Potential and Theranostics Applications of Novel Anti-Cancer Nano Drugs Delivery Systems in Preparing for Clinical Trials of Synchrotron Microbeam Radiation Therapy (SMRT) and Synchrotron Stereotactic Radiotherapy (SSRT) for Treatment of Human Cancer Cells, Tissues and Tumors Using Image Guided Synchrotron Radiotherapy (IGSR)

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Abstract

Novel anti-cancer Nano drugs delivery systems in preparing for clinical trials of Synchrotron Microbeam Radiation Therapy (SMRT) and Synchrotron Stereotactic Radiotherapy (SSRT) are the most promising human cancer cells, tissues and tumors treatment to be developed in the past decade. The current Image-Guided Synchrotron Radiotherapy (IGSR) market is over $1000 billion. There have been over 25 FDA approvals for Image-Guided Synchrotron Radiotherapy (IGSR) in the past year alone, and several pharmaceutical companies are heavily vested in developing their own synchrotron radiotherapies for human cancer cells, tissues and tumors treatment using Image-Guided Synchrotron Radiotherapy (IGSR) and imaging. Unfortunately, the percentage of human cancer patients for whom this treatment works remains modest. Novel anti-cancer Nano drugs delivery systems can be utilized to increase the efficacy of tumor Image-Guided Synchrotron Radiotherapy (IGSR) in the unresponsive patient population by altering the localization and pharmacokinetics of the therapeutic agents. In this paper, we would like to provide a condensed review of the current trends in potential and theranostics applications of novel anti-cancer Nano drugs delivery systems in preparing for clinical trials of Synchrotron Microbeam Radiation Therapy (SMRT) and Synchrotron Stereotactic Radiotherapy (SSRT) for treatment of human cancer cells, tissues and tumors using Image-Guided Synchrotron Radiotherapy (IGSR) and imaging research, promising new approaches, and conclude by emphasizing on both the importance of novel anti-cancer Nano drugs delivery systems in preparing for clinical trials of Synchrotron Microbeam Radiation Therapy (SMRT) and Synchrotron Stereotactic Radiotherapy (SSRT) for treatment of human cancer cells, tissues and tumors using Image-Guided Synchrotron Radiotherapy (IGSR) and imaging as well as some of the existing hurdles in translation of these technologies into the clinic.

Keywords: Proton beam therapy; Synchrotron radiation therapy; IGSR; SMRT; SSRT; Novel anti-cancer nano drugs; Tissues and tumors

Introduction

The three pillars of cancer treatment-radiation, surgery and chemotherapy- have remained the standard of care for human cancer patients for the past several decades [1-37]. However, these treatments are toxic, invasive and fail to produce durable remission in a significant portion of the human cancer patient population [38-89]. These treatments cannot distinguish between the patient’s healthy and tumor cells, resulting in limited survival rates especially amongst late-stage human cancer patients [90-95]. In this regard, Image-Guided Synchrotron Radiotherapy (IGSR) (IGRT) is the use of imaging during radiation therapy to improve the precision and accuracy of treatment delivery (Figure 1). IGRT is used to treat tumors in areas of the body that move, such as the lungs [96-99]. Radiation therapy machines are equipped with imaging technology to allow your...
The importance of Image Guided Synchrotron Radiotherapy (IGSR)

The excitement surrounding human cancer Image-Guided Synchrotron Radiotherapy (IGSR) is mainly due to its ability to produce durable remission, even amongst patients whose cancer cells, tissues and tumors were previously thought to be untreatable [124-167]. Most synchrotron radiotherapies utilize Nano molecules to activate the human body’s own immune system, which is capable of specifically attacking and eliminating human cancer cells, tissues and tumors [168-220]. The immense potential of Image-Guided Synchrotron Radiotherapy (IGSR) lies in its ability to eliminate pre-existing tolerance for the human cancer cells, tissues and tumors and in some cases even induce radiotherapical memory to prevent human cancer recurrence [221-252].

Significant Progress to Improve Image Guided Synchrotron Radiotherapy (IGSR)

Despite these successes, there are some major hurdles for Image-Guided Synchrotron Radiotherapy (IGSR) to overcome. Synchrotron radiotherapies can produce severe side effects such as over-activation of the immune system, and only produce effective results for certain cancer types and patients [253-283]. Oncologists, scholars, scientists and scientific researchers have attempted to improve its efficacy by using combination Image-Guided Synchrotron Radiotherapy (IGSR) and imaging such as Synchrotron Microbeam Radiation Therapy (SMRT) and Synchrotron Stereotactic Radiotherapy (SSRT). Despite producing modest improvements in treatment outcomes, there is still room for significant improvement [284-316].

