3rd TPCF Preclinical Imaging Symposium (TPIS2020)
5-6 August 2020, Tehran University of Medical Sciences

EDITORIAL

Is Preclinical Imaging the Cross Talk between all Branches of Science?

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Abstract

The path of discovering/designing a molecule to developing a novel drug could take up to an average of 12 years and costs around $1 billion (USD). Preclinical phase is a major step on this path and is the part where scientists perform additional studies on their molecules prior to moving the drug into clinical studies. Preclinical studies consist of anything ranging from observing efficacy, dosing strategy, safety and toxicological studies and pharmacokinetics and pharmacodynamics. Pharmacodynamics consist of any studies performed in order to understand the relationship between the amount of drug in the body and its biological effect. In summary this means what does the drug do to the body and how potent and efficacious the drug is? In pharmacokinetics we are interested to identify the effect of body on the drug. Therefore, we would be interested in knowing the absorption, distribution, metabolism and excretion of the novel drug. In order to ensure reliability and consistency all of the preclinical results should be complied with the good laboratory practice and are required to be submitted to organization such as FDA before filing for approval of an investigational new drug.

Addressing all of the above questions requires time and money but with the rise of cutting-edge technologies such as preclinical imaging, advancement of preclinical studies has excelled. This is due to being able to see in real time and in the same preclinical model the majority of parameters needed to be identified for preclinical phase of drug development. There are numerous dedicated preclinical imaging devices that could be used. These devices consists of Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Computed Tomography (CT), Optical/Fluorescence and Ultrasound imaging. These technologies require advanced engineering and scientific skills for their development, usage and optimization.

This suggests that in order to have an enhanced preclinical imaging infrastructure, we would require an advanced multidisciplinary collaboration and network between engineering and sciences. In order to facilitate this, we at Tehran University of Medical Sciences (TUMS) Preclinical Core Facility (TPCF) organized a symposium branded as TPIS (TPCF Preclinical Imaging Symposium). This was our 3rd annual symposium and it was on online platform due to Covid-19 pandemic. The symposium consisted of talks by domestic and international presenters from various disciplines of science and engineering.

We are pleased that Frontiers in Biomedical Technology (FBT) is publishing these abstract in their journal. We at TPCF are also inviting the readers of FBT to attend our 4th annual TPIS (for more information visit our website on: www.TPCF.ir).

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Synthesis and Evaluation of a Gd(III)-RGD Peptide for MR Molecular Imaging in Non-Small Cell Lung Cancer (NSCLC)

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Abstract

Background: The $\alpha_v\beta_3$ integrin receptors are overexpressed on proliferating endothelial cells such as those present in growing tumors, as well as on tumor cells of various origins. Specific targeting of $\alpha_v\beta_3$ integrin receptors by these RGD (Arginylglycylaspartic acid)-containing peptides makes these short sequences a suitable candidate for imaging diagnosis and follow-up of lung cancer.

Objective: The RGD peptide with high affinity is designed based on molecular docking and modeling. This dimeric RGD radiolabeled peptide has a higher affinity for integrin αvβ3 with selective tumor targeting potential. Peptide labeling with gadolinium (Gd) (for imaging) was performed which allows effective MR cancer molecular imaging with high spatial resolution. Gadolinium-labeled dimeric RGD peptide will have higher sensitivity for early diagnostic purposes and it is suitable for following up the procedures.

Materials and Methods: DOTA-E(cRGDfK)$_2$ was labeled with Gd(III) efficiently. The stability was examined in different buffer systems. The cytotoxicity to NIH3T3, A549, and PC-3 cells was measured by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide reduction assay (MTT). The biodistribution of a Gd(III)-DOTA-E(cRGDfK)$_2$ in a small cell lung cancer xenograft mouse model was studied. In addition, the very early diagnostic potential of the Gd-labeled RGD peptide was evaluated using MR molecular imaging.

Results: MR imaging showed high binding specificity of Gd(III)-DOTA-E(c RGDfK)2 to A549 lung tumors in mice. Gd-DOTA-E(c RGDfK)$_2$ did not show cytotoxicity at high concentration and on different cell lines. Biodistribution studies confirm tumor uptake up to 24 h after the injection. The contrast agent resulted in improved tumor contrast enhancement tumor-bearing mice at a dose of 0.1 mmol Gd/kg. The peptide targeted MRI contrast agent is promising for high-resolution MR molecular imaging of lung tumors. Tumor uptake peaks were at 30 min post-injection for Gd(III)-DOTA-E(c RGDfK)$_2$. The tumor was clearly visualized in all images.

Conclusion: Gd(III)-DOTA-E(c RGDfK)$_2$ can be used as a peptide-based imaging agent allowing very early detection of different cancers overexpressing $\alpha_v\beta_3$ integrin receptors and can be a potential candidate in clinical peptide-based imaging for non-small cell lung cancer.

Keywords: E(c RGDfK)$_2$; Gadolinium; A549; Peptide-Based Imaging; Non-Small Cell Lung Cancer.

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Correlation of Age, Sex, Cervical Vertebrae Maturation (CMV) and Spheno-Occipital Synchondrosis (SOS): A Cone Beam Computed Tomography (CBCT) Based Study

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Abstract

Background: Determining the stage of skeletal maturation is often needed for proper orthodontic treatment planning including orthopedic functional therapy and, suture expansion. There are several methods of determining skeletal maturity in dentistry including the hand-wrist index, dental age, and Cervical Vertebrae Maturation (CVM). The Spheno-Occipital Synchondrosis (SOS) has been used in forensic dentistry and, recently attempts to correlate it with CVM as an index of skeletal maturity has attracted attention.

Objective: The primary intent of this research is to determine whether there is a significant correlation between CVM and SOS and if there is any sex dimorphism.

