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Roles of Nanobiotechnology in Brain Cancer Treatments

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Dr. Fymat's current research interests are focused on neurodegenerative diseases (Alzheimer's, Parkinson's, dementias, epilepsy, and others), oncology (glioblastoma), epigenetics & ecogenetics, and nanomedicine & nanobiotechnology. These are represented in part in his latest books: "From the Heart to the Brain: My collected works in medical science research (2016-2018)", "Alzhei ...Who? Demystifying the disease and what you can do about it", "The Odyssey of Humanity's Diseases: Epigenetic and ecogenetic modulations from ancestry through inheritance, environment, culture and behavior" Volumes 1, 2, and 3, "Parkin..ss..oo..nn: Elucidating the disease and what you can do about it", "Lyme disease: The great invader, evader, and imitator", "Dementia: Fending-off the menacing disease... and what you can do about it", "The Human Brain: Wonders and Disorders", and "Cancer: The pernicious, clonally-evolving disease braided in our genome"

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Abstract

Cancer cells are notoriously good at becoming resistant to drugs meant to kill them by rerouting their signaling networks. Therapies with one or multiple drugs are employed to attack both the primary and alternate pathways, the overarching goal being to preemptively block the cancer's escape route. Nanobiotechnology offers multiple notable advantages technologically, clinically, and patient-related by decreasing the risks of the procedure and increasing the probability of survival. In nanochemotherapy, several methods are employed whereby cytotoxic drugs are either anchored in or encapsulated to specially-designed nanoparticles and their carriers. The ten types of nanoparticles and the seven varieties of nanodevices that carry them are discussed. Particular emphasis is on glioblastomas (brain cancers). A comparison between conventional chemotherapy and nanochemotherapy evidences several clinical advantages. However, experiments with laboratory animals have unfortunately not translated into successful clinical results. As a result, I urge new directions to improve cancer nanobiotechnology and outline future prospects.

Abbreviations:

BBB: Blood-brain barrier; BRB: Blood-retinal barrier; CSF: Cerebrospinal fluid; EM: Electromagnetic; GBM: Glioblastoma; 3HM: 3-helix micelles; iCSF: internal CSF (barrier); IR: Infra-red; LP: Lipid polymers; LPH: Lipid-coated polymeric hybrids; MDR: Multiple drug resistance; MRI: Magnetic resonance imaging; NBT: Nanobiotechnology; ND: Nanodevices; NDD: Neurodegenerative diseases; NP; Nanoparticles; oCSF: Outer CSF (barrier); PET: Positron emission tomography; P-gp: P-glycoprotein; RCT: Rational combination therapy; SERS: Surface-enhanced Raman spectroscopy; SPIO: Super-paramagnetic iron oxide nanoparticles; T-MOC: Tumor-microenvironment-on-a-chip.; USPIO: Ultra small super-paramagnetic iron oxide nanoparticles.

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Drugs listed: Accurin; Apoferritin; Bradykinin; Cisplatin; Curcumin; Daunomycin; Docetaxel; Doxorubicin; Kinase inhibitors (Aurora B); Mannitol; Osteopontin.

On chemotherapy of cancer

Cancer cells are notoriously good at becoming resistant to drugs meant to kill them. One way they do this is by rerouting their signaling networks (specifically those responsible for the growth, proliferation, and survival of cancer cells). We distinguish between two types of chemotherapy: (1) 'monodrug therapy' wherein a single drug attacks the primary pathway and (2) 'multidrug therapy' (aka "rational combination therapy" or RCT) in which multiple drugs are employed to attack both the primary and alternate pathways. In either modality, the overarching goal is to preemptively block the cancer's escape route. However, because of their different chemical properties, the drugs travel to different body parts and enter cancer cells at different rates.

We further distinguish drugs on the basis of their hydrophilicity or/and hydrophobicity with preference to certain tissues.

Nanobiotechnology applied to cancer

It must first be observed that biological processes (including the ones necessary for life and those that lead to cancer) occur at the nanoscale. Nanobiotechnology (NBT) offers multiple advantages including the: (1) possibility of rapidly and sensitively detect cancer-related molecules, enabling us to detect molecular changes (even for a small percentage of cells), (2) continual patient monitoring during treatment, and (3) study and manipulation of macromolecules in real-time during and after the earliest stages of cancer.

Other important advantages of NBT are that it: (1) offers the means to target chemotherapies either directly or/and selectively to cancerous cells and neoplasms, (2) provides a guide in surgical resection of tumors, (3) enhances the therapeutic efficacy of radiation-based and other treatment modalities, (4) decreases the risks of the procedure to patients, (5) increases the probability of patient survival, and (6) potentially allows the generation of entirely novel and highly effective therapeutic agents, thus enabling an earlier and more accurate initial diagnosis.