Results and Discussion

Nanotechnology offers the ideal solution for specifically targeting image-guided synchrotron radiotherapeutics towards human cancer cells, tissues and tumors which can greatly reduce the side effects and increase the efficacy of the Image Guided Synchrotron Radiotherapy (IGSR). Nanoparticles are synthetic agents which can be loaded with therapeutics for concentrated delivery and sustained release at a specific target site within the body. Due to their high surface to volume ratio, they can be loaded with surface Nano molecules and ligands for specifically targeting human cancer cells, tissues, and tumors and/or facilitate controlled release of image-guided synchrotron radiotherapeutics at the tumor site. This improvement in pharmacokinetic properties of the anti-cancer Nano drug payload has the potential to widen the benefit of Image Guided Synchrotron Radiotherapy (IGSR) to all human cancer patients. There has been a lot of interest in utilizing anti-cancer Nano drugs delivery systems for developing Dendritic Cell (DC) vaccines. Despite the fact that DCs are the main antigen presenting cells, and are present abundantly in lymph nodes, their antigen presentation property may not be sufficient at all times to generate adequate anti-tumor responses. Delivering antigens or adjuvants without any targeted approaches leads to insufficient DC activity and can even result in radiotherapical tolerance. For generating robust anti-tumor responses, both antigens and adjuvants need to be specifically targeted to DCs. Several cell surface receptors on DC cells have already been investigated as targets for nanoparticles containing activating agents. Progress has also been made towards development of nanovaccines that do not depend on viral-vectors, thereby greatly increasing their safety profile. Meanwhile, Synchrotron Microbeam Radiation Therapy (SMRT) is a novel, preclinical RT in which synchrotron generated X-rays are segmented into a lattice of micro beams, usually 25 µm to 50 (µm) wide. The beams have minimal divergence and are spaced at regular intervals of 200 µm to 400 µm. Typical radiation doses are 300 Gy to 800 Gray (Gy) in the beam (peak dose), and 5 Gy to 20 (Gy) in the valley between the beams (Figure 3). In studies published to date, synchrotron MRT has shown equivalent or superior tumor control to conventional RT in different animal models, with the added benefit that there is significantly less damage to normal tissues. Currently, SMRT is only possible at a small number of synchrotron facilities world-wide, including the National Synchrotron Light Source (NSLS-II). The underlying radiobiology of SMRT is not well understood with numerous hypotheses proposed to explain the effectiveness of a treatment which exposes the tumor to a very steep gradient of ‘peak’ and ‘valley’ doses of radiation (Figure 4).

Several immune cells such as tumor-associated macrophages and regulatory T-cells play an important role in tumor metastasis and inhibiting anti-tumor surveillance. Anti-cancer Nano drugs delivery systems are being actively applied to alter tumor microenvironment and reactivate tumor surveillance, thereby eliminating tumor cells. Nanoparticles that utilize special properties of the tumor microenvironment (such as the extracellular acidic pH of tumor tissues or over expression of mannose receptor) are utilized by...
nanoparticles to release the Image-Guided Synchrotron Radiotherapy (IGSR) agents specifically at the site of tumor tissues. For example, biopolymer scaffolds have been used for delivering, expanding and dispersing tumor-reactive T cells. In the other words, currently, up to 50 per cent of human cancer patients receive radiotherapy and although effective there are some significant limitations to treatment including damage to normal tissue. Due to targeting a tumor with a broad beam X-ray, the radiation dose administered must be delivered over several days to give the normal tissue time to recover. Synchrotron Microbeam Radiation Therapy (SMRT) is a radiotherapy technique that treats tumors with narrow wafers of very high doses of synchrotron radiation and is delivered in very short amounts of time. These wafers result in peaks and valleys of radiation where the dose differential could be several 100 Gray (Gy) (Figure 5). Using the Imaging and Medical Beam Line (IMBL) at the National Synchrotron Light Source (NSLS-II), we have developed several models to evaluate the X-rays generated by the synchrotron for novel, preclinical radiotherapy studies. Recently, we have characterized the response of established tumors, cell lines and normal tissue to SMRT in comparison with conventional broad beam and synchrotron-broad beam radiation. Interestingly, normal tissue can tolerate X-ray doses 100 times greater than conventional radiotherapy when delivered by SMRT. In fact, we are currently investigating the mechanisms of normal tissue tolerance to SMRT and how tumors are destroyed by SMRT when only a tenth of tumor volume is irradiated at the peak SMRT dose (Figure 6). Combining nanotechnology with Image-Guided Synchrotron Radiotherapy (IGSR) can increase the therapeutic efficacy of the delivery, decrease systemic toxicity while substantially reducing treatment cost. For example, nanoparticles conjugated to surface targeting ligands have been used to deliver Image-Guided Synchrotron Radiotherapy (IGSR) cargo such as tumor-reactive T-cells and dendritic cells specifically to the cancer site. Furthermore, platforms comprising of nanoparticles such as Cadmium Oxide (CdO), Ruthenium (IV) Oxide (RuO₂), Rhodium (III) Oxide (Rh₂O₂), Rhenium (IV) Oxide (ReO₂), Rhenium Trioxide (ReO₃), Rhenium (VII) Oxide (Re₂O₇), Iridium (IV) Oxide (IrO₂) and quantum dots coated with special materials are being researched for large-scale manufacturing of artificial antigen presenting cells for activation of cytotoxic T-lymphocytes.