Materials and Methods: The study population was normal healthy subjects aged 7-18 evaluated by CBCT. Six-stage CVM (Baccetti *et al.*, 2005) and 5-stage SOS (Bassed *et al.*, 2010) indices were implemented. Patients with the maxillofacial syndromes, history of trauma to maxillofacial region or fracture, and systematic diseases affecting bone growth were excluded.

Results: This study included 253 subjects (female: 125, male: 128). The mean age was 12.36±3.3 years (female: 12.58 3.3, male 12.11± 3.08). There was a significant positive correlation between age vs. SOS ($r = 0.74$) and age vs. CVM ($r = 0.68$). Generally, CVM and SOS were strongly correlated ($r = 0.82$), when split by sex, $r = 0.85$, and $r = 0.75$ were found for female and male subjects, respectively. Prediction of CVM was obtained by an accurate ordinal regression model ($R2=0.66$, $p<0.001$) by sex ($p<0.001$) and age ($p=0.004$) as predictor variables. Similar accurate model ($R2=0.7$, $p<0.001$) was obtained with age ($P<0.001$) and CVM as predictors ($P<0.001$) to estimate SOS.

Conclusion: The cervical vertebrae maturation stage and the time of fusion of the Spheno-Occipital suture are strongly correlated. The SOS may be used as an adjunct to predict skeletal maturity.

Keywords: Skeletal; Maturation; Vertebrae; Suture; Cone Beam Computed Tomography.

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Human Organ Dose Estimation from Biodistribution Data of Rat in Renography Using ^{18}F-PFH and ^{124}I-OIH PET Agents

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Abstract

Background: Dosimetry is a crucial step for every treatment procedure including ionizing radiation. Recently two radiotracers Para-^{18}F-fluorohippuric acid (^{18}F-PFH) and ortho-^{124}I-iodohippuric acid (^{124}I-OIH) are introduced as potentially usable for renography with Positron Emission Tomography (PET). This study was performed with the aim of making a preliminary assessment of human organ doses due to receiving ^{18}F-PFH and ^{124}I-OIH with using the biodistribution data reported in healthy rats. Then results were compared with the data of the other renography radiotracer, Technetium-99m-Mercaptoacetyltriglycine (^{99m}Tc-MAG3).

Materials and Methods: Human organ absorbed doses were extrapolated from rat data with using the Medical Internal Radiation Dose (MIRD) formulation. S-factors were obtained by Monte-Carlo N-particle (MCNP) simulation. Absorbed dose data for ^{99m}Tc-MAG3 were used as documented in the International Commission on Radiological Protection (ICRP) publication 80.

Results: Estimations show the effective absorbed dose of 0.09 and 0.17μSv for the whole body with ^{18}F-PFH or ^{124}I-OIH injection in humans and the values reported for ^{99m}Tc-MAG3 are 135 and 73 times greater, respectively. Absorbed doses for ^{18}F-PFH or ^{124}I-OIH were less than 0.1μSv/MBq in all organs except kidneys with 0.83 or 0.77 μSv/MBq for ^{18}F-PFH or ^{124}I-OIH, respectively.

Conclusion: It seems that much safer levels of radiation organ doses cause by ^{18}F-PFH and ^{124}I-OIH PET agents respect to ^{99m}Tc-MAG3. Accurate approximations can be provided in clinical trials.

Keywords: ^{18}F-PFH; ^{124}I-OIH; Positron Emission Tomography; Para-^{18}F-Fluorohippurate; Ortho-^{124}I-Iodohippurate; Renal Agent; Tubular Secretion; Renography; Dosimetry.

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A Review on the Monitoring of the Effect of Protective Drugs against Ionizing Radiation, Cisplatin and Gentamicin Using ^{99m}TC-DMSA

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Abstract

Background: Radiotherapy and chemotherapy or their combination are the main modalities for cancer treatment. However, Nephrotoxicity is an important side effect that limits ionizing radiation and drug dosages in these schedules. Kidney injures may appear acutely or after a duration. Some renoprotective agents are provided to decrease the toxic effects. Histological and biochemical methods are currently used for kidney damage assessments but these approaches are invasive and time-consuming with low sensitivity for acute injuries. Quantitative renal ^{99m}TC-DMSA scintigraphy is a non-invasive, precise, and sensitive procedure with the ability to indicate acute kidney damages and long-term follow up studies.

Conclusion: This study reviews the recent preclinical and clinical evaluations using ^{99m}TC-DMSA to monitor the extent of nephrotoxicities due to cisplatin, gentamicin, and ionizing radiation and also to screen the effects of renoprotective agents to decrease or prevent the injuries.

Keywords: Renoprotective Agents; ^{99m}Tc-DMSA; Ionizing Radiation; Cisplatin; Gentamicin; Nephrotoxicity.

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Synthesis and Evaluation of ^{99m}TC-DOTA-(Lys-Dabcyl6, Phe7)-ARA-290 as Potential SPECT Tracer for Targeting the Cardiac Ischemic Region

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Abstract

Background: Myocardial ischemia and cardiac infarction are the major causes of mortality in the world, therefore early diagnosis can reduce death and health care costs. Erythropoietin (EPO) have tissue-protective effects in the hypoxic and ischemic situations because of Pyroglutamate Helix B Surface Peptide (ARA-290; pHBSP), which has been derived from B-subunit of the EPO.

Materials and Methods: The two primary aims of this study include: 1. To synthesis DOTA-(Lys-Dabcyl6, Phe7)-ARA-290 using Fmoc solid-phase peptide synthesis method and labeling by ^{99m}TC. 2. Evaluate synthesized peptide for radiochemical purity, serum stability, specific cellular binding in H9c2 cells, biodistribution, and SPECT scintigraphy in the cardiac ischemic rats.

