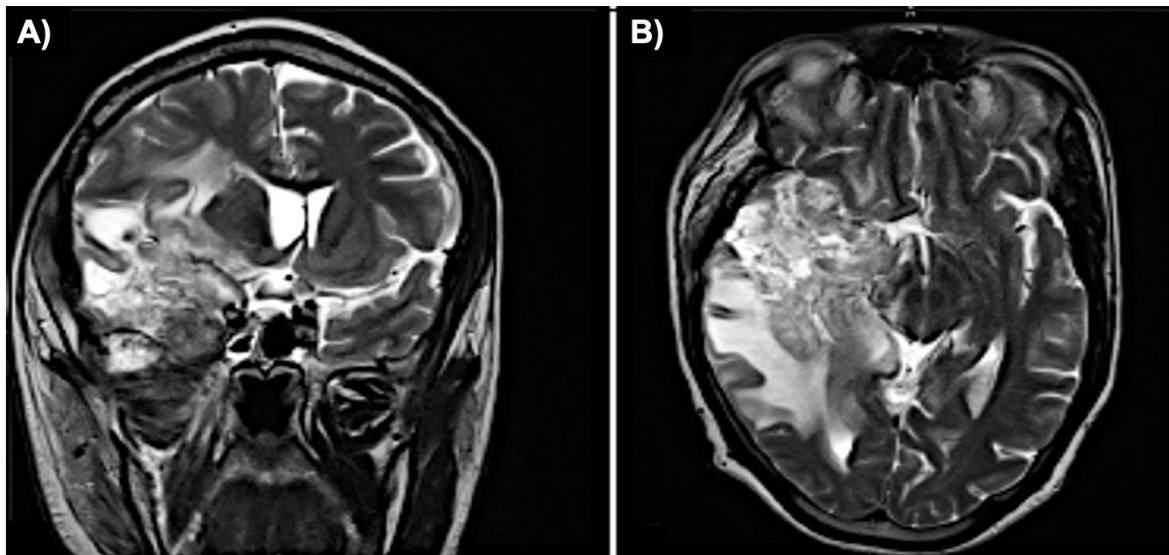


Figure 2: Magnetic resonance imaging (MRI) coronal (A) and axial (B) views of the tumor in T2-weighted sequences.

Tumor heterogeneity, both intertumoral and intratumoral, allows for the coexistence of multiple cell subpopulations with varying resistance capacities. When clinically evaluating the patient, this variability can be analyzed from a spatial perspective (sampling in a single surgical procedure) or a longitudinal perspective (differences between the primary tumor and its recurrences).^[11-13] This phenotypic plasticity is driven by glioblastoma stem cells (GSCs), which are responsible for resistance to conventional therapies and recurrence.

Although current diagnosis relies on clinical-radiological correlation, histopathology, and molecular profiling (IDH status and MGMT methylation), scanning electron microscopy (SEM) studies have identified calcium carbonate (CaCO_3) deposits in tumor tissue. The discovery of these microcalcifications opens a new avenue of research as a potential bioinorganic biomarker for the diagnosis of high-grade neoplasms and other pathologies.

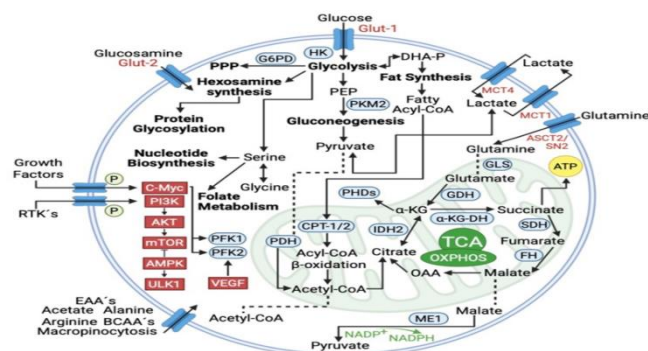


Figure 3: Overview of central metabolic pathways and regulatory interactions in cancer cells. The diagram illustrates the uptake and intracellular flow of key nutrients, primarily glucose, glutamine, essential amino acids,

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and acetate, as well as their integration into the major catabolic and anabolic pathways that support cancer cell growth.

