distribution around ^{192}Ir and ^{137}Cs sources in phantom water, which has been tested to verify the usefulness of EGSnrc code in modeling ^{192}Ir and ^{137}Cs sources in dose distribution in brachytherapy. From the DF results, all sources show the direction of risk distribution as precisely as expected. Sources show that the direction increases at points near 3 cm distance; the direction will decrease with the increase of the distance because the first direction increase due to the difference between the effect of plain dark theorem less. The external directional decrease of about 3 cm is due to the increased radiation dose. The increasing radiation dose will compensate for the first dose variation caused by different reductions in sources and shells—trendy best expressed for Ir source with platinum coating. The difference in the direction of Ir sources is in line with the physical difference of their shells, as well as the core of the source has a larger volume platinum-shell source of stainless-steel-shell. Since platinum has greater atomic volume and density than stainless steel and thus decays faster, dose distribution from sources with platinum-shell is expected to be more orientated due to more significant depreciation. The deviation from 3 cm to 12.5 cm from the platinum-shell sources also corresponds to the more significant depreciation due to the greater appreciation for platinum. Verify the usefulness of Monte Carlo EGSnrc code in modeling Ir and Cs sources to obtain risk distributions. It plays a significant role, especially in applied radiation compared to other computational techniques, because they are complex and easy to error.

P-233
Development and evaluaton of a trans-cyclooctene (TCO) probe for pretargeted PET imaging

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Objectives: Bioorthogonal pretargeting through inverse electron demand diels alder (IEDDA) reaction between a radiolabelled 1,2,4,5-tetrazine (Tz) and a trans-cyclooctene (TCO) conjugated to a monoclonal antibody (mAb) has attracted considerable interest in the field of molecular imaging and targeted delivery of radionuclides. This multistep approach provides the advantage of increased target-to-background ratios and decreased radiation burden to healthy tissues compared to single-step approaches. However, the liability of the TCO to isomerize to its less reactive cis-form and the internalization of the mAb conjugates over time has hampered its way towards clinical trial as a powerful theranostic tool. Given this we envisaged to develop more stable 18F-labelled d-TCO-probes and investigate their utility in pretargeted immuno-positron emission tomography (PET) imaging using a tetrazine-modified antibody.

Methods: A small library of fluorinated (19F) d-TCOs was synthesized and the binding to a Tz-conjugated antibody was assessed. Briefly, a pretargeted blocking in vivo study was performed with the fluorinated (19F) d-TCOs to assess their capability to target and react with pretargeted tetrazine-tagged CC49 antibody in tumor bearing mice [1]. Human colorectal cancer LS174T cells (5x106) were inoculated in the right hind leg of BalbC nude mice. CC49-Tz (100µg/100µL) or CC49 alone (100 µg/100 µl; negative control) were intravenously administered 72h before fluorinated (19F) dTCO. After 1h TCO-Cy5 was administered followed by in vivo and ex vivo fluorescence imaging using an IVIS scanner after 24h. From this study we have selected a d-TCO compound for radiolabeling with 18F. Briefly, the tosylated d-TCO precursor (5mg) in dry DMF was added to a reactor vial containing dry [18F]F- and reacted for 10 min at 100°C. Afterward, purification was performed using semi-preparative HPLC. Radiochemical purity was determined by analytical HPLC. LogD was determined using the shake flask method. Stability of radiotracer was evaluated in PBS and mouse plasma at 37°C.

Results: From the compound library, a novel d-TCO derivative showed an excellent blocking efficiency (97%) against TCO-Cy5 in a pretargeted blocking study, confirming good in vivo ligation with the Tz-conjugated antibody. This led to the further radiochemical development of this compound. The radiolabeling of d-TCO with 18F resulted in a RCY of 5.5% (decay-corrected to EOB) and >98% radiochemical purity. The tracer showed moderate lipophilicity with a logD value of 0.59 ± 0.07. The tracer showed no isomerization to cis-form after incubation in PBS for up to 2 h, and up to 30% intact tracer was found in mouse plasma after 2h.

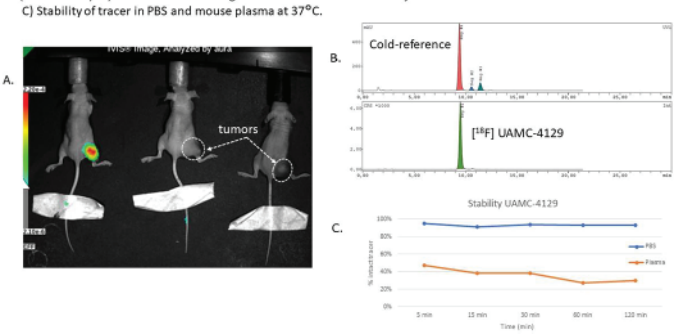

Figure 1: A) From left to right, tumor uptake of TCO-Cy5 in positive control, negative control and blocked group (UAMC-4129). B) HPLC radiochromatogram of the isolated tracer co-injectecd with cold-reference. C) Stability of tracer in PBS and mouse plasma at 37°C.