Results: Labeling yield was obtained more than 96% by ITLC and the in vitro stability of the radiolabelled peptide up to 6 h was 85%. The binding of ^{99m}TC-peptide to hypoxic cells was significantly more than normoxic cells (3-fold higher compared to normoxic cells at 1 hour). Biodistribution and SPECT imaging on the cardiac ischemic model showed that radiopeptide considerably accumulated in the ischemic region (cardiac ischemic-to-lung rate = 3.65 ID/g % at 0.5 h).

Conclusion: The in vitro and in vivo results indicated that ^{99m}TC-DOTA-(Lys-Dabcyl6, Phe7)-ARA-290 could be a suitable candidate for early detection of cardiac ischemia.

Keywords: Ischemia; Erythropoietin; ARA-290; Technetium-99m; Molecular Imaging.

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Application of Radiolabeled Peptides in Tumor Imaging and Therapy

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Abstract

Objective: The main goal of the present paper is to review some essential aspects in developing a valuable radiolabeled peptide and some radiolabeled peptides with regard to their applications in tumor imaging and therapy in preclinical and clinical phases.

Materials and Methods: A systematic search of PubMed, MEDLINE, Web of Science, and Google Scholar based on various sets of keywords was conducted. Based on their abstracts, all results were evaluated and irrelevant studies were neglected and qualified studies were used for the review.

Results: Scientists are looking for new therapies to cope with the rise in cancer worldwide. Since cancer cells overexpress peptide receptors and owing to small size, easy uptake by tumor cells, easy preparation, and with no toxicity, the use of radiolabeled peptides with high specificity and affinity for accurate imaging and therapy has attracted much attention. To develop an ideal imaging or treatment radiolabeled peptide, there are some aspects in the components of radiolabeled peptide including radionuclide, peptide, chelator, and spacer that should be considered. Some peptides, including somatostatin, RGD (Arginylglycylaspartic acid), neurotensin, bombesin, exendin, vasoactive intestinal peptide, and gastrin are currently under (pre)clinical investigations.

Conclusion: According to the overexpression of peptide receptors in cancers, radiopeptides provide a promising research area in tumor imaging and therapy which can be optimized to be considered as one of the personalized medicine strategies.

Keywords: Cancer; Radiolabeled Peptides; Chelator; Tumor Imaging and Therapy; Radionuclide.

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Molecular CT Imaging of Cancer Cells Using Targeted Gold Nanoparticles

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Abstract

Background: Recently, cancer research and advances in molecular biology have led to the recognition of sensitive ligands that are associated with different types of cancer cell. However, in vivo cancer cells identification procedures with computed tomography, based on the detection of these molecular cancer cell markers, are rare today.

Objective: This study investigated in vivo the possibility of cancer cell diagnosis using clinical computed tomography based on molecular ligands rather than on anatomical structures.

Materials and Methods: In this study, Gold nanoparticles attached to folic acid via cysteamine (FA-Cys-AuNPs) with a size of ~15 nm were synthesized and characterized using UV-Vis spectrophotometry, TEM, FTIR, and ICP-OES analyses. The non-toxicity of nanoparticles was confirmed by MTT assay. FA-Cys-AuNPs were intravenously injected into nude mice implanted with human nasopharyngeal head and neck cancer. CT imaging was performed using a Clinical CT scan.

Results: The findings clearly illustrated that a small tumor, which is undetectable via computed tomography, is enhanced by X-ray attenuation and becomes visible (2-times) by the molecularly targeted AuNPs. It was further demonstrated that active tumor cells targeting (FA-Cys-AuNPs) are more specific and efficient than passive targeting (AuNPs).

Conclusion: This noninvasive molecular cancer imaging technique can provide researchers with a new modality to study in vivo the activity of cancer molecular processes and make possible early tumor detection. According to the results, FA-Cys-AuNPs can be employed as a promising contrast agent in CT scan imaging and radiotherapy that require enhanced radiation dose.

Keywords: Molecular Computed Tomography Imaging; Gold Nanoparticles; Cancer.

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Imaging of Head and Neck Cancer Cells Using a New Contrast Agent by Dual-Energy CT

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Abstract

Background: Head-and-neck cancer is the sixth most common cancer worldwide with the number of cases consistently increasing in developing countries. The successful development of effective, safe, and cost-effective nanoprobes for head-and-neck cancer-targeting imaging is a big challenge.

Objective: The purpose of this study is to measure the concentration of gold nanoparticles (AuNPs) attached to folic acid through cysteamine as the linker (FA-Cys-AuNPs) and AuNPs in KB human nasopharyngeal cancer cells using Dual-Energy CT (DECT).

Materials and Methods: In this study, nanoparticles with a size of ~15 nm were synthesized and characterized using UV-Vis (Ultraviolet–visible spectroscopy) spectrophotometry, TEM (Transmission Electron Microscopy), FTIR (Fourier-Transform Infrared), and ICP-OES (Inductively Coupled Plasma-Optical Emission Spectrometry) analyses. The toxicity of nanoparticles was evaluated by MTT assay under various concentrations (40-100 µg/ml) and incubation times (6, 12, and 24 h). To develop an algorithm for revealing different concentrations of AuNPs in cells, a corresponding physical phantom filled with 0.5 ml vials containing FA-Cys-AuNPs was used. The CT scan was performed at two energy levels (80 kVp and 140 kVp). One feature of DECT is material decomposition, which allows separation and identification of different elements. The values obtained from the DECT algorithm were compared with values quantitatively measured by ICP-OES. KB cells were also incubated with AuNPs and FA-Cys-AuNPs at concentrations of 40-100 µg/ml for 6, 12, and 24 h for DECT imaging.