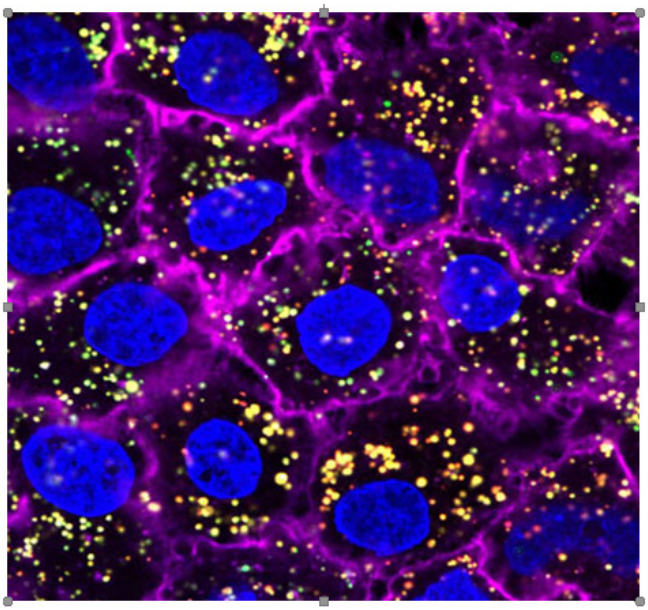
Nanochemotherapy of cancer - Nanoparticles

Nanochemotherapy uses both nanoparticles (NP) and nanodevices (ND) in its application to cancer treatment. Several methods are employed whereby cytotoxic drugs are either anchored in or encapsulated to specially-designed NPs and NDs.

There are eleven (10) NP types, namely: (1) multi-layered shell design nanotags, (2) gelatin NPs, (3) platelet-coated NPs, (4) nutshells, (5) shape-shifting engineered NPs, (6) kinase inhibitors, (7) bioavailability-improved NPs, (8) biodegradable lipid polymers and polymeric hybrid NPs, (9) lipid-based surface-engineering of PLGA NPs, and (10) super-paramagnetic iron oxide (SPIO) NPs for the detection of faint cancer signals by magnetic relaxometry. It would take an inordinate amount of time to study and analyze each such NP and so, for more details on each of them, references have been provided at the end of this article. Brief remarks will, however, be made regarding many of them.

1. Multi-layered shells NPs - The purposes are multiple, namely to: (1) stabilize the NPs, (2) prevent drug leakage at all points during the NP's transmission process, (3) target the NPs to the slightly acidic environment of the tumor, (4) minimize the NPs' interactions with non-cancerous cells, and (4) pass through the body unnoticed by the immune system. To achieve the listed purposes, the NPs are structured as multi-layered shells with core vesicles (filled with water and a fatty, double-layered membrane) containing both hydrophilic and hydrophobic drugs. The exterior layer targets the NPs to the cancer cells and prevents them from being detected by the immune system. Figure 1 illustrates a multi-layered shells NP. (Note: the yellow spots are NPs engulfing the cancer cells.)

Figure 1 – A multi-layered shell nanoparticle in action



2. Gelatin NPs to deliver multiple drugs to the brain - The purposes here are to: (1) deliver drugs to the brain by bypassing the blood-brain barrier (BBB), (2) reduce inflammation, and (3) prevent brain cell death. The NPs are laced with the drug **Osteopontin*** and administered intra-nasally along olfactory nerve cells (this is a noninvasive, direct route to the brain). The gelatin NPs offer the following advantages being: (1) biocompatible, biodegradable, and generally recognized as safe by the FDA, (2) most effective in delivering drugs that cannot otherwise cross the BBB, (3) able to deliver therapeutic agents to specific regions of the brain, and (4) target damaged brain tissues thanks to an abundance of gelatin-munching enzymes produced in injured regions. Their main disadvantage at the present time is that they have not yet been clinically tested to treat glioblastomas (GBMs).

3. Platelet-coated NPs - These NPs have a small size (100 nm**)** that enables delivery of drugs to targeted sites in the body, particularly

injured blood vessels and organs infected by harmful bacteria and (2) increase the therapeutic effects by direct deposition of a much higher dose of medication without saturating the entire body with drugs. They can also be used in the treatment of brain neurodegenerative diseases (NDDs).

4. Nutshells NPs – Like the platelet-coated NPs, these nutshells are of small diameter (120 nm). They bond to cancerous cells by conjugated antibodies or peptides. Gold NPs associate with blood proteins (albumin, fibrinogen, gamma-globulin, histone, and insulin). Gold is sufficiently heated by an infrared (IR) laser to cause the death of cancer cells.

5. Shape-shifting engineered NPs – The purposes here are to: (1) respond to biological molecules to gain access to diseased tissues (2) target the cancer cells, (3) expose a drug molecule to them, and (4) tag the cancerous cells with a signal molecule. The NPs are minuscule chunks of metal with attached strands of DNA. They are delivered by a system that uses modular NPs whose shape, size, and chemistry can be altered by the presence of specific DNA sequences. The NPs have the following interesting properties: (1) they float around harmlessly in the blood stream until a DNA strand binds to a sequence of DNA known to be a cancer marker, (2) they can be tailored to deliver drugs to specified tumors and nowhere else, and (3) the approach can theoretically be imbedded in *personalized* nanomedical treatments.

6. Kinase inhibitors in NP formulations – This is a new approach of molecularly-targeted agents (kinase inhibitors, e.g.. *Accurin*) that departs from the exclusive use of cytotoxic drugs to improve the therapeutic index. The *Accurin* polymeric NPs encapsulate AZD2811 (an Aurora B kinase inhibitor) using an ion-pairing approach. The advantages of *Accurin* are to: (1) provide an extended release of the encapsulated drug payloads and (2) show accumulation and retention in tumors with minimal impact on bone marrow pathology. They result in lower toxicity, increased efficacy, and Increase in the therapeutic index. Their main disadvantage is that other kinase inhibitors than *Accurins* can present considerable therapeutic index limitations.