Conclusions, Perspectives, Useful Suggestions and Future Challenges and Studies

Great efforts have been applied towards the development of novel anti-cancer Nano drugs delivery systems in preparing for clinical trials of Synchrotron Microbeam Radiation Therapy (SMRT) and Synchrotron Stereotactic Radiotherapy (SSRT) for treatment of human cancer cells, tissues and tumors using Image-Guided Synchrotron Radiotherapy (IGSR) and imaging, which has been enhanced by our improved understanding of the immune system as well as the interaction mechanisms between nanoparticles and human cancer cells, tissues and tumors. By designing nanoparticles appropriately, we can greatly improve synchrotron radiotherapy efficacy via targeted delivery of radiotherapical therapeutics as well as engaging the patients’ innate and adaptive immune system to specifically kill human cancer cells, tissues and tumors.
of these nanoparticle-based synchrotron radiotherapies to the clinic can pose significant challenges—such as optimization of in vitro assays and validity of animal models. Emphasis also needs to be placed on development of safe smart biomaterials for the synthesis of anti-cancer Nano drugs. New evidence suggests that novel anti-cancer Nano drugs delivery systems in preparing for clinical trials of Synchrotron Microbeam Radiation Therapy (SMRT) and Synchrotron Stereotactic Radiotherapy (SSRT) for treatment of human cancer cells, tissues and tumors using Image-Guided Synchrotron Radiotherapy (IGSR) and imaging holds great promise for improving Image-Guided Synchrotron Radiotherapy (IGSR) and will greatly affect patient lives by generating robust and durable responses when compared to these radiotherapical therapeutics being administered as free anti-cancer Nano drugs.

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References

34. Eizenkop J, Avrutsky I, Auner G, Georgiev DG, Chaudhary V. Single pulse


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2012;18:5201-12.


99. Heidari A. Study of irradiations to enhance the induces the dissociation of hydrogen bonds between peptide chains and transition from helix structure to random coil structure using ATR-FTIR, Raman and ‘HNMR Spectroscopies, J Biomol Res Ther. 2016;5:e146.


110. Heidari A. Measurement the amount of vitamin D2 (Ergocalciferol), vitamin D3 (Cholecalciferol) and absorbable calcium (Ca²⁺), iron (II) (Fe²⁺), magnesium (Mg²⁺), phosphate (PO₄⁻) and zinc (Zn²⁺) in apricot using high-performance liquid chromatography (HPLC) and spectroscopic techniques. J Biom Biostat. 2016;7:292.

111. Heidari A. Spectroscopy and quantum mechanics of the helium dimer (He₂⁻), neon dimer (Ne₂⁻), argon dimer (Ar₂⁻), krypton dimer (Kr₂⁻), xenon dimer (Xe₂⁻), radon dimer (Rn₂⁻) and unouncto dimer (Uuo⁻) molecular cations. Chem Sci J. 2016;7:112.


114. Heidari A. A combined computational and QM/MM molecular dynamics study on boron nitride nanotubes (BNNTs), amorphous boron nitride nanotubes (a-BNNTs) and hexagonal boron nitride nanotubes (h-BNNTs) as hydrogen storage. Struct Chem Crystallogr Commun. 2016;2:1.


