Project Title: PET-imageable nanoparticles for radiotherapy and molecular imaging applications

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Project Description: In this research we are developing positron emitting nanoparticles (NPs; small particles of a few millionth of a millimeter diameter) with near-identical radiosensitization as gold nanoparticles (GNPs) while imaged using Positron Emission Tomography (PET).

GNPs have been actively investigated for various applications in cancer diagnosis and therapy. When injected into target human tissue and irradiated by primary radiotherapy beams, GNPs generate cascades of secondary radiation producing a local “amplification” of the radiation dose. Therefore, if cancer patients are injected with GNPs prior to radiation therapy, cancer cells often suffer from double cell-kills; first, from the primary radiotherapy beams, then from the secondary radiation from GNPs. This radiosensitization has been the focus of many investigations in mice treated with GNPs and radiotherapy in which complete tumor regression has been observed. However, there are some challenges to overcome for successful transition to human clinical practices. In order to obtain sufficient radiosensitization in the tumor and minimal toxicity to healthy tissues, GNPs have to be taken up maximally to tumor cells and minimally to healthy tissues.

Thus, the development of a non-invasive imaging tool for monitoring the distribution of GNPs in vivo is critical for a successful transition of GNP-mediated radiosensitization into clinical practices. PET is a very sensitive imaging tool for cancer diagnosis, most popularly FDG (radioactive glucose) is injected in patients prior to PET studies. While FDG is preferably taken up by (sugar-hungry) tumors, PET imaging can indicate the location of this radioactive glucose, and therefore the locations of the tumors.

The long-term goal of the Medical Physics lab at Oklahoma State University (OSU) is increasing the effectiveness of radiation therapy while reducing its side effect. By developing PET-imageable and highly radiosensitizing NPs, we can achieve that goal. Once injected, NPs’ intra-tumoral as well as healthy tissue uptake will be monitored using PET, then radiation therapy can be administered for maximal tumor damages and minimal collateral damages to healthy tissues.

Preliminary Results: Spherical 7 nanometer zinc NPs were chemically synthesized and were coated with gold to 7 nanometer thickness to make spherical Zn@Au (zinc cores and gold shells) NPs (98.6/1.4% gold/zinc) (Figures 1 & 2). Monte Carlo simulations show that Zn@Au NPs have near-identical (< 4% difference) radiosensitization as solid GNPs when bombarded by X-ray and proton radiotherapy beams. Samples of Zn@Au NPs were proton activated by a cyclotron with 5-μA current for 5 minutes using 8 MeV protons. After irradiation, a very small fraction (<1 mg) of the Zn@Au NP sample was placed in a HPGe detector and gamma spectrum was obtained. The sample provided dominant 511 keV gamma peaks, from mostly long lived positron-emitting 66Ga (T1/2 = 9.5 hours). Subsequently, the target was PET/CT scanned which showed a strong PET signal despite a relatively long delay (12 hours) and short acquisition time (5 min) (Figure 3).

Figure 1. Transmission electron microscopy images of (L) zinc NPs and (R) gold-coated zinc (Zn@Au) NPs.

Figure 2. (L) Configuration of Zn@Au NPs. (R) When irradiated with protons, zinc cores are activated to generate positron emitters – 66Ga (T1/2 = 68 minutes), 68Ga (T1/2 = 9.5 hours) whose 511 keV gammas are detected by PET.

Figure 3. PET/CT fusion images of a 23-mg Zn@Au NP sample irradiated with 8-MeV protons.
Research Plan: The objective of this proposal is to develop Zn@Au NPs with 1) a near-identical (difference < 1%) radiosensitization as solid GNPs while providing 2) a high yield PET signals (specific activity of > 5 mCi/g) with 3) relatively small effective dose (< 50 mSv) for patient. The specifics follow.

Specific Aim 1: Determine the optimal Zn core diameter and Au shell thickness for optimal PET signals and radiosensitization. The core diameter and shell thickness will be calculated both analytically and using Monte Carlo simulation in order to obtain optimal PET signals (> 5 mCi/g for 20-µA and 1 hr proton bombardment) and near-identical (difference < 1%) radiosensitization. Consequently, these Zn@Au NPs will be chemically synthesized and their stability will be tested. The uniformity of core size and shell thickness will be tested using transmission electron microscopy (TEM) before and after proton bombardments to measure the degradation of coating due to heating from proton bombardments.

