ARTIGO

A promising way to detect and fight different types of tumors and cancer by using nuclear science and magnetic carbon

Uma maneira promissora de detectar e combater tipos diferentes de tumores e canceres usando ciências nucleares e carbono magnético

Abstract

In this review of our own work, we show a promising way to detect and fight different types of tumors and cancer by using nuclear science and magnetic carbon. Almost two decades ago, we reported by the first time on a chemical route aiming to synthetize stable magnetic carbon/graphite. By using the Nuclear Magnetic Resonance (NMR) technique we have verified that its magnetism is an intrinsic property of this synthetized material and not originated from ferromagnetic impurities of any kind. Through direct measurement of the local magnetic field using Carbon-13 we have concluded that its magnetism is originated from defects in the structure. From its biocompatibility, we have been working in the use of magnetic carbon/graphite to deliver many compounds aiming to fight different diseases. Despite all scientific and technological advances of present days, cancer is a multifactorial and difficult to treat disease, killing hundreds of thousands of people a year worldwide. Therefore, the development of a new and efficient drug delivery system to fight cancer and biological agents – among other diseases - is as important as the discovery of a novel active molecule. In this work, we show the drug delivery system named MAGUS® (an acronym for Magnetic Graphite Universal System) we have built based on nanostructured magnetic carbon/graphite. This is an innovative and promising system composed by a biocompatible nanostructured particle of magnetic carbon/graphite functionalized with different molecules and materials. MAGUS®, depending on what we link to its structure, is so versatile and can be used to detect a wide range of specimens, from tumors and cancers to chemical and biological agents used as non-conventional weapons. That is why we call it universal. In the present work, MAGUS® will be acting as a biosensor, where the magnetic carbon/graphite is functionalized with radioactive particles of Iodine-131 and antibodies of different types of cancer. Then, by focusing on both the antigen-antibody interaction and the spatial guiding through an external magnetic field we are providing our drug delivery system a double way to detect and reach just the target. Based on these strategies, the functionalized magnetic carbon/graphite will reach only

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the neoplasm and not the surrounding healthy cells around. In a general view, it means that we are giving specificity to the MAGUS® drug delivery system as a pioneering and effective way to detect and treat cancers. We are also working on this unprecedented and efficient drug delivery system using the principles of Boron Neutron Capture Therapy (BNCT) with Boron-10 instead of Iodine-131. BNCT technique uses neutron as the external source and is frequently employed to treat specific tumors that are radioresistant or very difficult to kill using conventional radiation therapy. In summary, we show here by the first time that our Magnetic Graphite Universal System associated with nuclear techniques can be successfully used as a biosensor to detect and fight cancers and tumors with powerful features that conventional delivery drugs systems and other treatments do not have at all.
Key words: biosensors; biodefense, detectors; radioactive Iodine; cancer; magnetic carbon/graphite; drug carriers; radioactive Boron; BNCT technique; nanostructured carbon; antibody-antigen interaction.

Introduction[1]

Throughout history, countless technological advances, originally intended for the development of military products and systems, have spilled over to other sectors generating disruptive innovations with enormous benefits for society. Particularly in the twentieth century, sophisticated research of military interest boosted innovations and the economic growth of pioneer countries. One of those advances was derived from nuclear science and engineering. Today, the so-called *fourth industrial revolution* is transforming the way people relate, work, and enjoy their leisure and rest hours. On a broader spectrum, it is affecting economic growth, development, security and sovereignty of countries, international relations, and the nature of warlike conflicts among other areas. Unlike its predecessors, which are based on disruptive innovations in specific areas, the fourth industrial revolution develops from the confluence of innovations that have occurred in various areas. Physics comprises incessant and surprising advances in new materials, sensors, nanotechnology, microelectronics and physical infrastructure of information and communication technologies; communication protocols and algorithms used in a wide range of applications. Genetic algorithms, artificial neural networks, learning techniques, genetic sequencing, bioprinting and drone swarms, are some of the lines of research inspired by such studies[1]. Recently, artificial intelligence (AI) through ChatGPT (or GPT-3, *Generative Pre-Trained Transformer*) by Open IA has started a worldwide scientific, technological, and social revolution in almost all possible aspects, by using 175 billion parameters. Its new generation, called GTP-4, is planned to use amazing 100 trillion parameters[2]. Scientist are considering that a further version, called GTP-5 (which will be available by the end of 2024) will have complete human capabilities.