7. Bioavailability-improved NPs and molecules – The focus is on maximizing bioavailability both at specific places in the body and over a period of time. This can be achieved by employing nano-engineered devices that target the molecules and deliver drugs with cell precision.

8. Biodegradable lipid polymers and lipid-coated polymeric hybrid NPs – Their purposes are to overcome both the (1) dose-limiting side effects of conventional chemotherapeutic agents and (2) therapeutic failure incurred from multiple drug resistance (MDR). These core-shell NP structures comprise polymer cores and lipid/lipid-PEG shells. These lipid polymer (LP) and lipid-coated polymeric hybrid (LPH) NPs are loaded with multiple drugs. They have been used to treat several forms of cancer: The following drug combinations have thus been employed: (1) (*Docetaxel* + *Curcumin*) to combat metastatic castration-resistant prostate cancer patients and overcome multidrug resistance (MDR), (2) (*Doxorubicin* + *Curcumin*) to combat osteosarcoma, and (3) (*Cisplatin* + *Curcumin*) to combat cervix adenocarcinoma cell line (HeLa cells) with significantly higher *in vitro* cytoxicity and better *in vivo* anti-tumor activity than other formulations. It is to be noted that LPHs are more efficacious than PNPs and free drugs.

9. Lipid-based surface-engineered polylactic glycolic acid NPs – These NPs are one of the most promising drug and gene delivery systems for crossing the BBB. The challenges faced are that they require further engineering for clinical and research applications. The following four development generations are recognized: (1) set forth strategies to facilitate travel from the injection site, (2) develop strategies that involve the BBB to enhance passage across the brain endothelial cells (pre-transcytosis strategies), (3) achieve targeting of the impaired system cells (post-transcytosis strategies), and (4) fuse all or some of above strategies.

10. Super-paramagnetic iron oxide NPs – Two types of iron oxide magnetic resonance imaging (MRI) contrast agents exist: superparamagnetic iron oxide (SPIO) and ultrasmall superparamagnetic iron oxide (USPIO). They consist of suspended colloids of iron oxide nanoparticles and, when injected during imaging, reduce the magnetic relaxation time T2 signals of absorbing tissues. Such particles are:

- Feridex I.V. (also known as *Endorem* and ferumoxides). This product was discontinued by AMAG Pharma in November 2008.
- Resovist (also known as *Cliavist*). This product was approved for the European market in 2001, but production was abandoned in 2009.
- Sinerem (also known as *Combidex*). Guerbet withdrew the marketing authorization application for this product in 2007.
- Lumirem (also known as *Gastromark*). Gastromark was approved by the FDA in 1996 and was discontinued by its manufacturer in 2012.
- Clariscan (also known as PEG-fero, *Feruglose*, and NC100150): This iron based contrast agent was never commercially launched and its development was discontinued in early 2000s due to safety concerns. In 2017 GE Healthcare launched a macrocyclic extracellular gadolinium based contrast agent containing gadoteric acid as gadoterate meglumine under the trade name *Clariscan*.

With their small size (~ 25 nm), these SPIO NPs are employed for the following purposes to: (1) find faint early traces of cancer never detected by X-rays and (2) detect tumors with as few as 20,000 cells (best other methods to detect tumors require more than 10 million cancer cells). The approach uses the phenomenon of magnetic relaxometry in which signals from SPIO NPs that find and attach themselves to cancerous cells are enhanced with the antibody proteins that target biomarker proteins produced by cancer cells. Once bound to the cells, their range of motion is severely restricted. Upon applying an external magnetic field, the particles' dipoles will align to counteract this field. The SPIO NPs have the following properties: (1) they can locate cancer cells because once the dipoles face each other, the net magnetic field is

essentially zero. Quantifying this relaxation phase marks the location of cancer cells and (2) unbound NPs randomly reorient themselves in 1 msec and are measured by MRI relaxometry. However, because antibody-associated NP complexes that are bound to cancer cells are restricted in their movement, their magnetic relaxation is a lot slower </~ 1 sec. Also, moments relax at a very different rate when they belong to NPs bound to cancer cells.

Nanochemotherapy of cancer – Nanodevices

Seven (7) nanodevices (NDs) have been devised for ferrying the drug-laden nanoparticles to cancerous sites. These are:

1. Surface-enhanced Raman spectroscopy (SERS) nanotags - The purpose of these nanotags is to target molecules using lasers, resulting in light scattered at different electromagnetic (EM) wavelengths (gold or silver NPs are usually employed to amplify the EM signals) and subsequently analyzed by a Raman spectrometer. The NPs consist of an inner metallic core surrounded by a spiky metallic outer shell with a 3-nm spacing. They offer several advantages including: (1) they can produce signals that are enhanced tenfold compared to smooth-shell core structures, (2) they enable the detection of minute amounts of organic molecules (such as DNA for particular diseases), (3) their spiky structure is more efficient in generating heat that can, in turn, be used for attacking the cancer cells, (4) their increased surface area can accommodate more drugs to deliver greater targeted blasts, allowing to target, image, and release drugs all with one device, and (5) they are significantly better at cancer detection and treatment. Notwithstanding all these advantages, their process of action is highly sensitive and fraught with challenges such as difficulties with reproducibility, signal stability,and apparent lack of quantitative information. In addition, these NDs loaded with life-saving drugs may: (1) revolutionize chemotherapy, (2) reduce the debilitating side effects of the therapy, (3) make medications more effective, (4) preserve healthy living cells, and (5) deliver clot-busting drugs to the brain.