Results: The non-toxicity of nanoparticles was confirmed by MTT assay under various concentrations (40-100 µg/ml) and incubation times (6, 12, and 24 h) and the nanoparticles had favorable biocompatibility. By increasing the incubation time and concentration in the presence of FA-Cys-AuNPs, in comparison with AuNPs, DECT pixels were increased. DECT imaging revealed that cells that incubated with FA-Cys-AuNPs had higher concentration than the cells incubated only with AuNPs.

Conclusion: FA-Cys-AuNPs could be a suitable candidate for targeted contrast agent in DECT molecular imaging of head and neck cancer cells.

Keywords: Dual Energy Computed Tomography Imaging; Gold Nanoparticles; Cancer.

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Review on Application of Multiphoton Imaging in Stem Cells Researches

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Abstract

Background: Intravital microscopy is a powerful research technique that combines the resolution and sensitivity found in microscopic studies of cultured cells with the relevance and systemic influences of cells in the context of the intact animal.

Objective: In this paper, we reviewed a variety of Multiphoton Microscopy (MPM) imaging approaches being investigated in stem cell imaging researches. Intravital microscopy, microscopy of living animals, is a powerful research technique that combines the resolution and sensitivity found in microscopic studies of cultured cells with the relevance and systemic influences of cells in the context of the intact animal. Multiphoton microscopy is an imaging technique that has significant advantages over standard confocal microscopy for intravital studies, including increased depth of tissue penetration and decreased phototoxicity. However, certain technical issues have curbed its usage to date, including limited depth of tissue penetration and high background emission of endogenous signals.

Materials and Methods: Most previous studies have used the excitation range 700–1000 nm and newer excitation lasers with longer wavelengths may provide solutions to these problems. On the other hand, MPM offers a level of resolution that is currently unmatched by other intravital imaging techniques and is thus a powerful tool to study cellular and organelle function in intact organs in living animals. Especially, in stem cell research there is a high demand for techniques for the observation of growth, proliferation, differentiation, the stability of living stem cells under physiological conditions, etc. Several big questions in cancer are also so far have remained unanswered, including the existence and origin of a cancer stem cell and the meaning of epithelial to mesenchymal transition for metastasis in human cancers in vivo. Such questions are predestined for study because single-cell tracking and lineage tracing in vivo are required. The recent advancements that have been made in microscopy techniques and genetic model systems for IVM allow for direct observation of such events and will likely provide answers in the coming years.

Results and Discussion: The IVM has proven invaluable as a tool for fundamental research on cancer, it can also be particularly helpful for the development or improvement of new anti-cancer drugs because it offers the possibility of assessing the effects of therapeutics over a course of time. IVM has evolved from a method for visualization of the only vasculature in live organisms into a technique that has become instrumental for today's cancer research because it can unveil dynamics and signaling pathways involved in different cancer processes in vivo. Due to its unique ability to capture spatiotemporal information in living systems, intravital imaging – alone and in combination with “traditional” techniques has been able to answer a large number of previously unresolvable questions.

Keywords: Intravital Multi-Photon Imaging; Stem Cell.

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Advanced Multimodal Drug Molecular Imaging with High Applications

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Abstract

Background: Molecular imaging, where the location of molecules or Nano scale constructs can be tracked in the body to report on disease or biochemical processes, is rapidly expanding to include combined modality or multimodal imaging. No single imaging technique can offer the optimum combination of properties (e.g. resolution, sensitivity, cost, availability). The rapid technological advances in hardware to scan patients, and software to process and fuse images, are pushing the boundaries of novel medical imaging approaches, and hand-in-hand with this is the requirement for advanced and specific multimodal imaging agents.

Objective: There has been a huge amount of research work to produce Nano constructs for imaging, and the parameters for successful clinical translation and validation of diagnostic applications are now becoming much better understood.

Materials and Methods: Water-soluble Gd-doped silicon nanoparticles were prepared according to the literature and experimental design. Then conjugation of nanoparticles down with biomolecule as a small molecule. At the end of the preparation, a 4 k Da dialysis bag was used to purify the solution with and the prepared complex conjugation solution was collected and lyophilized as white or light yellow solid in 59.89% yield, then stored at 4◦C for use. 99mTc radiolabeling of complex conjugated was prepared. Characterization of nanoparticles as FL, UV, FTIR, TEM/MAP, SEM, EDS, DLS.zeta potential, ICP mss, LC mss, SLS carried out. Cell viability, in vitro tests: Cell cytotoxicity assay, Apoptosis (programmed cell death) Necrosis assay (Flow cytometry), X Vivo experiments for complex conjugated: optical, fluorescent and confocal microscopic imaging as cellular uptake, in vivo experiments for complex conjugated: MR, CT, PET, SPECT, SPECT/CT and OI imaging, also statistical analysis and Experimental design carried out.

Results: For resolution testing on micro CT systems, and micro PET systems with data from imaging experiments, micro SPECT, SPECT/CT, and OI the most common method used. A key step in cellular uptake is the physical interaction between the NPs and the CM, which can lead to segregation and clustering of NPs on the cell surface and a subsequent CM response. We acquired the best tumor organ ratio in biodistribution.

Conclusion: These agents can be detected using a selection from radioisotope, magnetic resonance, and optical imaging, among others. Nanoparticles offer great scope in this area as they lend themselves, via facile modification procedures, to act as multifunctional constructs. They have relevance as diagnostics and drug delivery agents that can be tracked by molecular imaging techniques with the particular development of applications in optically guided surgery and as radiosensitizers. It is an exciting time of progress for these agents as their potential is closer to being realized with translation into the clinic. The coming 5–10 years will be critical, as we will see if the predicted improvement in clinical outcomes becomes a reality.

Keywords: Nanoparticles; Multimodal Imaging; Experimental Design.