[1] This work is based in one of our more recent publications (Annals of Advances in Chemistry; 7: 047-050 (2023); DOI: 10.29328/journal.aac.1001042) whose main results we reproduce here in a summarized way.

Surprisingly, despite all these incredible advances, some threats to humans, such as biological weapons and some diseases such as cancer, are still difficult to detect and eliminate. Remarkably, both threats can be detected and dealt with from the superparticle called MAGUS® that we will describe in the following sections.

In the specific case of cancer, it is a difficult-to-treat disease associated with a negative prognosis (depending on the stage of detection), that kills hundreds of thousands of people a year worldwide. Each year, the American Cancer Society estimates the numbers of new cancer cases and deaths in the United States and compiles the most recent data on population-based cancer occurrence and outcomes. Worldwide, cancer is a leading cause of death, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths[3,4]. In 2022, 1,918,030 new cancer cases and 609,360 cancer deaths were projected to occur just in the United States, including approximately 350 deaths per day from lung cancer, the leading cause of cancer death. Even today, most methods to treat that disease are based in ionizing radiation (like gamma) or in some medicines, both methods result in broad unwanted side effects. They have no specificity and reach not only the cancer but other parts of the human body. Unquestionably, both methods have saved hundreds of thousands of lives, however cancer is still killing too many people worldwide. Surely in both, due to a high dose in the tumor neighbor tissues or due to a lower dose insufficient to kill the cancer, it is highly desired to develop new and more effective methods to specifically fight it.

MAGUS®, which we will describe in the next section, is a nano-structured carbon (or a *nanocarbon*) like other well-known structures like graphene, nanotubes and buckyballs. Among them, graphene is the most famous, which is a semi-metal with small overlap between the valence and the conduction bands (zero bandgap material). It is an allotrope of carbon consisting of a single layer of carbon atoms arranged in a hexagonal lattice. It is the basic structural element of many other allotropes of carbon, such as graphite, diamond, charcoal, carbon nanotubes, fullerenes etc. (figure 1). Graphene has many uncommon properties. It is the strongest material ever tested, conducts heat and electricity efficiently, and is nearly transparent. Graphene shows a large and nonlinear diamagnetism greater than that of graphite and can be levitated by neodymium magnets. However, MAGUS® allows applications such as those described in this work but where graphene cannot yet be used.

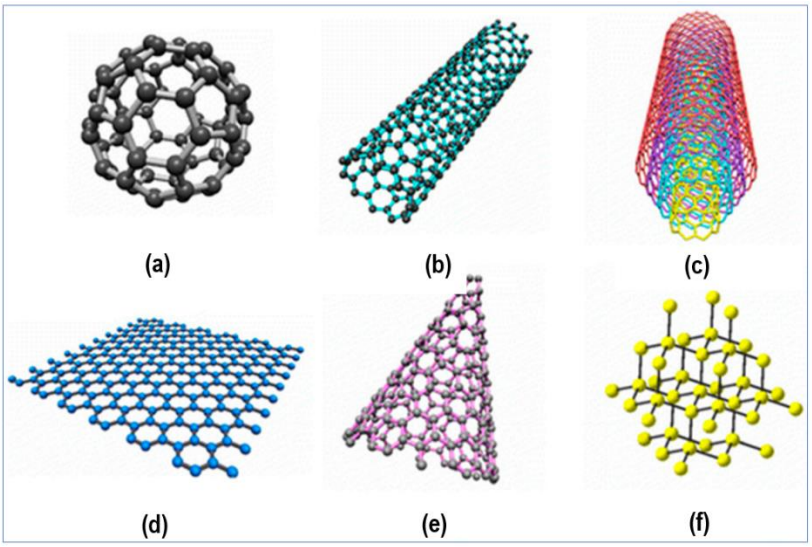

Figure 1: Different forms of nanocarbons: (a) fullerene; (b) SWNT (single-wall nanotube); (c) MWNT (multi-walls nanotube); (d) graphene sheet; (e) nano-cone; and (f) nano-diamond.