Another fundamental aspect in characterizing glioblastoma is its intratumoral heterogeneity, which allows for the coexistence of multiple cell subpopulations with varying resistance capabilities. This plasticity is largely due to glioblastoma stem cells (GSCs), which possess self-renewal capacity and are responsible for tumor recurrence and resistance to conventional chemotherapy. Diagnosis is generally based on clinical suspicion, imaging studies, histology, and molecular biology. However, recent findings using scanning electron microscopy (SEM) have identified solid deposits of calcium carbonate (CaCO_3) in the tumor tissue, which could serve as a novel marker for the early diagnosis of various neurological pathologies.

MATERIALS AND METHODS

The synthesis of the Pt/TiO₂ nanomaterial was carried out using the Sol-gel method, following the standardization parameters described by patent WO 2019/017723 A2. Using titanium butoxide (Sigma-Aldrich, 97%) as a precursor of the titanium dioxide (TiO₂) matrix and acetylacetone (Sigma-Aldrich, 99%) as a solvent. acetylacetonate (Sigma-Aldrich,) was dissolved in the reaction mixture until a final platinum concentration of 1 mol% was reached. Furthermore, to enhance selectivity, functionalizing agents were added to create an analogy with cells. Finally, the resulting gel was subjected to a vacuum drying process, yielding the dry nanoparticles.

The patient underwent surgery for the first time, with the placement of 1 g of nanoparticles. A year later, because the GB tumor had grown back, the patient underwent surgery once again to impregnate the tumor with 2 g of nanoparticles.