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Magnetic Particle Imaging (MPI)

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Abstract

Background: Tomographic imaging has revolutionized medical diagnosis over the last decades and has become an indispensable tool for the diagnosis of several diseases. In general, the methods can be categorized into two groups. The first method measures a parameter, which is directly coupled to the property of the tissue under examination. The second applies a tracer to the human body and then images the spatial distribution of the tracer concentration within the body. Among the named modalities, CT (Computed Tomography) and MRI (Magnetic Resonance Imaging) fall into the first category and measure the X-ray attenuation and the proton density, respectively, while PET (Positron Emission Tomography) and SPECT (Single Photon Emission Computed Tomography) fall into the second category and image the distribution of a radioactive tracer. However, tracer material is used in CT and MRI as well, though mainly for contrast enhancement and only rarely for direct tracer imaging.

Magnetic Nano Particle Imaging (MPI) is a new medical imaging modality introduced in 2005 and still under development. The MPI scan uses the nonlinear re-magnetization behavior of magnetic nanoparticles to determine their local concentration. Therefore, it is a tracer-based method and free of ionizing radiation. Furthermore, it has a combination of unique features that make it a promising medical imaging technique. The MPI method promises to deliver a high spatial and temporal resolution. These advantages can be exploited to perform true real-time imaging. The MPI measurement is inherently quantitative; its signal, therefore, is a direct measure of how much material is present at a certain location.

Objective: In this paper, the properties of nanoparticles that are used as tracers in MPI, the properties of magnetic fields, and the coils that are applied in these fields, are discussed. It aims to introduce MPI and its applications to the Iranian scientific community.

Materials and Methods: In order to get MPI to work, two basic ingredients are needed: First, one has to find a way to get the particles to emit some kind of characteristic signal that reveals their existence. As a second component, one needs a way to determine where the signal comes from in relation to the object under examination. The magnetic nanoparticles can be excited using electromagnetic fields and respond with a change of their magnetization. A magnetic gradient field features a Field-Free Point (FFP) leading to a spatially varying particle response. In order to speed up the imaging process and moving the FFP in the FOV (Field of View), a magnetic field as the derived field is applied. The scanning volume that can be covered by the drive field is limited to a few centimeters in length. To overcome this limitation, a method for scanning large scanning volumes has been introduced, which utilizes a so-called focus field. As MPI is inherently a tracer-based method, since the beginning, the research foci lay on both the tracer material and the scanner instrumentation.

Keywords: Magnetic Particle Imaging; Magnetic Nanoparticles; Super Paramagnetic Iron Oxide Nanoparticles; Imaging.

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Intravital Multi-Photon Imaging in Cell Interaction Detection of Immune System

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Abstract

Background: Intravital Multi-Photon microscopy is an essential tool in immunology research. This microscope in combination with marker molecules holds promise for the development of single-cell approaches in the intracellular environment. Using this device in immunology has led to the development of powerful techniques for analyzing the microscopic world of the immune system.

Objective: In current experiments, whether in the in vivo or in vitro environment, the immune response is a set of complex and dynamic individual cellular behaviors that are shaped by many environmental factors. Two-photon microscopy has shown great potential for imaging tissue-dependent, dynamic, and asynchronous individual cellular behaviors in intact lymph nodes and can provide information that is indistinguishable in purely in vitro population measurement. This method promises to help our understanding of the immune system, from the transmission of lymphocytes to the presentation of antigens and subsequent effective responses.

Materials and Methods: Laboratory imaging systems that combine BRIGHT-FIELD or NOMARSKI microscopy with FLUORESCENCE microscopy are particularly good at detecting individual behaviors and cell interactions in the immune system. This system is subsequently used to express dynamic molecular changes during the formation of immunological synapses. Fluorescent tools are used to detect and visualize the distribution of molecules. For example, flow cytometry is a method for analyzing the expression of specific molecules by specific cell subsets. Specific fluorescent antibodies for cell surface markers can be used to detect cytokine expression by identifying lymphocyte phenotypes as well as assessing their activation status and function using methods including intracellular staining protocols. Antigen-specific T cells can be detected in vivo using MHC fluorescent peptide tetramers.

Results: Despite having sufficient knowledge of the molecular and physiological aspects of the immune system, we do not have a detailed picture of how cells coordinate in initiating or suppressing the immune response. Video sequences are now taking a fresh look at the behavior of lymphocytes and APCs in living lymph organs and have already revealed unexpected and exciting findings. Two-photon microscopy is a beautiful solution to elucidate the movement between T cells, B cells, and DCs in these tissues and is suitable for correlating the results obtained by in vitro and in vivo methods.

Conclusion: Two-photon microscopy, combined with new probes to detect Ca^{2+} signals, gene expression, cell division, and molecular interactions, constitutes a powerful repository of biophotonic techniques for investigating immune responses. Preliminary tissue and imaging techniques are beginning to expand the use of these tools in vivo. The imaging system uses T-cell dynamics in vitro.

This method provides "optical segmentation" capability, but has the benefit of greater depth of imaging and minimal radiation and toxicity white spots. Also in this device, the excitation is confined exclusively to the focal plane, while other areas of the sample are only exposed to relatively safe infrared light.

Keywords: Intravital Multi-Photon Imaging; Immunology; Cellular.

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Application of Intravitrl MultiPhoton Imaging (IMI) in Neuroscience

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Abstract

Background: Intravitrl MultiPhoton Imaging (IMI) is currently an important technology in the cellular and subcellular biology of living organisms, not only in the brain tissue but also in the kidneys, skin, and lymph nodes to investigate the physiology of these organ cells are used.

Objective: In this method, we can excite the tissue at the molecular and submolecular levels by transmitting multiple photons with near-infrared wavelengths in a few femtoseconds and then by recording back-waves with special separators can obtain information about the physiology and function of the target tissue.