135. Heidari A. Linear and non-linear quantitative structure-anti-cancer-activity relationship (QSACAR) study of hydrenous ruthenium (IV) oxide (RuO₂) nanoparticles as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and anti-cancer nano drugs. J Integr Oncol. 2016;5:e110.


137. Heidari A. Coplanarity and collinearity of 4’-dinosyl-2,2’-bithiazole in one domain of bleomycin and pingyangmycin to be responsible for binding of cadmium oxide (CdO) nanoparticles to DNA/RNA bidentate ligands as anti-tumor nano drug. Int J Drug Dev & Res. 2016;8:007-8.


140. Heidari A. A gastrointestinal study on linear and non-linear quantitative structure (chromatographic) retention relationships (QSSR) models for analysis 5-aminosalicylates nano particles as digestive system nano drugs under synchrotron radiations. J Gastrointest Dig Syst. 2016;6:e119.


143. Heidari A. Computational study on molecular structures of C$_{20}$, C$_{30}$, C$_{50}$, C$_{60}$, C$_{70}$, and C$_{80}$ fullerene molecules under synchrotron radiations using fuzzy logic. J Material Sci Eng. 2016;5:282.

144. Heidari A. Graph theoretical analysis of zigzag polyhexamethylene biguanide, polyhexamethylene adipamide, polyhexamethylene biguanide gauze and polyhexamethylene biguanide hydrochloride (PFMB) boron nitride nanotubes (BNNTs), amorphous boron nitride nanotubes (a-BNNTs) and hexagonal boron nitride nanotubes (h-BNNTs). J Appl Computat Math. 2016;5:e143.


146. Heidari A. A comparative study of conformational behavior of isosRETinoin (13-Cis Retinoic Acid) and tretinoin (all-trans retinoic acid (ATRA)) nano particles as anti-cancer nanodrugs under synchrotron radiations using hartree-fock (HF) and density functional theory (DFT) methods. Insights in Biomed. 2016;1:2.


160. Heidari A. Electronic coupling among the five nanomolecules shuts down quantum tunneling in the presence and absence of an applied magnetic field for indication of the dimer or other provide different influences on the magnetic behavior of single molecular magnets (SMMs) as qubits for quantum computing. Glob J Res Rev. 2017;4:2.

161. Heidari A. Polymorphism in nano-sized graphene ligand-induced transformation of Au$_x$Ag$_y$/Cu$_z$/Ph$_w$B$_u$ to Au$_x$Ag$_y$/Cu$_z$/Ph$_w$B$_u$ (x=1-12) nanomolecules for synthesis of Au$_{x+1}$Ag$_{y+1}$/Cu$_{z+1}$/Ph$_w$B$_u$ (SC)$_{x+1}$ (SC)$_{y+1}$ (PET) and Au$_x$Ag$_y$/Cu$_z$/Ph$_w$B$_u$ (SC)$_{x+1}$ (SC)$_{y+1}$ (PET) nano clusters as anti-cancer nano drugs. J Nanomater Mol Nanotechnol. 2017;6:3.


166. Heidari A. Concurrent diagnosis of oncology influence outcomes in emergency general surgery for colorectal cancer and multiple sclerosis (MS) treatment using magnetic resonance imaging (MRI) and Au$_n$(SR)$_m$ to Au$_n$(Ag(SR)$_m$, Au$_n$(SR)$_m$, Au$_n$(SR)$_m$, Au$_n$(SR)$_m$, Au$_n$(SR)$_m$, Au$_n$(SR)$_m$. J Appl Bioinforma Comput Biol. 2017;6:1.


203. Heidari A. Vibrational decihertz (dHz), centihertz (cHz), millihertz (mHz), microhertz (µHz), nanohertz (nHz), picohertz (pHz), femtohertz (fHz), attohertz (aHz), zeptohertz (zHz) and yoctohertz (yHz) imaging and spectroscopy comparative study on malignant and benign human cancer cells and tissues under synchrotron radiation. Int J Biomedicine. 2017;7(4):335-40.


208. Heidari A. Vibrational decahertz (daHz), hectohertz (hHz), kilohertz (kHz), megahertz (MHz), gigahertz (GHz), terahertz (THz), petahertz (PHz), exahertz (EHz), zettahertz (ZHHz) and yottahertz (YHz) imaging and spectroscopy comparative study on malignant and benign human cancer cells and tissues under synchrotron radiation. Madridge J Anal Sci Instrum. 2017;2(1):41-6.