Scientists theorized about graphene for years. It had been produced unintentionally in small quantities for centuries through the use of pencils and other similar graphite applications. It was observed originally in electron microscopes in 1962, but it was studied only while supported on metal surfaces. The material was later rediscovered, isolated, and characterized in 2004 by Andre Geim and Konstantin Novoselov at the University of Manchester. This work resulted in the two winning the Nobel Prize in Physics in 2010 "*for groundbreaking experiments regarding the two-dimensional material graphene*." Graphene's stability is due to its tightly packed carbon atoms and a sp^2 orbital hybridization – a combination of orbitals *s*, p_x and p_y that constitute the σ-bond. The final p_z electron makes up the p-bond. The p-bonds hybridize together to form the p-band and p∗-bands. These bands are responsible for most of graphene's notable electronic properties, via the half-filled band that permits free-moving electrons. Graphene displays remarkable electron mobility at room temperature, with reported values in excess of 15000 $cm^2 \cdot V^{-1} \cdot s^{-1}$. Hole and electron mobilities were expected to be nearly identical. The mobility is nearly independent of temperature between 10 K and 100 K, which implies that the dominant scattering mechanism is defect scattering. Scattering by graphene's acoustic phonons intrinsically limits room temperature mobility to 200000 $cm^2 \cdot V^{-1} \cdot s^{-1}$at a carrier density of 10^{12} cm^{-2}, 4.5×10^3 times greater than copper. Graphene's unique optical properties produce an unexpectedly high opacity for an atomic monolayer in vacuum, absorbing p$\alpha \approx 2.3\%$ of red light, where α is the fine-structure constant. This is

a consequence of the "unusual low-energy electronic structure of monolayer graphene that features electron and hole conical bands meeting each other at the Dirac point.

Graphene is a disruptive technology; one that could open up new markets and even replace existing technologies or materials. It is when graphene is used both to improve an existing material and in a transformational capacity that its true potential can be realized. The vast number of products processes and industries for which graphene could create a significant impact all stems from its amazing properties. No other material has the breadth of superlatives that graphene boasts, making it ideal for countless applications.

We can see that graphene is a powerful material allowing disruptive applications. However, MAGUS® allows applications such as those described in this work but where graphene cannot yet be used. MAGUS® is a so versatile nanostructure and can be used to detect a wide range of specimens. Depending on the way it is functionalized, it can detect from tumors and cancers to chemical and biological agents used as non-conventional weapons. Next, we will focus on the use of MAGUS® to detect and fight tumors and cancers.

Experimental methods

Developing MAGNUS®

Taking this scenario into consideration we have been working in the use of magnetic carbon/graphite to deliver different compounds to fight many diseases. We know that the development of a new and efficient drug delivery system is as important as the discovery of a novel active molecule. Thus, based on nanostructured magnetic carbon/graphite we have built a drug delivery system named MAGUS®, which is an acronym for *Magnetic Graphite Universal System*. We have assembled this innovative and promising system as a biosensor composed by a biocompatible carbon particle functionalized with different molecules *simultaneously*. We reported how to obtain this magnetic carbon/graphite in 2005 and 2006[5,6] by following an inexpensive chemical route consisting of a controlled chemical etching on the graphite structure, performed by a *redox* reaction in a closed system between pure carbon/graphite and copper oxide (CuO). It allows to get macroscopic amounts of magnetic carbon/graphite stable at room temperature and even above. X-ray diffraction measurements suggest that magnetic carbon/graphite could be represented by the coexistence of a matrix of pristine graphite and a foamy-like carbon/graphitic structure compressed along the *c*-axis. At T = 300

K, the saturation magnetic moment, the coercive field and the remnant magnetization are 0.25 emu/g, 350 Oe and 0.04 emu/g, respectively. Besides the phase transition at 300K, it is possible to observe a low-temperature anomaly in the dependence of the zero-field-cooled magnetization in samples with an average granular size L of about 10nm. We have attributed it to the manifestation of the size effects below the quantum temperature $T_L \propto \hbar^2/L^2$. This behavior is well fitted by a periodic function proportional to the bulk magnetization and the thermal De Broglie wavelength[7]. Related to that behavior, we have proposed a theoretical interpretation for both intragranular and intergranular contributions based, respectively, on super-exchange interaction between defects induced localized spins in a single grain and proximity mediated interaction between grains through the barriers created by thin layers of non-magnetic carbon/graphite[7]. In 2015, we experimentally confirmed that magnetism in carbon/graphite originates from defects in the structure (and not from ferromagnetic impurities of any type) from direct measurement of the local magnetic field using Carbon-13 nuclear magnetic resonance (NMR) associated to the numerical results obtained from DFT (*Density-functional theory*) calculations. These experiments allowed us, for the first time, to directly evaluate the local hyperfine magnetic field in magnetic carbon/graphite samples corroborating the intrinsic and true nature of the magnetism. A comparison of the experimental hyperfine fields to DFT calculations showed reasonable agreement, supporting the view that magnetism originates from various defects in the material structure[8,9].