Materials and Methods: In this study, various articles and researches on the structure of the device (IMI), the advantages of this imaging method over other methods, the structure of the nervous system of the brain tissue, and the application of IMI in studying the physiology of the brain's neural structure have been studied.

Results: This method is noninvasive or minimally invasive capable of high-resolution spatial and temporal imaging of physiology, morphology, and cell-cell interactions in the natural tissues of living animals. Its penetration depth in the brain is up to 1000µm and in the spinal cord up to 150µm. The neurons and dendrites attached to them up to a depth of half to one millimeter below the surface of the skin are visible.

Conclusion: The advantages of the IMI imaging system, such as high spatial resolution as well as the non-absorption of infrared photons, which make them suitable for use in some applications such as retina imaging, have made this imaging different from other methods.

Keywords: Intravital Multi Photon Imaging; Neuroscience; Near Infrared; Calcium Indicator; Multi Color Imaging.

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Technetium-99m-PEGylated Dendrimer-G2-(Dabcyle-Lys6,Phe7)-pHBSP: A Novel Nano-Radiotracer for Molecular and Early Detecting of the Cardiac Ischemic Region

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Abstract

Background: In cardiac ischemic disorder, pyroglutamate Helix B Surface Peptide (pHBSP) which derived from erythropoietin causes to increase cell stability.

Materials and Methods: To improve the serum stability of pHBSP, two lipophilic amino acids Arg6, Ala7 were replaced with Fmoc-(Dabcyle)-Lys-OH and Fmoc-Phe-OH during the peptide synthesis. This peptide was subsequently conjugated to PEGylated dendrimer-G2 and labeled with ^{99m}TcO4- to detect cardiac ischemic region. Radiochemical purity (RCP) of ^{99m}Tc-PEGylated dendrimer-G2-(Dabcyle-Lys6,Phe7)-pHBSP was evaluated by ITLC method. In addition, the radiopeptide was investigated for stability in human serum and binding affinity to hypoxic cells in myocardium H9c2 cell lines. Biodistribution and SPECT/CT scintigraphy were assessed in cardiac ischemic rats.

Results: Radiochemical yield indicated that the anionic dendrimer has a very high potential to complex formation with $^{99m}TcO^{-}_{4}$ (RCP>94%) which was stable in human serum with RCP 89% up to 6 h. The binding of ^{99m}Tc- nanoconjugate to hypoxic cells was significantly more than normoxic cells (3-fold higher compared to normoxic cells at 1 hour). In biodistribution studies, erythropoietin receptor-Beta common receptor (EPO-BcR)-positive uptake in the cardiac ischemic region was 3.62±0.44 % ID/g 30 min post-injection.

Conclusion: SPECT imaging showed a prominent uptake of 99mTc-nanoconjugate in EPO-BcR expressing ischemic heart.

Keywords: Ischemia; PHBSP; PEGylated Dendrimer-G2; Technetium-99m; Labeling.

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Synthesis, Characterization and MRI Application of Cobalt-Zinc Ferrite Nanoparticles Coated with DMSA: An In-Vivo Study

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Abstract

Background: The aim of this study was to synthesize and characterize the Dimercaptosuccinic Acid (DMSA) cobalt-zinc (Co-Zn) ferrite magnetic Nanoparticles (NPs) and its efficiency as a contrast agent in in-vivo MR imaging of rat liver.

Materials and Methods: Co-Zn ferrite NPs were synthesized by the thermal decomposition method and stabilized by DMSA. The NPs were characterized by different analyses to study their physical and magnetic properties and were injected into 6 adult male rats. Liver MRI was performed to measure the signal intensity at different times.

Results: The average nanoparticle size was estimated at about 8 ±1 nm using Transmission Electron Microscopy (TEM). The r2 and r2* relaxivity of these particles were obtained at 32.85 and 168.96 mmol L-1s-1, respectively, using an agarose phantom imaged by MRI. In the in-vivo condition, injection of SNPs (Superparamagnetic Nanoparticles) (2.5 mg Fe/kg) showed negative contrast in a way that for T2 and T2* weighted the maximum contrast enhancement was 58.46 and 77.13 %, respectively.

Conclusion: Regarding our results, the synthesized Co-Zn ferrite NPs stabilized by DMSA are appropriate agents for increasing the contrast in both T2 and T2* weighted based on MR imaging in rat liver.

Keywords: Cobalt-Zinc Ferrite; Nanoparticles; Dimercaptosuccinic Acid; Magnetic Resonance Imaging; Superparamagnetic; Rat Liver.

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Fluorescence Bioimaging of Wst/Chitosan Composite as a Novel Acid Resistant Composite Used for Oral Delivery of Insulin

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Abstract

Background: To improve insulin bioavailability and overcome multiple barriers for oral delivery of insulin the composite carriers have shown good effects. Biological imaging has taken serious steps since 2010 in areas such as routing drug delivery systems and quantitative studies on drug delivery with the least amount of damage from the stomach environment and its release by the drug carrier in the intestinal environment.

Objective: The chemical stability of loaded insulin against digestive enzyme was established in the present of Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF).

Materials and Methods: WST (Water-Soluble Tragacanth), chitosan and insulin were mixed by ultrasonication. It was revealed by the in vitro release studies that the best composite was the chitosan/insulin/WST by around 10 % release in pH = 1.2 (pH of stomach) in 2 hours and 90 % release of insulin over 12 hours in pH = 7.4 (pH of the colon) proving the importance of order also besides of chitosan and WST and the role of WST as a control-releasing agent. In vivo fluorescence, the bioimaging method was implemented to track fluorescence degradation of the chitosan/WST composite in the mice by the Invitrogen BODIPY FL dye. It was observed that the composite remained for 105 minutes in the stomach while it did not degrade. This study using control mice and dissection also showed that no fluorescence composite entered the liver. A quantitative Elisa test was also conducted showing insulin is 100% available in chitosan/insulin/WST composite. These composites were characterized using FESEM, BET, IR, Zeta potential, and dynamic light scattering. Circular dichroism spectra of insulin in different pHs illustrated that ultrasonication does not destroy insulin two peptide chain structure. Also in-vivo and MTT assay performed.