Several "nano-carriages" for drug delivery have been created. The carriers usually encapsulate drugs through long-range electrostatic interactions wherein the carrier attracts oppositely charged medicines. Other tools are available to trigger the release of drugs such as an external magnetic field, ultrasound waves, different pH values, etc. Many challenges remain, chief among them being how not to let the medicines act before they get to the right place in the body. In each case, researchers face the problem of efficiency of the drug release.

2. Engineered NDs – The purpose is to deliver high drug levels at a tumor site to increase the therapeutic efficacy These minute devices deliver drugs more efficiently and more safely to the location of diseased cells. They can be used to develop new "smart" nanotherapeutics to "time" the release of any given drug or to deliver multiple drugs sequentially in a timed manner at several locations.

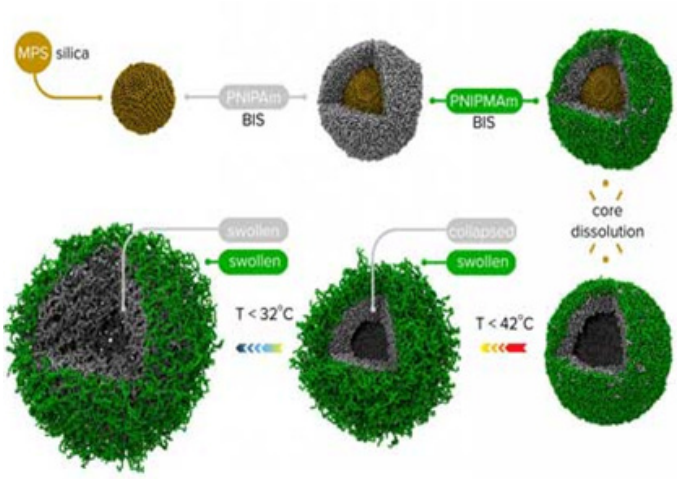
3. Hybrid nanocrystals – Their purpose is multi-functional and multi-tasked. Formed from ordered atom clusters, these new tools or molecular tags enable and aid targeted drug delivery. Their fabrication can be precisely controlled to create different shapes and sizes, allowing assessment of the drug impact along its propagation path within the body. A library of 800 different and uniquely shaped hybrid nanocrystals has been so far developed.

4. Protein cages – These cages use *Apoferritin,* the same ball of natural proteins that carries iron around in the blood without letting it leak out. The drug is made of 24 pieces that can conveniently open and close, depending on the surrounding acidity. The cages have been used successfully for lung cancer. While lung cancer is not of interest in this article, the experience gained in this case with protein cages may be helpful. The cage's exterior is **mo**dified with a ligand (a signal triggering molecule) to render the cage particularly attractive to a common cancer cell receptor. The anti-cancer drug, *Daunomycin* is subsequently inserted into the cage. With addition of a small amount of acid and adjusting the pH to below neutral, the protein cage slightly opens to let the drug jump inside, where it stays until contact with the cancer cell. Penetrating the cancer cells selectively and entering the acidic environment of the cancer cell, the cage opens, delivers the drug directly, and kills >70% of them without attacking healthy cells.

5. Microbubbles – These tiny balls (diameter ~ $1/100^{th}$ of a human hair) of gas are enclosed in an ultra-thin layer of fat and contain anti-cancer drug(s). When injected into the blood stream, upon reaching the unhealthy part of the body, the bubbles burst with ultrasound waves, releasing the drug(s) exactly where needed. Because the entire blood stream is not being flooded with the drug(s), side-effects from chemotherapy can be greatly reduced.

6. Multi-shell hollow nanogels with responsive shell permeability – These gel nano-capsules are filled with guest molecules, locking them in the cavity and releasing them under temperature control. The carrier is surrounded by two "membranes" (or shells) of different chemical structures around a silica core which, at the end of the synthesis, will be chemically dissolved leaving only the "empty space" (cavity). The outer porous shell plays a protective (stabilizing) role and hinders the aggregation of the nano-capsules. The pores of the inner shell can open and close depending on the temperature. At the time of filling, the pores of both shells are open and the nanogel absorbs the drug molecules as a sponge. The temperature is then changed and the pores of the inner shell close locking-in the cavity and readying the drug for delivery. The pores will open again and the guest molecules will be released only in the places where the temperature allows. The above design departs from the standard multi-layered shell design in that it does not depend on any electrostatic force (i.e., whether the medicines are either electrically charged or neutral).

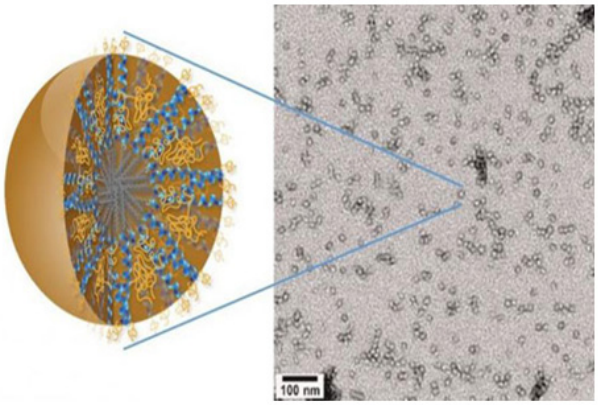
Figure 2: Multi-Shell hollow nanogels with responsive shell permeability.