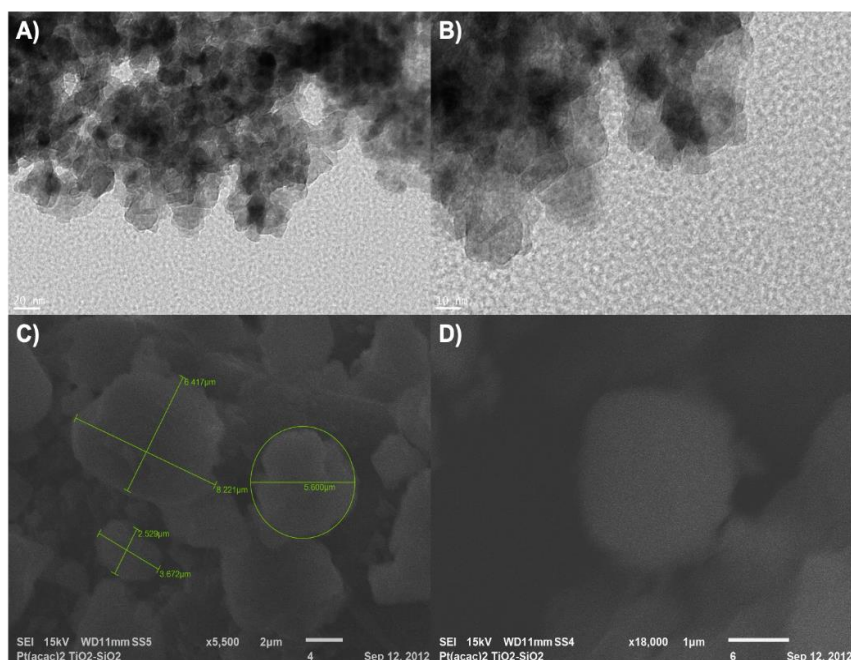
RESULTS AND DISCUSSION

Figure 4: Electron microscopy. A and B) TEM. C and D) SEM

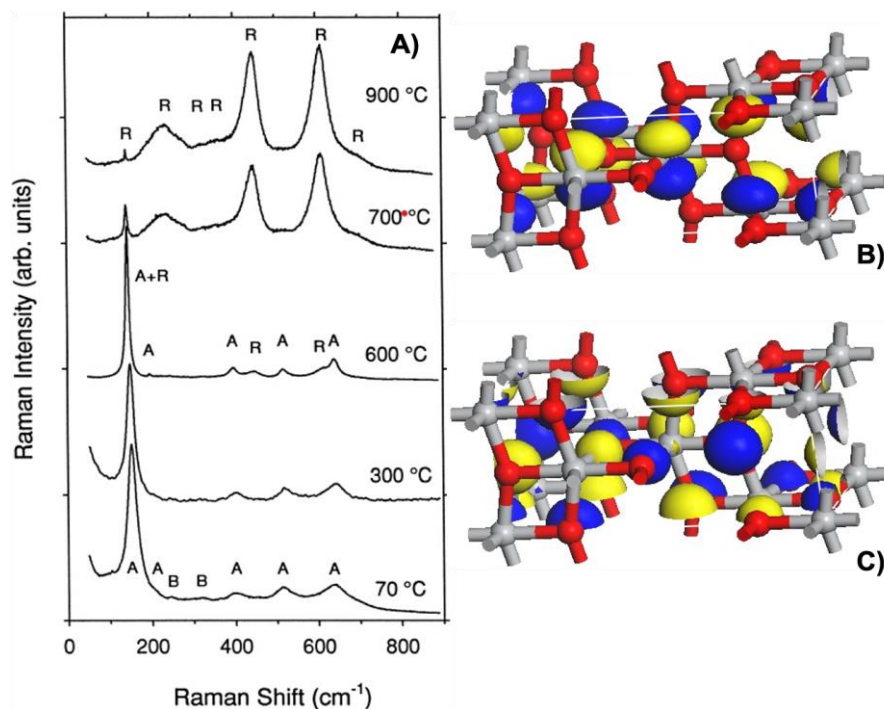


Figure 5: A) Raman Spectroscopy. Raman spectra of Pt/TiO₂ powders obtained using H₂SO₄ as a catalyst after different annealing temperatures. B and C) The peak nomenclature is as follows: A = anatase, B = brookite, R = rutile.

The Raman spectroscopy results of the dry gel obtained with HCl (Figure 5) showed that the bionanocatalyst is composed of anatase and is differentiated by the presence of broader bands. X-ray diffraction (XRD) revealed a minimal brookite content (13%). Changes in the material were observed as the annealing temperature increased; rutile appeared at 400°C and was obtained almost in its pure form at 800°C. These results are consistent with the XRD and infrared (IR) absorption measurements. When using NPt in brain tumors, it is necessary for anatase to be present in the majority of the sample, as the other two phases are not active enough to reach nuclear and mitochondrial DNA.^[7,8,11,12,]

The Raman spectra of the dry gel, obtained with acetic acid as a catalyst (pH 5), are similar to those obtained with HCl, but do not exhibit the characteristics of brookite. Anatase was the only crystalline phase present up to 700 °C. The width of the Raman bands decreased with increasing temperature, as observed with HCl. At 800 °C, a mixed phase of anatase and rutile was observed, while at 900 °C, rutile was the predominant phase. This represents a significant difference compared to the samples prepared with hydrochloric acid, where a small amount of brookite was detected. The absence of this phase indicates that acetic acid favors a more selective crystallization towards anatase.^[12,13] Previous published studies indicate that maintaining the anatase phase is essential to preserve the catalytic activity of Pt/ TiO₂ bionanocatalysts.

The dry gel obtained with oxalic acid as a catalyst exhibited a complex Raman spectrum that could not be attributed to a TiO₂ phase, although it is likely due to oxalic acid coordination compounds; the bonds between oxalic acid and titanium are stronger than those produced by acetic acid. Consequently, the material requires higher temperatures to completely remove organic residues by pyrolysis. Between 400 °C and 900 °C, only anatase was detected in the Raman spectra. The only difference between these spectra was a decrease in

bandwidth as the treatment temperature increased. No trace of the rutile phase was detected at any temperature.

[9-14]