Conclusion: A novel fluorinated d-TCO-probe was successfully synthesized, and demonstrated high in vivo IEDDA reactivity in tumor-bearing mice, as shown by the blocking effect. A new [18F]-d-TCO tracer was successfully radiolabelled in good RCY and good in vitro stability. Further in vivo evaluation of this radiotracer will determine its future use towards pretargeted imaging approaches of internalizing targets.

References:

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P-234
Uncovering the role of modified citrus pectin in cancer

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Background: Modified citrus pectin (MCP) is a polysaccharide consisting of galacturonic acid with anti-cancer activity that can act synergistically with other treatments to reduce tumor growth, stimulate programmed cell death and reduce the number of metastases. In addition, MCP prevents acute and severe renal syndromes caused by radiation/chemotherapy. All of these effects were reported to be due to MCP ability to specifically inhibit Galectin-3 protein functions.

Aims: The aim of this work was to evaluate the anticancer effect of MCP in a Balb/c nude mice xenograft model of ovarian cancer.

Methods: The human ovary cancer cell line, SKOV-3, was subcutaneously injected in Balb/c nude mice and tumor growth was monitored daily with a caliper. When tumors reached 250-300 mm^3, 20 mg/kl of MCP was administered intravenously (I.V.) in a daily based for 21 days. Tumor growth and mice weight were monitored daily. Additionally, MCP was radiolabeled with 99m-technetium (^{99m}-Tc) with the incubation of MCP (2.5 mg) in saline with $SnCl_2$ (4 mg/ml), HCl (0.01 M), NaOH (0.01 M) and ^{99m}Tc (129,5 MBq) at pH=7 for 30 min. The radiochemical purity was determined by iTLC-SG with acetone and ethanol/NH3/H2O (1:2:5). ^{99m}Tc-MCP (37 MBq) was administrated I.V. in Balb/C nude mice bearing SKOV-3 tumors and after 1, 2 and 4 hours, µSPECT/CT image was acquired (Albira SI Buker). *Ex-vivo* biodistribution studies were performed after the I.V. injection of 10 MBq of ^{99m}Tc-MCP for 1-hour. The % of injected dose

per gram (%ID/g) of tissues of interest was calculated. The tumors were removed, fixed, cut and used for autoradiography studies and stained with hematoxylin and eosin (H&E) to verify hypoxic regions.

Results: The I.V. administration of MCP was able to significantly reduce SKOV-3 tumor growth (52% tumor volume reduction) in comparison with the non-treated group, after 21 of treatment. Our biodistribution studies showed that ^{99m}Tc-MCP was mainly found in kidneys, bladder and liver of mice (%ID/g = 12.25, 38.57 and 5.71, respectively), and was able to reach the tumor (%ID/g = 0.765 ± 0.045) 1-hour after I.V. administration. ^{99m}Tc-MCP accumulation in the tumor site was visualized by μSPECT/CT imaging 1 hour after I.V. administration. The autoradiography and stained (H&E) study demonstrated a correlation between MCP and regions of tumor necrosis. Because of MCP high accumulation in kidneys, renal toxicity was also evaluated. We were able to find that MCP doesn't induce renal toxicity when administered in a daily base at a concentration of 20 mg/Kg.

Conclusion: In this work we demonstrated that a daily treatment of MCP was able to reduce tumor growth of ovarian tumor xenografts (SKOV-3 cells) without showing renal toxicity. We found too that MCP can reach the tumor site, binding mainly in regions of necrosis. However, other studies are needed to unravel the mechanisms of action that act on the antitumor effect of MCP.

P-235
Novel [^{124}I]ATRi VE-821 analogue PET tracer in mouse models for prostate cancer

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Introduction: More than 30,000 patients die of metastatic castration resistant prostate cancer (mCRPC) annually due to uncontrollable disease with a median 5-year survival rate of less than 5%. [1] Life-prolonging drugs are limited and makes the development of targeted radiotherapy an urgent clinical need.