223. Heidari A. Heteronuclear correlation experiments such as heteronuclear single-quantum correlation spectroscopy (HSQC), heteronuclear multiple-quantum correlation spectroscopy (HMQC) and heteronuclear multiple-bond correlation spectroscopy (HMBC) comparative study on malignant and benign human endocrinology and thyroid cancer cells and tissues under synchrotron radiation. J Endocrinol Thyroid Res. 2018;3(1):555603.


247. Alireza H. Atomic force microscopy based infrared (AFM-IR)
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250. Heidari A. Angelic acid, diabolic acids, draculin and miraculin nano molecules incorporation into the nano polymeric matrix (NPM) by immersion of the nano polymeric modified electrode (NPME) as molecular enzymes and drug targets for human cancer cells, tissues and tumors treatment under synchrotron and synchrocyclotron radiations. Med & Analy Chem Int J. 2018;2(1):000111.


256. Heidari A. Cadaverine (1,5-pentanediamine or pentamethylenediamine), diethyldiazodicarboxylate (DEAD or DEADCAT) and putrescine (tetramethylenediamine) nano molecules incorporation into the nano polymeric matrix (NPM) by immersion of the nano polymeric modified electrode (NPME) as molecular enzymes and drug targets for human cancer cells, tissues and tumors treatment under synchrotron and synchrocyclotron radiations. J Oncol Res. 2018;1(1):1-20.


263. Heidari A. Uranocene (U(CH8)2) and bis(Cyclooctatetraetrae)Iron (Fe(CH8)2 or Fe(COT)2)-enhanced precatalyst preparation stabilization and initiation (EPPSI) nano molecules. Chemistry Reports. 2018;1(2):1-16.


266. Heidari A. C70-carboxylfullerenes nano molecules incorporation into the nano polymeric matrix (NPM) by immersion of the nano polymeric modified electrode (NPME) as molecular enzymes and drug targets for human cancer cells, tissues and tumors treatment under synchrotron and synchrocyclotron radiations. Glob Imaging Insights. 2018;3(3):1-7.


268. Heidari A. A clinical and molecular pathology investigation of correlation spectroscopy (COSY), exclusive correlation spectroscopy (ECOSY), total correlation spectroscopy (TOCSY), heteronuclear single-quatum correlation spectroscopy (HSQC) and heteronuclear multiple-bond correlation spectroscopy (HMBC) comparative study on malignant and benign human cancer cells, tissues and tumors under synchrotron and synchrocyclotron radiations using cyclotron versus synchrotron, synchrocyclotron and the large hadron collider (LHC) for delivery of proton and helium ion ( Charged Particle) beams for oncology radiotherapy. Eur J Advances Eng Technol. 2018;5(7):414-26.


280. Heidari A. Fusitol, peroytacadiene, DEAD or DEADCAT (DiEthyl AzodicarboxylylTe, skatole, the nanoptopus, thebeacon, pikachurin, tie fighter, sperrmide and mirasorvone nano molecules incorporation into the nano polymeric matrix (NPM) by immersion of the nano polymeric modified electrode (NPME) as molecular enzymes and drug targets for human cancer cells, tissues and tumors treatment under synchrotron and synchrocytolon radiations. Glob Imaging Insights. 2018;3(4):1-8.


282. Heidari A, Gobato R. First-time simulation of deoxyuridine monophosphate (dUMP) (deoxyuridylic acid or deoxyuridylate) and vomitoxin (deoxynivalenol (DON)) (5α,7α-3,7,15-trihydroxy-12,13-Epoxytrichothec-9-En-E-8-One)-enhanced precatalytic preparation stabilization and initiation (EPPSI) nano molecules incorporation into the nano polymeric matrix (NPM) by immersion of the nano polymeric modified electrode (NPME) as molecular enzymes and drug targets for human cancer cells, tissues and tumors treatment under synchrotron and synchrocytolon radiations. Parana J Sci Edu. 2018;4(6):46-67.

283. Heidari A. Buckminsterfullerene (Fullerene), bullvalene, dickete and josiphos ligands nano molecules incorporation into the nano polymeric matrix (NPM) by immersion of the nano polymeric modified electrode (NPME) as molecular enzymes and drug targets for human hematology and thromboembolic diseases prevention, diagnosis and treatment under synchrotron and synchrocytolon radiations. Glob Imaging Insights. 2018;3(4):1-7.


294. Heidari A. FT-Raman spectroscopy, coherent anti Stokes raman