Specific Aim 2: Determine the optimal Zn@Au NPs bombardment and yield conditions. For a high yield FDG (radioactive glucose) production, bombardment of 18O-enriched water using 50-µA proton current for 2 hours is routine for a high FDG yield; however, we used low beam current and time (5-µA and 5 min) for Zn@Au NPs due to possible heating and melting of NPs, therefore providing a lower activity yield. We will use the two techniques – 1) depositing water dissolved Zn@Au NPs onto an aluminum target and baking it, and 2) taping over dry Zn@Au NPs using a high temperature (Aluminum/Silicone-adhesive based) tape with water/gas cooling in order to obtain a high yield. Proton bombardments minimum of 1 hour and 20-µA current will be tested to achieve the minimum of 5 mCi/g yield.

Specific Aim 3: Dose and risk calculation from activated Zn@Au NPs. A typical FDG PET study provided the effective dose up to 32 mSv which increased the associated lifetime cancer incidence up to 0.5%. A comparable outcome is expected from injected Zn@Au NPs since they are almost pure positron emitters, however, the different physical half-life and biological clearance may give somewhat different outcome. Therefore, a similar internal dose study is warranted to test the radiation safety of Zn@Au NPs for human use. MIRDOSE (personal computer software for internal dose assessment in nuclear medicine) will be used to calculate the expected dose and risk for different scenarios (adult/child) using known physical half-life of Zn@Au NPs and biological clearance half-life of equivalent GNPs. Aim 3 will be performed in conjunction with Aims 1 and 2 in order that the developed Zn@Au NPs deliver effective dose less than 50 mSv (lifetime cancer incidence less than 0.8%) to patients.

Expected Outcome: We expect to develop Zn@Au NPs with near identical radiosensitization as normal GNPs while being PET visible for tens of hours or days with a minimal patient dose. We envision those NPs be used for radiation therapy as well as molecular imaging for cancer diagnosis. The developed Zn@Au NPs as well as their physical characteristics determined in this proposed research will be used as preliminary data to apply for OCAST (Oklahoma Center for the Advancement of Science and Technology) grants and NIH (National Institute of Health) grants. Studies of in vitro and in vivo imaging followed by radiotherapy will be proposed for the OCAST and NIH grants to investigate the effectiveness of Zn@Au NPs injected in mice or larger animals.

The preliminary results presented here were presented during the 2015 annual conference of American Association of Physicists in Medicine (AAPM) and is under review as a peer-reviewed journal paper at Nanotechnology (2014 impact factor: 3.821). Once the proposed research is completed, the results will be presented at an AAPM annual conference or a similar meeting and will be submitted for publication to Physics in Medicine and Biology or Nanotechnology also as a peer-reviewed journal paper.

Anticipated summer support: One-month salary is supported as start-up from the department of physics. With the College of Arts & Sciences Summer Research Program (ASR) and Travel Support, PI will work full-time (3 months) in summer and is able to travel to Houston for experiment. This full-time effort during summer (without teaching) will make a significant impact on the success of the proposed research and consequently for the successful OCAST and NIH grant applications. The PI will benefit greatly through this summer support as he tries to build a new line of cancer research at OSU as a first year tenure-track professor in collaboration with UT MD Anderson Cancer Center. Thank you.
POSITIONS AND EMPLOYMENT:

Aug 2015 – present Assistant Professor, Dept. of Physics, Oklahoma State University, OK
Jun 2014 – July 2015 Postdoctoral fellow, Radiation Physics, UT MD Anderson Cancer Center, TX
Jul 2008 – Aug 2010 Faculty, School of Allied Health, Loma Linda University, CA
Oct 2005 – Aug 2010 Medical Physicist, Loma Linda University Medical Center, CA
Mar 2004 – Jul 2005 Medical Physicist Resident, Roger Maris Cancer Center, ND
Jul 2001 – Nov 2003 Research Assistant, British Columbia Cancer Agency, Canada
Jan 2001 – Jul 2003 Teaching Assistant, University of British Columbia, Canada
Apr 2000 – Dec 2000 Linux System Admin., INTEC Internet Technology, Co. Ltd. South Korea
Jan 1998 – Oct 1998 Research Assistant, Samsung Medical Center, Seoul, South Korea

EDUCATION:

Aug 2010 – May 2014 PhD Medical Physics, UT HSC MD Anderson Cancer Center, TX
Jan 2001 – Feb 2004 MS Medical Physics, University of British Columbia, Vancouver, Canada
Mar 1996 – Feb 1998 MS High Energy Physics, Seoul National University, South Korea
Mar 1992 – Feb 1996 BE Electrical Engineering, Inha University, South Korea

GRANT:

Title: Design of practical proton-activated implantable markers for proton range verification using PET
Principal investigator: Jongmin Cho, PhD., DABR. – UT MD Anderson Cancer Center, Houston, TX.
Funding Source: AAPM Research Seed Grant 2014
Amount: $25,000.00 Duration: Jul. 1, 2014 – Jul. 30, 2015

BOARD CERTIFICATION:

DABR (Diplomate of American Board or Radiology) in Therapeutic Radiologic Physics, 2008.