7. Micelles – With a diameter of 20 nm, micelles have very good attributes for the treatment of brain cancers including (1) long circulation, (2) deep tumor penetration, and (3) low accumulation in off-target organs (liver, spleen). They can be administered intravenously rather than invasively. Experiments with rats confirmed the effectiveness of 3-helix micelles (3HM) as delivery vessels for glioblastoma multiform (GBM). Positron emission tomography (PET) and magnetic resonance imaging (MRI) of NP distribution and tumor kinetics can be used to improve the future design of NPs for GBM treatment. FDA-approved GBM therapeutics are ferried across the BBB in special liposomes (size ~ 110 nm). Unfortunately, however, they have had little impact so far. 3HM (coiled-coil 3-helix micelles) are self-assemblies of amphiphilic peptides and polymers with unique hierarchical structure allowing better pharmacokinetics and biodistribution. Cu-64 is used to label both 3HM and liposome nanocarriers for systematic PET and MRI studies.

Now, amphiphiles are chemical compounds that feature both hydrophilic and hydrophobic properties. They can cross the BBB and accumulate inside GBM tumors at nearly twice the concentration rate of current FDA-approved nanocarriers.

Figure 3: 3HM nanocarriers for effective delivery of therapeutic drugs to GBM.



Application to glioblastomas

1. On glioblastomas – GBMs are most common (there are ~ 15,000 cases/year in the U.S.) and most aggressive primary brain tumors in adults. They are virtually inoperable and resistant to therapies. They are always fatal within 15 months of onset.

Figure 4: Pictorial representation of a glioblastoma multiform.

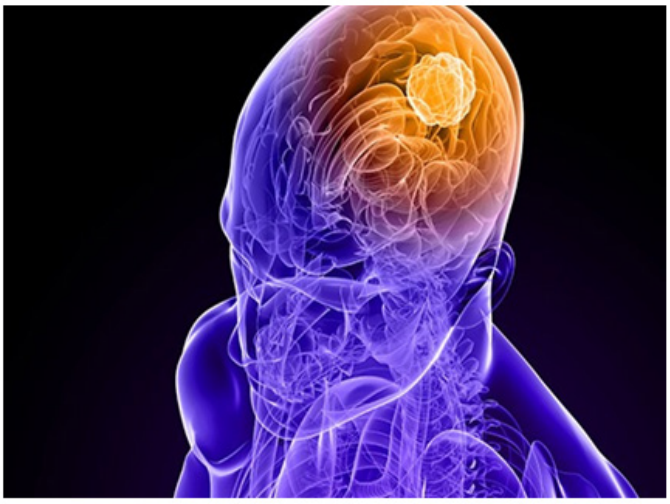
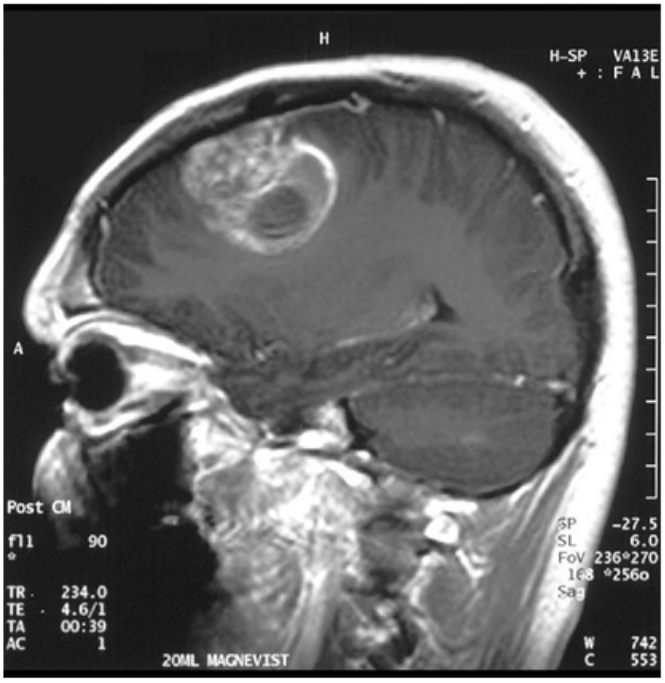


Figure 5: A computed tomography contrasted image of a glioblastoma multiform.



2. Treatments of GBMs - Most treatments cannot eradicate most tumor cells, one of the major obstacles to treatment being the BBB. The first treatment line has been defined since 2005. The second treatment line has not been standardized for recurring tumors. There are no prevention strategies. The various surgical and non-surgical management and treatment approaches have been described at length in the author's eBook (Fymat 2017g) and will not be further discussed here. These are:

- Symptomatic
- Chemotherapy
- Conformal
- Immunotherapy
- Antiangiogenic
- Alternating electric fields
- Intensity-modulated proton beam
- Boron neutron capture
- Vaccines
- Palliative
- Complementary & Alternative
- Lifestyle changes

Figure 6: Surgical resection of a glioblastoma multiform.