Developing MAGUS® associated to a conventional drug (Ibuprofen®)

We have verified the efficiency of this new drug delivery system by developing a magnetic bio-hybrid system from the assembly of the biopolymer alginate and magnetic carbon/graphite[9]. In this case we have nanostructured the magnetic carbon/graphite particles as a nanofluid[10,11]. The drug *Ibuprofen®* (IBU) intercalated in a Mg–Al layered double hydroxide (LDH) was chosen as a model of drug delivery system to be incorporated as a third component of the magnetic bionanocomposite drug delivery system. The IBU was incorporated either as the pure drug or as the LDH–IBU intercalation compound and processed as beads or films for application as drug release systems. The presence of magnetic carbon/graphite nanoparticles improved the physical and mechanical properties of the resulting bionanocomposites, decreasing the speed of drug delivery due to the protective effect as a physical barrier against water absorption into the beads. The control on the release rate was specially improved when the drug was incorporated as the LDH–IBU

intercalation compound, being this fact attributed to the additional physical barrier afforded by the inorganic layered host solid. These bionanocomposite systems could be stimulated by an external magnetic field as well, enhancing the levels of the released IBU, which would be advantageous to modulate the dose of released drug when required[12].

Developing MAGUS® associated to radioactive particles

Besides the work carrying IBU described previously, we have also verified the concept and well-functioning of this complex carrier system by using the nanostructured biocompatible magnetic carbon/graphite functionalized with different cancer antibodies focusing on the antigen-antibody interaction besides other molecules and materials. These targeting techniques include functionalizing the magnetic carbon/graphite with radioactive nanoparticles like Technetium-99m, Indium-11, and Iodine-131. These radioactive nanoparticles can be produced by either synthesizing the nanoparticles directly from the radioactive materials, or by irradiating non-radioactive particles with neutrons or accelerated ions[13]. Following this principle, at the present time we are functionalizing the nanostructured biocompatible magnetic carbon/graphite with both Iodone-131 radioactive particles and the corresponding cancer antibody for targeting cancer cells (figure 2). This isotope decays with a physical half-life of 8 days to stable Xe-131. It releases radiation during the decay process by emitting beta particles and gamma. The beta particles travel about 2 mm in tissue, thereby ensuring local treatment of the cancer tumor by causing mutation and death in cells that it penetrates. For this reason, high doses of the isotope are sometimes less dangerous than low doses since they tend to kill normal tissues that would otherwise become cancerous because of the radiation. Thus, Iodine-131 is increasingly less employed in small doses in medical use but increasingly is used only in large and maximal treatment doses, as a way of killing targeted cancer tissues. Iodine-131 is given for therapeutic use since about 10% of its energy and radiation dose is via gamma radiation while the other 90% is the beta radiation mentioned before.

Developing MAGUS® associated to Boron Neutron Capture Therapy (BNCT)

Another promising application we are at present working on, is based on MAGUS® associated to Boron Neutron Capture Therapy (BNCT). This technique uses neutron as the external source and is frequently used to treat

specific tumors that are radioresistant or very difficult to kill using conventional radiation therapy[13].

It can be employed as a standalone radiation therapy or in combination after conventional radiotherapy methods. Some examples where it has proven to be very powerful and effective is at treating salivary gland tumors and certain forms of cancer, such as adenoid cystic carcinoma, inoperable/recurrent salivary gland malignancies resistant to standard low-LET radiotherapies and glioblastoma (high-grade glioma, GBM), a prevalent and aggressive brain tumor[14].

The BNCT uses Boron-containing drugs to deliver a natural isotope of the Boron-10 to tumors and while it is confined to tumors, as radionuclides tend to accumulate at the sites of tissue damage, a subsequent bombardment with neutrons provides an isotope of Lithium-7 and an alpha particle with a short range of action[13]. It means that the alpha particle deploys an amount of energy that is delivered in a high linear energy transfer (LET) due to its nature. In that case, their high energy will be delivered along their very brief pathway (<10μm) conveying about 150 keV/μm. In other words, the dose is deposited inside a pathway that is the size of the diameter of a single cell[15].