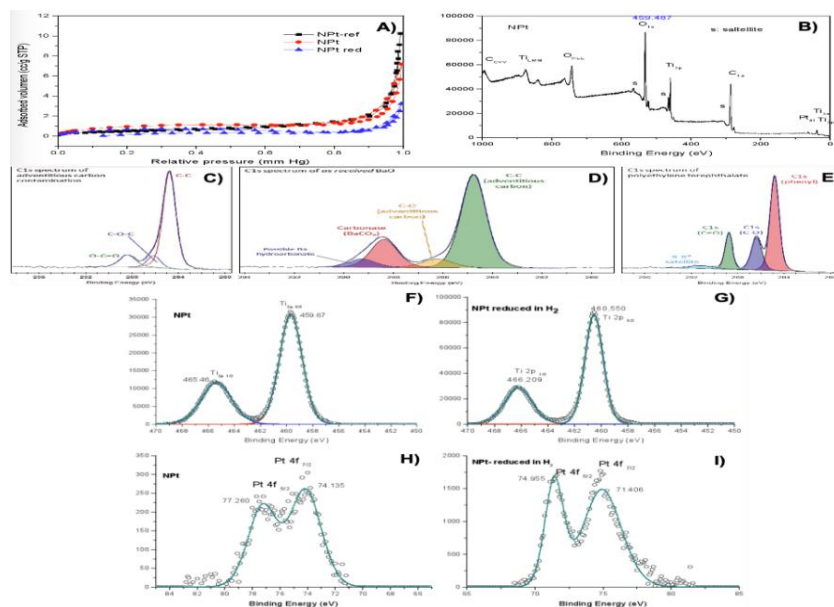


Figure 6: XPS. A) N₂ adsorption-desorption isotherms of NPt and reference NPt. B) Complete XPS spectrum of NPt. C, D, E) Interpretation of the bond energy in eV of Ti 2p_{1/2} and Ti 2p_{3/2} of the different C-C bonds. F) Ti spectra obtained from NPt. G) Ti from the same sample reduced in H₂. H) Bond energy in eV of Pt 4f V. I) Same sample reduced in H₂.

REACTION MECHANISM

The breaking of the C-C bond, which involves hydrogenolysis, occurs with a supported platinum catalyst. Compared to petroleum hydrocracking, this process must be carried out at temperatures above 300 °C; however, in the breaking of this bond in the DNA nitrogenous base cycle, the bionanocatalyst (BNC) used has a very high hydrogen concentration in its structure.

As a first step, adsorption followed by dehydrogenation takes place: the nitrogenous bases come into contact with the functionalized Pt/TiO₂ nanocatalyst, and the network subsequently dehydrogenates them. The CC cleavage site of the ring is protonated, due to the presence of Brønsted and Lewis acid sites. As the final step of the mechanism, the metal site is hydrogenated, the carbocations migrate and capture H⁺ from the metal, at which point the breaking of the CC bond is imminent.

When CO bond cleavage occurs, metal catalysts supported on solid acid are required. The most suitable metals for this process are platinum and palladium supported on silica, magnesia, titanium dioxide, or zirconia. The BNC is functionalized Pt/TiO₂, and the reaction proceeds as follows: The Pt must interact with the aromatic ring of the nitrogenous bases. When the Pt/TiO₂ comes into contact with them, the ring begins to activate, becoming more susceptible to changes (losing stability). Subsequently, the Brønsted and Lowry acidic sites become

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involved, dehydrating the adenine, guanine, cytosine, thymine, and uracil, ultimately producing a hydrogenolysis reaction. In this reaction, the carbocations accept an H^+ ion from the sulphur-containing bionanocatalyst, thus breaking the carbon-oxygen bond.

Upon contact with DNA, BNC hydrogenates the aromatic ring, resulting in the breaking of double bonds, producing the following chemical reactions. Dehydrogenation, hydrogenation, protonation carbocation, isomerization and cleavage/ β cleavage forming a secondary carbocation.

The hydrogens needed for saturation come from the hydrogenated NPt network, by hydrogen transfer: $[MH] + R/R^+ \rightarrow M + RH$ (hydrogen saturation, radicals and carbocations). [10,11,14,15,]

Nanoparticles are approximately 500 times smaller than a cell. They enter cells via receptor-mediated endocytosis, penetrate the mitochondria, destroy mitochondrial DNA, and then use the energy to migrate to the nucleus. However, they do not interact with healthy cells; healthy cells have been observed to repel nanoparticles due to differences in their receptors, which generate electrostatic repulsion.