An estimate 25% of PC patients have a deficiency in their DNA damage response including BCRA - most abundant - followed by ATM. Tumors with BRCA DDR deficiencies have been shown to respond to PARP inhibitors (e.g., Olaparib) but ATM-deficient tumors remain uncontrollable within this line of treatment. ATM mutated PC is sensitive to ATR inhibition, which provides a promising strategy for diagnosis and treatment. Ataxia telangiectasia and Rad3-related (ATR) threonine/serine kinase is one of the three key members of the PIKK family orchestrating in the DNA damage response responsible for preserving genome integrity via checkpoint 1 activation. [2] Triggered by ssDNA breaks via e.g., UV light and drugs like cisplatin ATR engages in the immediate repair of breakages. [3]

We aim to rationally design and subsequently evaluate a radiolabeled ATRi probe for non-invasive PET imaging allowing the localization of tumor lesions. Due to the rare mutation of ATR, it serves as a promising target expressed in cancer cells. We have shown previously the potential of a fluorine-18 based ATRi PET tracer in a glioblastoma mice model. [4] However, the half-life of iodine-124 will allow longer monitoring of the uptake and distribution of the developed probe. Prostate cancer as a disease model was chosen to investigate whether the newly designed [^{124}I]ATRi is a suitable radiotracer. Here, we present the radiolabeling and the results of its *in vitro* and *in vivo* evaluation in murine models of disease.

Methods: Based on the known inhibitor VE-821 radiolabeling with iodine-124 resulted in the respective [^{124}I]ATRi inhibitor as a new PET tracer. Western blot analysis of different prostate identified LNCaP cells and, furthermore, *in vitro* assays support their suitability to test the applicability of [^{124}I]ATRi as a preclinical probe. Immunocompromised mice were subcutaneously injected with LNCaP cancer cells followed by PET imaging with [^{124}I]ATRi 6 MBq/mouse (150 μCi/mouse) recorded on an Inveon microPET/CT instrument. Biodistribution studies were conducted sacrificing mice after the scan to evaluate subsequent organ uptake.

Results: The radiolabeled [^{124}I]-ATR inhibitor was synthesized in high specific activity of 24 GBq/μmol (0.65Ci/μmol) and radiochemical yield of 80%. *In vivo* imaging experiments show good contrast in tumor lesions and could be blocked specifically with VE-821.

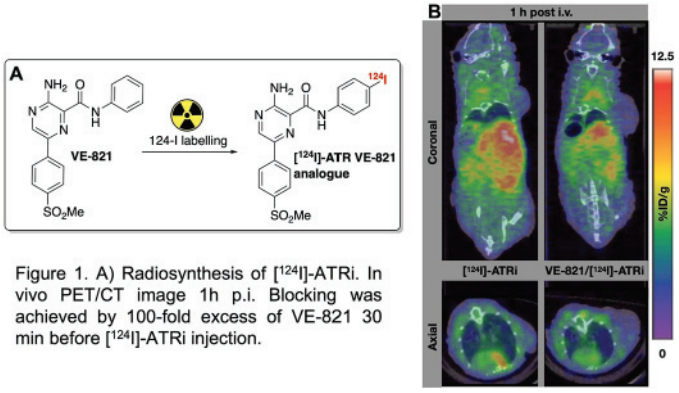

Figure 1. A) Radiosynthesis of [^{124}I]-ATRi. In vivo PET/CT image 1h p.i. Blocking was achieved by 100-fold excess of VE-821 30 min before [^{124}I]-ATRi injection.

Conclusion: Our findings show that the newly synthesized [^{124}I]-ATRi shows potential for preclinical application with good sensitivity toward tumor lesions.

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P-236
Synthesis and in vivo characterization of a heterobivalent radiotracer targeting PSMA and GRPR for prostate cancer imaging

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Introduction: Over the last years, the world of nuclear imaging has shown an increasing interest in multireceptor targeting justified by tumor heterogeneity and the concomitant overexpression of different membrane receptors by tumor cells[1]. In this context, the use of monomolecular heterobivalent tracers is expected to offer higher affinity for tumor tissue as well as longer residence time on tumor cells compared to the corresponding monovalent tracers[2] (Figure 1). A striking example of multireceptor overexpression is prostate cancer where both PSMA and GRPR are overexpressed[3,4].

Methods: To access a large variety of heterobivalent tracers, our group has developed a modular and straightforward method based on a trifunctional platform[5]. The procedure started with the sequential functionalization of 3,6-dichlorotetrazine *via* nucleophilic aromatic substitutions. To control the distance between the vectors, they were separated from the platform by *bis*-β-alanine spacers. The resulting tetrazines were then coupled with a BCN-functionalized chelator (DOTA or NODAGA) thus forming bivalent tracers. A conjugate with affinity towards PSMA and GRPR was labeled with ^{67}Ga and its pharmacological properties (association kinetics, K_D) were determined *in vitro*. It was then labeled with ^{68}Ga and PET-CT and biodistribution studies were conducted on double-xenografted athymic nude mice.

Results/Discussion: A series of bivalent ligands were successfully synthesized with yields ranging from 2 to 18%. The reported procedure