Results: The presence of insulin contributes to the broadening of peak related to NH and OH group appeared at wavenumber higher than 3000 cm-1. The FESEM image of chitosan/insulin/WST which can be attributed to the presence of insulin. The maximum surface area for chitosan/insulin/WST is calculated to be 195.142 m2/g. The average pore diameter and pore volume for chitosan/insulin/WST are, 2.8 nm and 0.78 cm3/g, respectively. The comparison between the control and fluorescent liver and stomach of mice shows that no fluorescent composite remains in the liver and stomach. In-vivo studies shown that there is a continuous insulin release. Also, MTT assay showed lower cytotoxicity for WST/Insulin/Chitosan.

Conclusion: WST/Insulin/Chitosan has been prepared to overcome multiple barriers for oral delivery of insulin. Under the protection of a stabilizer, the morphologies of insulin- loaded WST/Chitosan could have remained their integrity during the application. In vivo studies shown the rats could undergo a prolonged hypoglycemic effect. This work suggests that the as-prepared composite carriers may be promising drug delivery carriers for oral administration of insulin and other biomacromolecules.

Keywords: Bioimaging; Insulin; Oral Delivery.

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Application of Imaging Techniques for Preclinical Models of Endometriosis

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Abstract

Background: Endometriosis is a common benign disorder in ~10% of women in which the presence of endometrial tissue outside the uterine cavity causes pelvic pain and subfertility. Due to its complex etiology and pathophysiology, endometriosis research requires careful selection of appropriate in vitro and in vivo models which can elucidate the pathophysiological mechanisms underlying this disease and enhance the identification of new therapies. The experimental models include Homologous models that are based on the syngeneic or autologous transplantation of uterine fragments into the peritoneal cavity of rodents and non-human primates or Heterologous models that are based on the xenotransplantation of endometrial human tissue into immunodeficient mice. Preclinical imaging is crucial in enhancing animal models and allowing a non-invasive and clinically translatable way to track the progression of disease in real-time.

Objective: Our goal is to demonstrate the advantages and limitations of various imaging modalities in animal models of endometriosis researches.

Materials and Methods: The relevant articles published up to the end of 2019 were collected by searching in PubMed, Scopus, and MEDLINE databases using the terms “Endometriosis”, “preclinical imaging” and “animal models”.

Results: Optical imaging is divided into fluorescence and bioluminescence. Different approaches, including fluorescent dyes, gene transduction, and transgenic animals have been introduced for non-invasive fluorescent imaging. However, they had some limitations such as not differentiation between live and dead cells in a lesion, poor transfection efficiencies or not satisfactory fluorescent intensity and persistence time during the observation of in vivo endometriosis lesions. In bioluminescence imaging, the growth of endometriotic lesions and early angiogenesis can be monitored noninvasively using a model of luciferase transgenic mice. This model will promote monitoring of initial implantation, initiation of angiogenesis, and tissue growth which may eventually contribute to the development of new therapeutic strategies that are desperately required for this disease. Compared to bioluminescent imaging, fluorescent imaging does not require the injection of a substrate and may be appropriate for applications where sensitivity is not as critical. High-resolution ultrasound imaging provides a noninvasive way that allows for the first time detailed repeatedly qualitative and quantitative analysis of growth, cyst development, and adhesion formation of endometriotic lesions. MRI allows for longitudinal studies and dynamic evaluation of ectopic uterine tissue growth/regression of an autologous rat model of endometriosis. The MRI monitoring of the early phase of this model allows us to study the progression of the disease and it gives a fast data analysis with minimal stress to the animals. PET seems to be a promising way to detect small superficial endometriosis lesions in humans since ectopic uterine tissue implants could be visualized after the administration of a radiopharmaceutical called 18F-fluorocholine in the homologous endometriosis rat model. The limitations of these imaging techniques will be discussed in the review.

Conclusion: In conclusion, the increasing use of imaging technologies in animal models supports its prominent role in translational research for reproductive disorders. Ongoing research is focusing on integrating different imaging modalities to facilitating successful translational applications to improve the efficacy in preclinical studies.

Keywords: Endometriosis; Preclinical Models; Imaging.

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Prospective of Molecular Imaging for Cell Therapy

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Abstract

Background: Cell-based therapies such as dendritic cells, T cells, and stem cells are being considered as new treatment approaches for various diseases. Assessment of the therapeutic efficacy of these methods is a critical issue in new cell-based therapies. The improvement of effective cell-based therapies, requires determination of the cellular population, location, distribution, stability, and long-term viability in different organs. The fate of adoptively transferred cells is usually assessed using traditional invasive methods such as histological studies or tissue biopsies. This means long-term and real-time monitoring is not feasible. Therefore, to improve the effectiveness of cell therapies, the non-invasive monitoring approach is essential. Molecular imaging is a rapid and non-invasive technology to detect cellular viability and function during cell therapy in vitro and in vivo studies. However, there are unanswered questions about the safety, and effectiveness of imaging modalities or related materials for cell therapy applications.

Objective: This study aims to focus on the new perspective of molecular and cellular imaging in pre-clinical and clinical cell therapy applications.

Materials and Methods: The non-invasive imaging modalities with different cell labeling methods, direct /indirect with a reporter gene, allows monitoring of cellular functions. The tracking techniques are based on different diagnostic modalities such as MRI, SPECT, PET, ultrasound, and optical imaging.