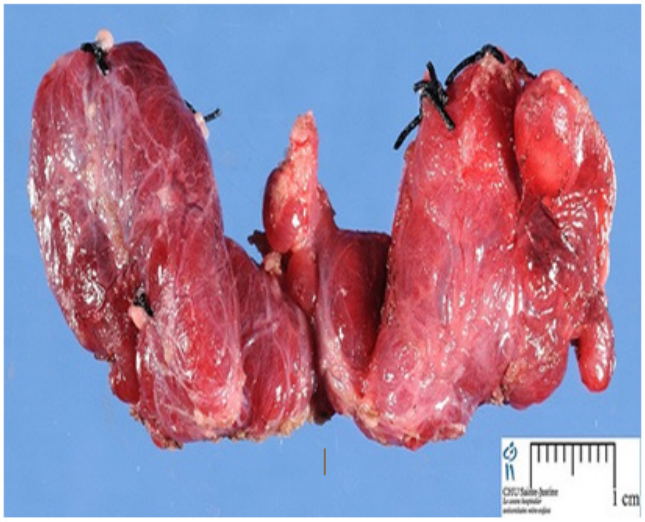
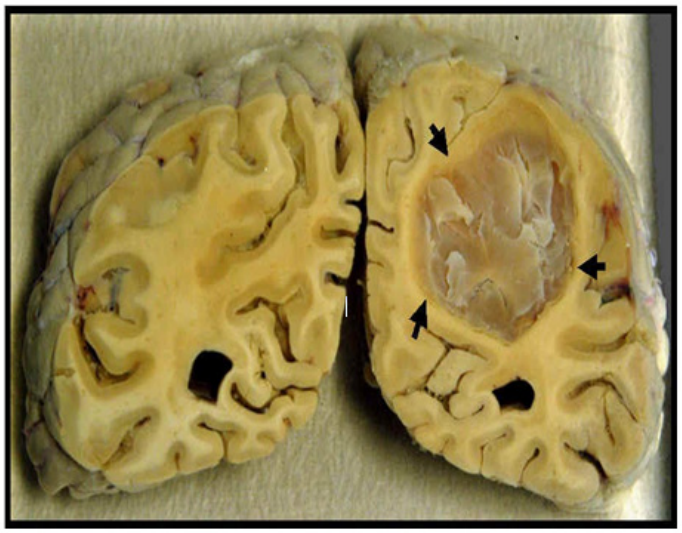


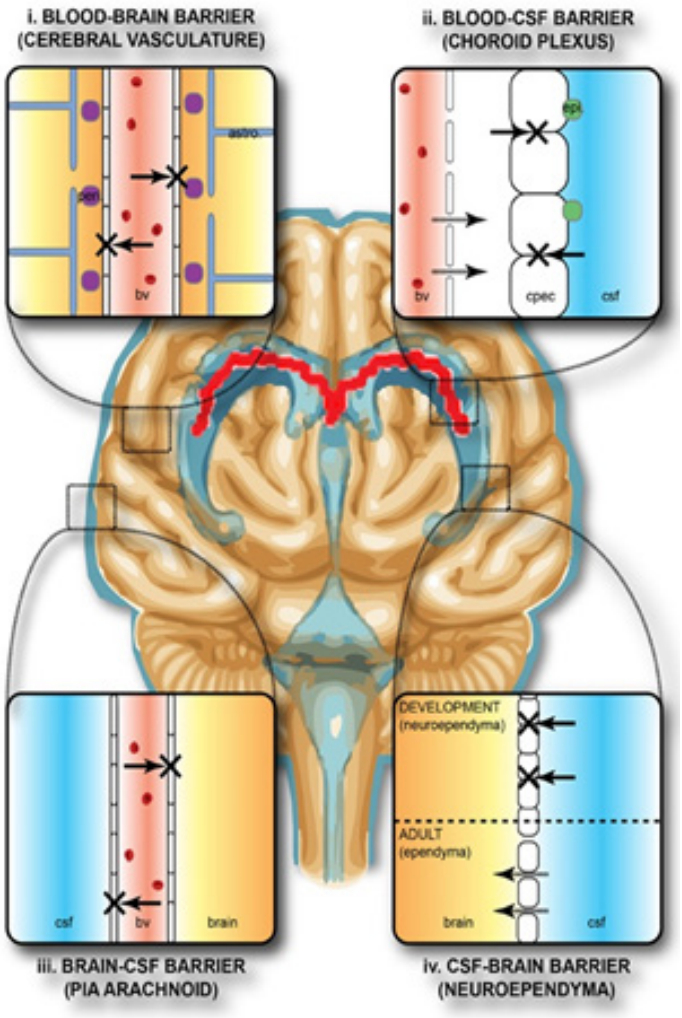
Figure 7: Excised brain showing a glioblastoma multiform



3. The brain protective barriers – There are 5 barriers:

• ***The blood-brain barrier (BBB) proper:*** It is formed by complex tight junctions between the endothelial cells of the cerebral vasculature;
• ***The blood-cerebrospinal fluid (CSF) barrier:*** It is formed by tight junctions between the epithelial cells of the choroid plexus;
• ***The outer CSF-brain barrier (oCSF):*** It is formed by tight junctions between the endothelial cells of the arachnoid vessels (pia arachnoid);
• ***The inner CSF-brain barrier (iCSF):*** It is formed by the strap junctions between the neuro-ependymal cells lining the ventricular surfaces (developmental; absent in the adult); and
• ***The blood-retinal barrier (BRB):*** It is of no particular interest here.

Figure 8: The brain protective barriers



4. BBB as an inhibitor of drug delivery – A major obstacle to treatments, the BBB nonetheless allows essential nutrients to enter the brain but blocks passage of other substances. It is an almost impervious barrier to the delivery of drugs, precluding the entry of many (if not most) therapeutic drugs. Actually, the FDA-approved drugs have had little impact because the BBB limits their accumulation. Nanobiotechnology (NBT) provides new hope for brain cancer treatment. Fortunately, drugs encased in NPs and delivered by NDs are able to overcome the BBB limitations.