Neutron's biological impact on cells is greater than other types of radiation. Since surprisingly they do not damage equally all cells, there are cases in which they can be more damaging to cancerous cells than to healthy cells surrounding the cancer. Therefore, for the same amount of radiation, a lethal dose can be delivered to the cancer cells, while a sub-lethal dose is delivered to the healthy tissue reducing the chances of its cell damage or death. Used thoroughly, this different impact can be an advantage in certain treatments. In general, neutron therapy shows high efficiency in the treatment of recurrent voluminous tumors of complex localization[15]. The approach we are working on for the BNCT application is based on functionalizing the nanostructured biocompatible magnetic carbon/graphite with Boron-10 (instead of Iodine-131) with the antibodies mentioned before. Then, we apply an external magnetic field to redirect the Boron-10 and employ the fast neutron dose more efficiently at the tumor, making it necessary a lower dose to accomplish the same results. This is especially important for BNCT because the fast neutron therapy is limited by high toxicity. And that is why we are providing once again to the system a double way to exclusively reach the target and not the healthy cells around increasing its efficiency and performance.

It is important to highlight that, by using both the interaction antigen-antibody and the guidance through external magnetic field, we are affording to our drug delivery system a *double way* to reach and act only the target, i.e., the cancer, and not the healthy cells around. Moreover, the target-specificity

achieved by our delivery system MAGUS® comes from years of research of our group and represent a pioneering and effective way to treat cancer.

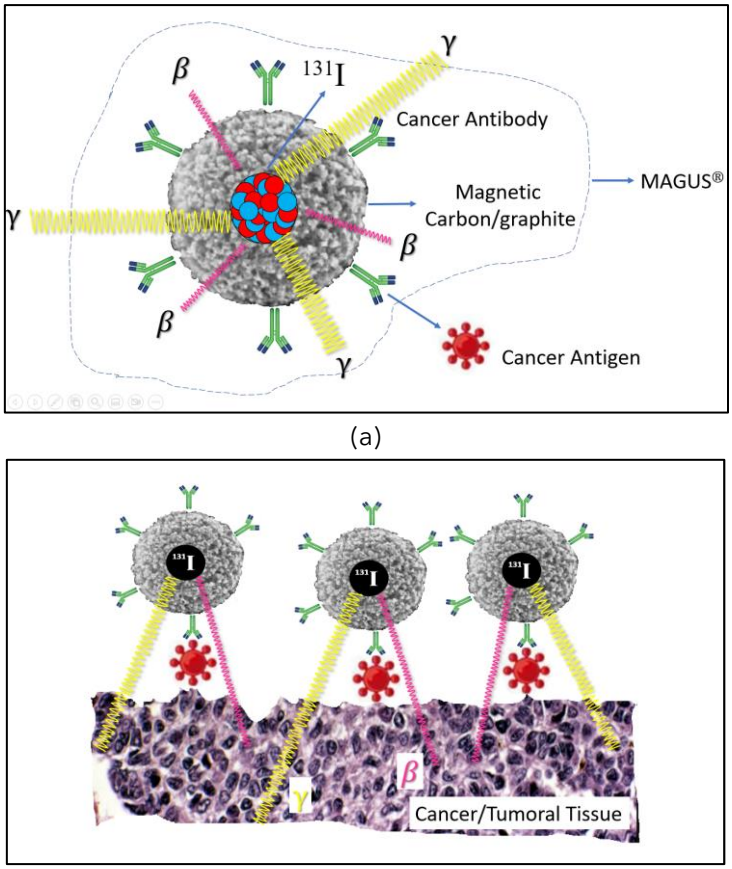

Figure 2. (a) Sketch of MAGUS®, the nanostructured drug delivery system consisting of magnetic carbon/graphite functionalized with radioactive particle of Iodine-131 for cancer irradiation treatment and the corresponding antigen-antibody interaction; (b) interactions of those particles with cancer/tumoral tissue through antigen-antibody driven force; both figures show the radiation from Iodine-131 (beta and gamma).

Summary

In conclusion, the nanostructured magnetic carbon/graphite we synthesize by the first time in 2005 by following an unprecedent simple chemical route, appears as a very promising way to achieve countless valuable goals mainly in medicine and biodefense, depending on the way MAGUS® is functionalized. Specifically, about fighting cancer, it has shown itself to be superior in many aspects to the available solutions for some aggressive and prevalent types of tumors or even for recurrent voluminous tumors of complex localization due to its combined physical properties coupled with biological and physical functionalization. This has a special significance and relevance in nuclear science by considering functionalizing the nanostructured magnetic

carbon/graphite with radioactive nanoparticles of Iodine-131 or Boron-10 following the BNCT technique to fight cancer with, most probably, no side effects. This is something that conventional drugs and other treatments do not have at all.

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Conflict of Interest

We declare that do not exist any financial or even conflicts of interest.