Results: In various studies, the direct or indirect labeling methods allowed the monitoring of cell therapy fate. These imaging studies showed the crucial role of therapeutic cells in particular their population and function. Imaging techniques are also used for studying stem cell differentiation in various organs.

Conclusion: We focused on the role of different types of imaging techniques via direct or in-direct labeling to monitor the fate of therapeutic cells. Specific and noninvasive tracking of cells is very important in cell therapy clinical trials to evaluate the outcome of therapy, and precise pathways involved.

Keywords: Molecular Imaging; Cell Therapy; Direct Cell Labeling; Indirect Cell Labeling.

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Classification of Preclinical Human Disease Modeling (PDM) Study in Experimental Animals Based on Medical Imaging Systems

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Abstract

Background: PDM program has different dimensions. Part of it is the simulation of all the features of human disease in animal models. Another part is choosing the right animal for the project. But the other dimension that is largely neglected in project design is choosing the right imaging system for monitoring the disease process and obtaining comprehensive data from it. This negligence is mainly due to the researcher's insufficient knowledge about the function of the existing imaging systems. This makes a lot of data unavailable or the PDM program fails altogether

Objective: In this study, by reviewing scientific literature, is suggested what system or set of medical imaging systems should be used, in each group of PDM studies.

Conclusion: Careful design of a pre-clinical study and optimization of monitoring methods, especially medical imaging, in addition to saving on the cost, the number of animals, and time required, provide more reliable, and documented data for new treatment protocols.

Keywords: Preclinical Study; Experimental Animals; Imaging Medical Systems.

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Utilizing Wavelet Coherence Analysis to Investigate the Frequency-Specific Functional Connectivity in Stroke Rats Based on Optical Intrinsic Signal Imaging

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Abstract

Background: The Optical Intrinsic Signal Imaging (OISI) method is an optical technique to evaluate hemodynamic responses of the activated neurons by measuring the reflected light from the cortex. This method has been used for investigating the Functional Connectivity (FC) of the cortex in animals.

Objective: Up to now, using this method, the FC of the cortex has been measured in time or frequency domain separately, and at frequencies below 0.08 Hz, which are not in the frequency range of hemodynamic oscillations able to track fast cortical events, including neurogenic, myogenic, cardiac and respiratory activities.

Materials and Methods: In the current work, we calculated the Wavelet Coherence (WC) transform of the OISI time series to evaluate the cerebral response changes in the stroke-afflicted rats. Utilizing WC, we measured FC at frequencies up to 4.5 Hz and could monitor the time and frequency dependency of the FC simultaneously.

Results: The results showed that the WC of the brain diminished significantly in ischemic motor and somatosensory cortices. According to the statistical results, the signal amplitude, responsive area size, resting-state correlation, resting-state WC, stimulus-related correlation, and stimulus-related WCs of the motor / somatosensory cortices for stroke-affected hemisphere were found to be significantly lower by 66% / 63%, 73% / 80%, 32% / 21%, 4% / 3.5%, 30% / 19%, 16% / 9% compared to the healthy hemisphere. Further, the signal latency for the stroke motor and somatosensory cortices was found to be significantly higher by 230% and 285% compared to the healthy cortices, respectively.

Conclusion: The obtained results confirm that the OISI-based WC analysis is more precise than other methods in diagnosis of the severity and size of the infarcted region after the stroke.

Keywords: Functional Connectivity; Intrinsic Signal Imaging; Wavelet Transform; Ischemic Stroke; Rat.

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Optical Spectroscopy Study of Treatment Response Monitoring of A375 Skin Melanoma Cell Line: An In-Vitro Model

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Abstract

Background: Due to the challenges in cancer including effective therapeutic dosage and preventing drug resistance, monitoring of the treatment response is critical for optimization. Recently, optical technologies like Diffuse Reflectance Spectroscopy (DRS), has been applied to improve the identification of cancerous lesions in various organs. Until now, the non-destructive application of optical sensing has been studied to diagnose and discriminate normal and cancerous lesions. Meanwhile, the response to the treatment can be monitored with the non-destructive technologies, and enabling further therapeutic modification.

Objective: This project aimed was to investigate the applicability of reflectance optical spectroscopy as a non-destructive approach in monitoring the A375 skin melanoma cancer cell response to treatment with vemurafenib.

Materials and Methods: The A375 human skin melanoma cell line, donated as a gift from Switzerland (University Hospital Basel) was cultured. Cell treatments were done using Vemurafenib (Zelboraf, Genentech/Roche). The VIS-NIR reflectance spectroscopy (USB2000 Ocean optics) was applied for data acquisition at different time intervals (before treatment, and on the days 1, 2,7,14 post-treatment for three drug doses 5, 25, 75 μM) on cell samples. After data acquisition, the refractive index analysis for the fore-mentioned doses and days in one selected wavelength of 620nm was performed using the Kramers-Kronig-based computer program developed in this group previously. Flowcytometry and qPCR were performed as gold standard biological tests, indicators of cell death, apoptosis, and drug resistance gene expression.

Results: A considerable decrease in the quantified refractive index of cell samples was found in cases that biological assay confirmed cell death. Based on the flow cytometry data, a vemurafenib dose of 25μM in day 7 seemed to induce the necrosis. These findings show that spectroscopic findings strongly agree with concurrent biological studies and might lead to their use as an alternative method for treatment response monitoring to achieve more optimized cancer treatment.

Conclusion: Optical reflectance spectroscopy seems to be feasible in providing quantitative information for treatment response determination in a non-destructive, real-time, label-free method that corresponds appropriately with biological assays which are expensive labeled tests.

Keywords: Melanoma; Treatment Response; Spectroscopy; Refractive Index.