5. D**rug delivery strategies –** The several strategies developed include:

• ***Modification of the drug itself****:* or its coupling to a vector for receptor-mediated or adsorption- mediated transcytosis;
• ***Chemical modification or development of more hydrophobic analogs:*** or linking an active compound to a specific carrier;
• ***Transient opening of the BBB:*** This can be achieved in humans by intra-carotid infusion of hypertonic *Mannitol* solutions or of

Bradykinin analogs;

• ***Modulation of the P-glycoprotein (P-gp):*** whose substrates are actively pumped out of the cell and into the capillary lumen; and, more particularly:

• ***Nanomedicine technologies:*** NBT can deliver drugs across, around, and beyond the BBB at the right location, the right time, and in the right dosage (such as with micelles).

Nanochemotherapy *vs* conventional chemotherapy

1. Nanobiotechnology technological advantages - Cytotoxic drugs kill cancer cells effectively but also healthy cells, leading to adverse side effects (nausea, neuropathy, hair-loss, fatigue, and compromised immune function). By contrast, nanochemotherapy utilizing nanoparticles and nanodevices for carrying them can deliver therapeutics directly while sparing healthy tissue. NBT has multiple advantages in that it: (1) protects drugs from degradation in the body before the NPs and NDs reach their target; (2) enhances drug absorption into cancerous cells themselves, (3) allows better control over the timing and distribution of drugs to tissues, and (4) prevents drugs from interacting with normal cells, thus avoiding side effects.

2. Nanobiotechnology clinical advantages – NBT is advantageous in several regards: (1) The NPs can circulate throughout the bloodstream without being attacked by the immune system, (2) they preferentially bind to damaged blood vessels and certain pathogens, allowing them to deliver and release drug payloads to specific body sites, (3) many NP components are non-toxic (these are platelet membranes made of a biodegradable polymer), (4) they can be safely metabolized by the body, (5) they
can be packed with many small drug molecules that diffuse out of the polymer core and through the platelet membrane onto their targets, (6) they can overcome multi-drug resistance ,particularly after failure of conventional chemotherapy and radiotherapy, and (7) they enable the tracking of the path of chemotherapeutic drugs in real time and at the cellular level.

New directions urged to improve cancer treatment with nanobiotechnology

Experiments with laboratory animals have, unfortunately, not translated into successful clinical results. New directions are therefore urged to improve cancer NBT:

- ***Designing NPs small enough to pass through pores in blood vessels around tumors:*** but not through pores of vessels in healthy tissue;
- ***Fabricating "tumor-microenvironment-on-a-chip (T-MOC)" devices:*** to allow the study of the complex microenvironment surrounding tumors (non-cancerous cells, blood vessel structure);
- ***Developing water-soluble drugs:*** to effectively deliver medicines;
- ***Evolving treatment approaches towards precision medicine***; and
- ***Fabricating in vitro platforms:*** as alternatives to animal testing.

Future prospects and conclusions

Bionanotechnology will reduce the need for invasive surgery although some devices (such as implanted catheters, reservoirs, etc.) may continue to be needed. Nanomaterials will improve the safety and efficacy of nanoparticles and nanodevices. Nano-engineered probes can deliver drugs at the cellular level using nanofluidic channels. Lastly, microchips and biodegradable polymeric nanoparticle carriers may be more effective therapeutically for brain tumors.

Next-generations (3HM micelles, NP nasal spray, and "sticky" NPs) are great advances in developing effective drugs also for other types of cancer.

Unfortunately, we still do not fully understand the deep biology of glioblastomas and cannot cure them. We should dedicate considerably more time on understanding that deep biology!

References

1. Alphandéry E. "Biodistribution and targeting properties of iron oxide nanoparticles for treatments of cancer and iron anemia disease". *Nanotoxicology.* 2019; 13(5):573-596.
2. Alphandéry E. "A discussion on existing nanomedicine regulation: Progress and pitfalls, *Applied Materials Today.* 2019; **17:**193-205
3. Alphandéry E. "Iron oxide nanoparticles as multimodal imaging tools", *RCS Advances.* 2019; **9(69):** 40577-40587.
4. Alphandéry E. "Iron oxide nanoparticles for therapeutic applications. *Drug Discovery Today.* 2020; **25(1):**141.
5. Alphandéry E. "Nano-therapies for Glioblastoma treatment," *Cancers.* 2020; **12(1):** 242.
6. Alphandéry E. "Bio-synthesized iron oxide nanoparticles for cancer treatment", *International*
7. Journal of Pharmaceutics. **586:**119472.
8. Alphandéry E. "Bio-synthesized iron oxide nanoparticles for cancer treatment", International
9. Journal of Pharmaceutics. 2020; 586:119472.
10. Alphandéry E. "Natural Metallic Nanoparticles for Application in Nano-Oncology", *International* Journal of Molecular Sciences. 2020; **21(12):** 4412.
11. Ashton. "Accurin nanoparticles dutifully deliver drugs", *Science Translational Medicine.* 2016; **8** (325): 325Ra17.
12. Fymat AL. "Nanotechnology and Cancer". *J Cancer Prev & Current Res.* 2016a; **5**(6): 1-7.
13. Fymat AL. "Recent Developments in Nanomedicine Research". *J Nanomed Res.* 2016b; **4**(4):1-12.
14. Fymat AL. "Nanochemotherapy: An Emergent Anti-Cancer Modality. *Global J of Nanomed.* 2017a; **1**(1): 1-6.
15. Fymat AL. "Nanoneurology: Drug Delivery Across the Brain Protective Barriers". *J Nanomed Res.* 2017b; **5**(1):1-4.
16. Fymat AL. "Nanooncology: Perspective on Promising Anti-Tumor Therapies". *J Tumor Med & Prev.* 2017c; **1**(1):1-10.