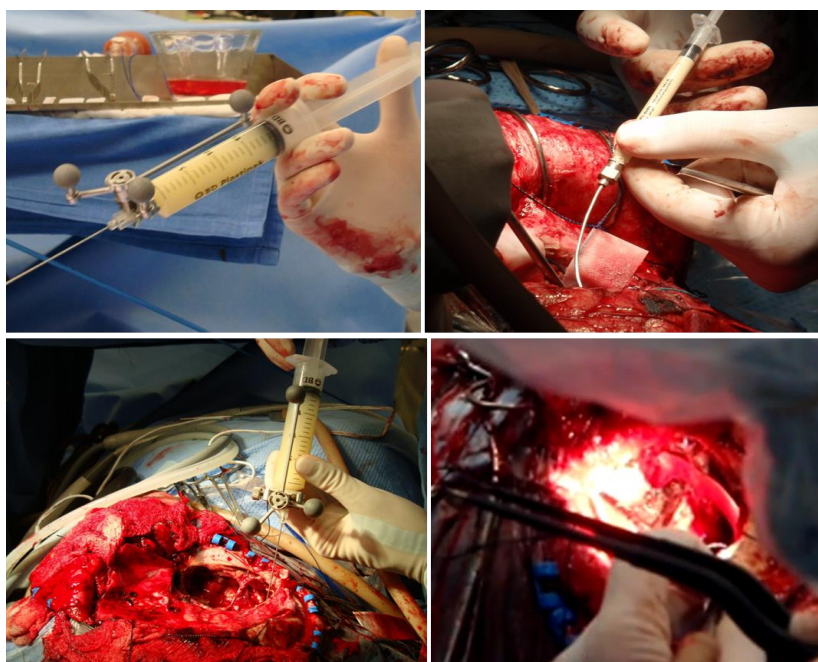


Figure 7: First surgery to impregnate the brain bed with the NPt bionanocatalyst.

The current standard treatment, known as the Stupp protocol, consists of maximal safe surgical resection, followed by concomitant radiotherapy with the alkylating agent TMZ and maintenance chemotherapy with the same drug. The efficacy of TMZ is strongly influenced by the methylation status of the MGMT gene promoter; when methylated, the tumor cell's ability to repair drug-induced DNA damage is reduced, significantly improving patient survival. However, more than 50% of patients do not benefit from this treatment due to acquired or intrinsic resistance mechanisms. The future of glioblastoma management is geared toward precision medicine and advanced immunotherapy. Emerging strategies include personalized neoantigen vaccines, CAR-T cell therapy tailored to recognize specific markers such as EGFRvIII or IL-13R $\alpha 2$, and the use of oncolytic viruses to induce immunogenic cell death. Furthermore, the implementation of liquid biopsy to detect

circulating tumour DNA and the use of artificial intelligence in mathematical models promise to improve early detection and monitoring of treatment response in a minimally invasive way.^[16]

Given this scenario, new therapies based on catalytic nanomedicine are emerging, including platinum bionanocatalysts of approximately 5-10 nm, which are implanted directly into the tumour bed using stereotactic surgery to preserve neurological function. This approach is advantageous because it avoids one of the major side effects of traditional therapies: systemic side effects. These agents selectively penetrate cancer cells via endocytosis and cause genotoxicity by breaking chemical bonds (lyase activity) in nuclear and mitochondrial DNA, reducing activation energy, disrupting vital energy processes in tumor cells (such as the Warburg effect), and activating programmed cell death (apoptosis). Unlike classic nanoparticle-based approaches in which chemotherapeutic drugs are placed in carriers to promote localized, controlled drug release, this case study aims to exemplify a therapy that differs drastically by not using a chemotherapeutic agent to target the tumour. This bionanocatalyst destroys the tumour directly by targeting the nitrogenous bases of DNA in the nuclei of cancer cells in a localized and selective manner, breaking bonds and lowering the activation energy. In this way, maximum elimination of tumour tissue is promoted, preserving healthy cells and neutralizing the harmful effects of traditional chemotherapy and radiotherapy on adjacent tissue.^[17-20]

CONCLUSION

New therapies using nanoparticles have marked a turning point in nanomedicine. However, they still rely on chemotherapeutic drugs delivered directly to the tumor. Bionanocatalysts can lower the activation energy to selectively break the bonds of nitrogenous bases in mitochondrial and nuclear DNA. Their functionalization allows these biocatalytic nanoparticles to cross the membranes of tumor cells and experience electrostatic repulsion from healthy cells. This is a highly biocompatible type of therapy, as it is a biological catalyst with precise functionality. To date, no adverse effects have been observed in phase 1 clinical trials. The purpose of this article is to demonstrate that there are other ways to convert tumor cells into products that are excreted through the normal brain pathway, passing through the spleen and kidneys, and being eliminated in the urine. The study of the excretion of products generated by the tumor, such as O₂, H₂O, N₂, SO₄²⁻, PO₄³⁻, among others, was carried out using micro-MRI and micro-PET in animal experiments.

Author's contribution

All authors contributed equally. All authors have approved the final version of the manuscript.

Expressions of gratitude

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