Referências

1. J. F. Galdino; *A importância da integração do sistema de inovação militar o e sistema nacional de inovação*; in: *Coletânea de artigos de opinião sobre estudos estratégicos em defesa e segurança*; ISBN 978-65-87080-44-4; Tiknet Publishers; Editors: J. C. Sanches and F. M. Araujo-Moreira; p. 155 (2023).

2. GPT-4 Heralds An Enormous Productivity Boost, And A Wrenching Transformation Of Work (forbes.com) (consulted in March, 2023).

3. Cancer statistics, 2022 - PubMed (nih.gov) (consulted in March 2023).

4. Cancer (who.int) (consulted in March 2023).

5. A. W. Mombrú, H. Pardo, R. Faccio, O. F. De Lima, E. R. Leite, G. Zanelatto, A. J. C. Lanfredi, C. A. Cardoso, and F. M. Araújo-Moreira (2005); *Multilevel ferromagnetic behavior of room-temperature bulk magnetic graphite*; Phys. Rev. B (Rapid Comm.) **71**, 100404(R).

6. H. Pardo, R. Faccio, F. M. Araújo-Moreira, O. F. De Lima, A. W. Mombrú (2006); *Synthesis and characterization of stable room temperature bulk ferromagnetic graphite*; Carbon **44**; 565–569.

7. N. S. Souza, S. Sergeenkov, C. Speglich, V. A. G. Rivera, C. A. Cardoso, H. Pardo, A. W. Mombrú, A. D. Rodrigues, O. F. De Lima, and F. M. Araújo-Moreira (2009); *Synthesis, characterization, and magnetic properties of room-temperature nanofluid ferromagnetic graphite*; Appl. Phys. Lett. **95**, 23, 233120.

8. Jair C. C. Freitas, Wanderlã L. Scopel, Wendel S. Paz, Leandro V. Bernardes, Francisco E. Cunha-Filho, Carlos Speglich, Fernando M. Araújo-Moreira, Damjan Pelc, Tonči Cvitanić, Miroslav Požek (2015); *Determination of the hyperfine magnetic field*

in magnetic carbon-based materials: DFT calculations and NMR experiments; Nature Scientific Reports **5**, 1, 1-9.

9. Lígia N. M. Ribeiro, Ana C. S. Alcântara, Margarita Darder, Pilar Aranda, Paulo S. P. Herrmann Jr, Fernando M. Araújo-Moreira, Mar. García-Hernández, Eduardo Ruiz-Hitzky (2014); *Bionanocomposites containing magnetic graphite as potential systems for drug delivery*; Int. J. Pharm. **477**; 553–563.

10. N. S. Souza, S. Sergeenkov, A. D. Rodrigues, C. A. Cardoso, H. Pardo, R. Faccio, A. W. Mombrú, J. C. Galzerani, O. F. De Lima and F. M. Araujo-Moreira (2012); *Stability issues and structure-sensitive magnetic properties of nanofluid ferromagnetic graphite*; J. of Nanofluids **1**, pp. 143–147.

11. N. S. Souza, A. D. Rodrigues, C. A. Cardoso, H. Pardo, R. Faccio, A. W. Mombru, J. C. Galzerani, O. F. De Lima, S, Sergeenkov and F. M. Araujo-Moreira (2012); *Physical properties of nanofluid suspension of ferromagnetic graphite with high Zeta potential*; Phys. Lett. A **376**, 4, 544-546.

12. F. M. Araujo-Moreira and N. F. G. Serrano (2022); *Stable Room-Temperature Magnetic Carbon Graphite: From Discovery to Bionanotechnological Applications*; Research and Development in Material Science **17**, 2.

13. K. Abbas, F. Simonelli, U. Holzwarth, P. Gibson (2009); *Overview on the production of radioactive nanoparticles for bioscience applications at the JRC Cyclotron – European Commission*; Journal of Labelled Compounds and Radiopharmaceuticals; **52**, S231–S255.

14. V. Kiseleva, K. Gordo, P. Vishnyakova, E. Gantsova, A. Elchaninov, and T. Fatkhudinov; *Particle Therapy: Clinical Applications and Biological Effects* (2022); Life **12**, 2071.

15. Y. Matsumoto, N. Fukumitsu, H. Ishikawa, K. Nakai, and H. Sakurai (2021); *A Critical Review of Radiation Therapy: From Particle Beam Therapy (Proton, Carbon, and BNCT) to Beyond*; Journal of Personalized Medicine, **11**, 825.