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Purpose/Objective(s): Colorectal cancer (CRC) is one of the most common and deadly cancers in the world. Currently, radio-therapy is one of the major treatments for CRC. NONO, an RNA/DNA binding protein, has been known to enhance radio-resistance by accelerating DNA repair, whereas its underlying mechanism remains largely unknown. In this study, we aimed to explore its molecular mechanism and clinical significance in CRC.
Materials/Methods: The radiation-induced NONO-binding protein was identified by Co-immunoprecipitation (CoIP) and mass spectrum (MS). The association between proteins was verified by CoIP, immunofluorescence and proximal ligation assay. The expression of RNAs and proteins were evaluated by quantitative real-time PCR and western blotting, respectively. The DNA damage level was evaluated by the analyses of γ-H2A.X level and counting of γ-H2A.X foci. The double strand break repair efficiency was examined by *in vitro* non-homologous end joining (NHEJ) assay.
Results: NONO knockout enhanced radio-sensitivity, reduced the repair of radiation-induced DNA damage and NHEJ efficiency. Through CoIP and MS, RPLP0 was identified as a novel NONO-binding protein, and their association was further enhanced upon irradiation. NONO bound to free RPLP0, but not that within ribosome, in nucleus. The RPLP0-binding domain of NONO was mapped to RRM1/2 domain. Furthermore, RPLP0 silencing reduced the repair of radiation-induced DNA damage and the efficiency of NHEJ. As translation blockage with Cycloheximide had no influence on DNA damage repair, RPLP0 silencing-induced DNA repair deficiency was not a result of translation inhibition. Mechanically, RPLP0 was recruited to DNA damage site by NONO and enhanced DNA repair. The analyses of clinical samples showed that both the RNA and protein level of NONO and RPLP0 were upregulated in colorectal cancer tissues, and high expression of NONO was associated with poor response of radio-therapy. Moreover, compared with adjacent normal tissues, the interaction between NONO and RPLP0 was stranger in CRC tissues.
Conclusion: NONO enhanced radio-resistance and DNA damage repair by recruiting RPLP0 to DNA damage site. High expression of NONO was a biomarker for poor treatment response of radio-therapy.
Author Disclosure: **Y. Wang**: None. **W. Zhao**: None. **S. Bai**: None. **X. Yin**: None. **M. Wei**: None. **X. Wan**: None.

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Intra-Tumoral Hepatic Administration Under CT Stereotactic and Ultrasound Guidance of in Situ Anti-Cancer Agent Derived from [188re]Rhenium Nitro-Imidazole Ligand Loaded 5th Generation Poly-l-Lysine Dendrimer

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Purpose/Objective(s): The most common hepatic malignancies are metastases from colorectal cancer primary. 85% of all patients with colorectal liver metastases are unresectable at the time of presentation. There is a clinical need for advances in loco-regional treatments in patients with advanced stage. In this context, we have recently developed a new potential anticancer agent from a fifth-generation dendrimer as a delivery nano system loaded with diffusible ββ emitter probes for targeting in particular hypoxic tumors resistant to conventional cancer treatments. In this abstract, we report outcome after hepatic administration of Imdendrim under stereotactic and ultrasound guidance respectively.
Materials/Methods: The experiment agent "ImDendrim" used in this study is consisting of poly-L-lysine dendrimer as nanovector mixed with complex of 188Rhenium- ligand (nitro-imidazole-methyl-1,2,3-triazol-methyl-di-[2-pycolyl] amine). Protocol (NCT03255343) was carried out in accordance with the strict ethical requirements. The response to treatment was evaluated thanks to quantitative standardized uptake values (SUVs) from [18F]-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT). Eligible Patients: Two male patients L.B. and L.W. aged 50 and 24 years respectively with stage IV adenocarcinoma colorectal cancer with multiple and voluminous hepatic metastases (From 3cm to 7 cm in diameter). The advanced tumoral stage without specific therapy of these non-operable tumors were confirmed , thus the patients were eligible for study. L.B. received 1850MBq of ImDendrim by direct CT guided stereotactic intrahepatic injection; the targeting tumor size is 5 cm in diameter (tumoral volume = 65 cm3). LW received 3700 MBq of imdendrim injected into 6 metastases (total tumoral volume 110 cm3) under ultrasound guidance.
Results: None complications post-administration were observed and the patients were discharged after 1-week post treatment and followed up regularly. 1-month post-injection, the patients decrease of SUVs was observed with a pre-/post-treatment ratio above 1.7, in presence of large tumoral volume necrosis. Both patients were considered as good responders and no adverse outcomes were observed three months post injection.
Conclusion: These preliminary outcomes highlight the safety and effectiveness of the Imdendrim. the clinical trial is currently in progress. Clinical trial information: NCT03255343
Author Disclosure: **B. Hafid**: None. **N. Sadeg**: None. **G. Yang**: None.

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Development of a Monte Carlo-Based Microdosimetry Platform for the Analysis of Targeted Radionuclide Therapy Agents in Vitro

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Purpose/Objective(s): There is a growing need for the development of a microdosimetric modeling tools that can characterize the dosimetric impact of therapeutic radiopharmaceutical agents at the cellular scale in order to improve drug development and clinical translation. Sub-cellular characterization of dose is necessary due to the heterogeneous spatial uptake of these agents in the tumor microenvironment and the short range of their decay products, especially for alpha- and auger electron-emitting drugs. In this work we present the initial steps of characterizing a GEANT4 Monte Carlo microdosimetry platform to evaluate sub-cellular dosimetry for human ovarian cancer cells (OVCAR3) treated with Auger electron-emitting Bromine-77 labeled compounds.
Materials/Methods: OVCAR3 cells were cultured, stained with DAPI and MitoSpy-Green and then imaged on a Leica SP8 3X STED super-resolution microscope to create a Z-stack image set of a single OVCAR cell. The Z-stack image set was imported into Amira to delineate the nucleus and cytoplasm. The images and contours were then imported into a computer algorithm script that created input files for GEANT4 defining both a voxelized OVCAR3 cell phantom and a radioactive source specification. GEANT4-DNA physics definitions were utilized to ensure accurate modeling of sub-micron level dose deposition. To validate the dosimetric accuracy of the platform, cellular S-values of voxelized spheres are compared to MIRDCELL values for multiple isotopes, including Bromine-77. To demonstrate the impact of realistic geometrical definitions, the dose distribution of a uniform source distribution is compared between a realistic voxelized OVCAR cell and a voxelized sphere of an equivalent volume.
Results: Computed cellular S-values S(N→N) for Iodine-125 agree within 1.3% of both MIRDCELL and other Monte Carlo calculations found in literature and S(N→N) values for Bromine-77 agree within 22% of MIRDCELL values, likely attributable to differences in physics definitions for low energy auger emissions.
Conclusion: Initial steps have been taken to develop a microdosimetry platform capable of elucidating microdosimetric properties of targeted radionuclide therapy agents at the sub-cellular level. Simulations performed demonstrate the importance of utilizing realistic and accurate simulation parameters such as realistic cellular geometries captured from Z-stacked confocal microscopy instead of simple spherical volumes.