PATENTS / TECHNOLOGY LICENCES:

- J Cho MS, G Ibbott Ph.D, and O Mawlawi Ph.D, Proton-activated Implantable Markers for Proton Treatment and Range Verification using PET, United States, MDA13-146.

SCHOLARSHIP / AWARDS:

AAPM Best in Physics American Association of Physicists in Medicine, Aug. 2013.
Young Investigator Award Society of Nuclear Medicine Molecular Imaging, Jun. 2013.
Young Investigator Award Society of Nuclear Medicine, Jun. 2011.
Research Award Seoul National University, Seoul, South Korea, 1997.
University Scholarships INHA University, Inchon, South Korea, 1992 – 1996.
PEER-REVIEWED RESEARCH PUBLICATIONS (past 3 years):

J Cho, M Wang, C Gonzalez-Lepera, O Mawlawi, and SH Cho 2016 PET-detectable bimetallic (Zn@Au) nanoparticles for radiotherapy and molecular imaging applications Nanotechnology (under review, the preliminary results in the research proposal are excerpted from this article)


J Cho, P Summers and G S Ibbott 2014 Implementation of an Anthropomorphic Spine Phantom as part of Baseline Phantom Irradiations for Radiological Physics Center’s Proton Approval for NCI-funded Cooperative Group Clinical Trials Journal of applied clinical medical physics / American College of Medical Physics Vol. 15, No. 3 252-265

J Cho, G Ibbott and O Mawlawi 2013 Regarding the tissue elemental composition calculation from “Dynamic PET/CT measurements of induced positron activity in a prostate cancer patient after 50-MV photon radiation therapy” EJNMMI (http://www.ejnmmires.com/content/3/1/6/comments)


OTHER PUBLICATIONS (CONFERENCE RECORD AND ABSTRACTS) (past 3 years):


J Cho, M Wang, C Gonzalez-Lepera, E Zubarev, S H Cho “PET-detectable bimetallic (Zn@Au) nanoparticles for radiotherapy and molecular imaging applications”, 2015 AAPM Meeting, (Oral)


J Cho, G Ibbott, M Gillin, U Titt, C Gonzalez-Lepera, O Mawlawi “Proton beam range verification using proton activated fiducials and off-site PET”, 2013 AAPM, Indianapolis, IN. (Best in Physics oral/poster)

J Cho, G Ibbott, M Gillin, C Gonzalez-Lepera, O Mawlawi, “Proton beam range verification with PET: Comparison of polycarbonate and copper activation”, 2013 Society of Nuclear Medicine and Molecular Imaging Annual Meeting, Vancouver, BC, Canada. (Young Investigator symposium oral)

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The proposed research requires travel support for collaboration with University of Texas MD Anderson Center for Advanced Biomedical Imaging Research as well as University of Texas MD Anderson Cancer Center located in Houston, TX.

Specific Aim 1 (*Investigation on the optimal Zn@Au NPs bombardment and yield condition*) requires me to travel to Houston, TX and will be conducted at UT MD Anderson with the following collaborators.

- Dr. Carlos Gonzalez-Lepera, Professor and Director of Cyclotron Radiochemistry Facility, Department of Nuclear Medicine, MD Anderson Cancer Center.
- Dr. Osama Mawlawi, Professor and Nuclear Medicine Physics Section Chief, Department of Imaging Physics, MD Anderson Cancer Center.

Specific Aim 3 (*Dose and risk calculation from activated Zn@Au NPs*) requires software such as MIRDOSE and OLINDA/EXM. This can be purchased at a cost of $1,000 or can be freely used at UT MD Anderson Cancer Center where the software is available for staff.

The completed research will also be presented at a conference meeting of Medical Physics or Nanotechnology such as:

- Chapter or Annual Meeting of American Association of Physicists in Medicine
- IEEE International Conference on Nanotechnology

Thus, I request additional $1,000 support for the proposed research travel(s).

Thank you for your time and consideration.

Sincerely,

Jongmin Cho, PhD.
Assistant Professor
Department of Physics
Oklahoma State University