17. Fymat AL. "Therapeutics Delivery Behind, Through, and Beyond the Blood-Brain Barrier", *Open Access J of Surgery.* 2017d; **5**(1): 1-9.
18. Fymat AL. "Glioblastoma Treatments: Where Do We Stand? *J Cancer & Oncology Res.* 2017e; **1**(1)1-12.
19. Fymat AL. "Antiangiogenic Targeting of Early Developing Glioblastoma Behind a Weakened Blood-Brain Barrier". *J Anti-Tumor Medicine* & Prev. 2017f; **2**(3):1-6.
20. Fymat AL. "Management and Treatment of Glioblastoma". eBook, Juniper Pub. 2017g;
21. Fymat AL. "Nanomedicine as a Precursor to Precision Medicine for Glioblastoma Treatment'.
22. *J Current Opinions in Neuro Sci.* 2017h; (4): 200-206.
23. Fymat AL. "Surgical and Non-Surgical Management and Treatment of Glioblastoma: I. Primary Tumors". *Open Access J of Surg.* 2017i; **7**(2):1-8.
24. Fymat AL. "Surgical and Non-Surgical Management and Treatment of Glioblastoma: II. Recurring Tumors". 2017j; **7**(1):1-7.
25. Fymat AL. "Nanobiotechnology Advances in Oncology". *Adv Bioen & Biomed Science Res.* 2108a; **1**(1):1-6.
26. Fymat AL. "Roles of Nanomedicine in Clinical Neuroscience', *Global J of Nanomed*. 2018b; ***4***(1):13-15.
27. Fymat AL. "Nanomedicine May Provide New Hope for Brain Cancer Therapy". Global journal of nanotechonology. 2021a; **4**(5):1-7.
28. Fymat AL. "Major Recent Developments in Cancer Treatment". *Cancer Therapy & Onc Inter Journal.* 2021b; 18(2):1-3.
29. Fymat AL. "Cancer – The Pernicious, Clonally-Evolving Disease Braided in our Genome, Tellwell Talent Publishers. 2021c;
30. Gobin AM, O'Neal DP, Watkins DM, Halas N, West J, Drezek R, et al. "Near-infrared laser tissue-welding using nanoshells as an exogenous absorber". Laser Surg Med. 2005; **37** (2): 123-129.
31. Greig NH. Drug delivery to the brain by blood–brain barrier circumvention and drug modification: Implications of the blood–brain barrier and its manipulation". Newwelt EA, Plenum Press. 1989; 311–367.
32. Kreuter J. "Nanoparticles and microparticles for drug and vaccine delivery". *J. Anat.* 1996; **189**(3): 503-505.
33. Kreuter J. "Nanoparticulate systems for brain delivery of drugs". *Adv. Drug. Del Rev.* 2001; **47**: 65-81.
34. Kreuter J, Alyautidin R, Kharkevich DA, and Ivanov AA. "Passage of peptides through the blood–brain barrier with colloidal particles (nanoparticles)". *Brain Res.* 1995; **674**(1): 171-174.
35. Marty JJ, Oppenheim RC and Speiser PP. "Nanoparticles–-A new colloidal drug delivery system". *Pharm. Acta. Helva*. 1978; **53**:17-23.
36. Moghimi SM. complement propriety and conspiracy in nanomedicine perspective and hypothesis. Liberty Publishing. Nucleic acid therapeutics. 2016; 26(2):67-72.
37. Nie, Shuming, Xiang Y, and Simmons JW. "Nanotechnology applications in cancer". Annual Review of Biomedical Engineering. 2007; **9:** 257-288.
38. Rivière B. *et al* (2016). "Magnetic nanoparticles can detect early traces of cancer" (reported in *Nanoworks).*
39. Schroder U and Sabel BA. "Nanoparticles, a drug carrier system to pass the blood-brain barrier, permit central analgesic effects of i.v. dalagrin injections", Brain Res. 1996; **710**:121-124.
40. Schroder U, Sommerfeld P, Ulrich S and Sabel BA. "Nanoparticle technology for delivery of drugs across the blood-brain barrier". *J Pharm Sci.* 1998; **87(11)**:1305-1307.
41. Smith QR. "Drug delivery to the brain and the role of carrier mediated transport" in *Frontiers in cerebral vascular biology:Transport and its regulation*, Editors: Drewes LR and Betz AL. Plenum Press. 1993; 83-93.
42. Zhang. "Bioinspired fluorescent dipeptide nanoparticles for targeted cancer cell imaging and real-time monitoring of drug release". Nature Nanotechnology. 2016; 11(4): 388-394.
43. Zheng G, Patolsky F, Cui Y, Wang WU and Lieber CM. "Cancer markers with nanowire sensor arrays". Nat Biotechnol. 2005; 23(10):1294-1301.