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effect of uncertainties is incorporated into margins for the planning target volume (PTV) and organ at risk volume (ORV), a practice that is not transferable to particle therapy in part because of uncertainties in the ranges of particles and, in part, due to the perturbation in dose distributions within, and not just at the boundaries, the anatomic structures caused by the factors mentioned above.
Particle dose distributions can be made less sensitive to uncertainties by using larger numbers of beam, making spot sizes larger, degrading distal edges and by reducing uncertainties in general. However, in order to account for residual uncertainties, it is necessary to resort to robust optimization. Robust optimization methods, which have long used in many fields such as statistics, finance, manufacturing, medicine, etc., can also be applied effectively in the optimization of IMPT to make the resulting dose distributions substantially more resilient to uncertainties. Several different IMPT robust optimization approaches are being explored. Examples include voxel-by-voxel worst-case, mini-max worst case and statistical approaches. Illustrative examples comparing results of different approaches with the traditional PTV-based approach will be presented. Current approaches have so far dealt with setup and range uncertainties only. Research to incorporate inter- and intra-fractional anatomic variations and uncertainties in biological effectiveness is just starting. Such research is essential to fully realize the potential of particle therapy.

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Parameterization of lateral dose profiles for proton therapy application at CNAO

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The main purpose of this work is to parameterize the FLUKA calculated lateral dose beam profiles for protons in water at CNAO (Centro Nazionale Adroterapia Oncologica). The CNAO Treatment Planning System (TPS) currently calculates plans using a double Gaussian model with a database of parameters that was customized for the Heidelberg Ion Beam Therapy Center (HIT). Before patients' treatment, studies have been performed in order to understand the impact of different beam profiles on dose calculations [1] and the results have been considered acceptable for therapy. After these studies, CNAO decided to improve dose calculations by introducing a more accurate database for its TPS, obtained by the FLUKA Monte Carlo (MC) [2,3] simulations accounting for the CNAO beamline. The second purpose of this work consists in the investigation of alternative models for the fitting function, to obtain a more accurate description of the tails of lateral dose distributions in water.
The analysis was performed for all the 147 TPS energies ranging from about 60 to 230 MeV. The work has been done with the ROOT framework [5], exploiting Minuit features [6] for a detailed error evaluation. For each beam energy we have fitted the lateral beam profiles at 124 depths along the longitudinal direction. For each energy and depth, the best fit gives four parameters for the TPS double Gaussian model [4]:

$$D(r) = N\left[(1-w)\frac{1}{2\pi\sigma_1^2}e^{-\frac{r^2}{2\sigma_1^2}} + w\frac{1}{2\pi\sigma_2^2}e^{-\frac{r^2}{2\sigma_2^2}}\right]$$

Where σ_1 and σ_2 are the sigma, w is the relative weight and N represents the normalization factor. For the second purpose we have studied two alternative fitting functions. The first one makes use of four parameters and is a sum of a Gaussian and a Rutherford hyperbole to describe the peak and the tails of the distribution, respectively. The second one depends on six parameters and adds a third Gaussian to the TPS model to better describe the tails of lateral dose profiles.
Best fit parameters have been obtained by optimizing the minimization procedure with different algorithms (gradient, simplex and MC) and the final values were compared with the HIT ones.
Comparing the actual TPS database and the one obtained in this work we have found a promising solution for upgrading the CNAO TPS for patient treatments.

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A novel TOF-PET detector based on organic scintillators

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A new concept of TOF-PET detection system developed at the Jagiellonian University [1,2] will be presented. The novel solution opens unique possibilities of combining PET with CT and PET with NMR, so that the same part of the body can be scanned at the same time with both methods without moving the patient [3]. The method allows also for three dimensional reconstruction of the gamma quantum interaction point [3] enabling significant reduction of parallax errors in reconstruction of PET images.
The novelty of the concept lies in employing large blocks of polymer scintillators instead of crystals as detectors of annihilation quanta, and in using predominantly the timing of signals instead of their amplitudes for the reconstruction of Lines-of-Response. The low efficiency for detection of annihilation quanta and low probability for photoelectric effect in polymer scintillators can be compensated by large acceptance and very good time resolution achievable with this kind of detectors. To take fully advantage of the fast signals a novel front-end electronics allowing for sampling in a voltage domain was developed [3], and new methods for the reconstruction of hit position of the gamma quantum based e.g. on the Compressing Sensing theory are elaborated [4]. The solutions are subject of ten patent applications submitted this year [3] which will be presented for the first time. The talk will include an overview of the novel detector, electronics and signal reconstruction concepts.
Two different designs of the diagnostic chamber will be presented. First, referred to as the Strip-PET [5], contains plastic scintillator strips read out by pairs of photomultipliers arranged around a cylindrical surface. The second solution, referred to as the Matrix-PET [6], uses plastic scintillator plates read out by arrays of photomultipliers. In both cases a

sampling of signals in voltage domain allow for localization of the interaction point.
The project is supported by the Foundation for Polish Science and the Polish National Center for Development and Research.

Keywords: Time-of-Flight Positroon Emission Tomography, Plastic Scintillators, Signals Sampling

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From Bench to bedside: experience of the glioblastoma model for optimization of radiosensitization
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Radioresistance of glioblastoma (GBM) is dependent on intracellular radioresistance but also on factors controlling the micro-environment both potentially being activated by irradiation. More recently, tumor heterogeneity and presence of GBM stem cells have been fully implicated in modulation of GBM radiosensitivity. Our team is involved since several years in translational research in radiobiology/radiotherapy in the aim to optimizing the efficacy of radiotherapy of patients treated for glioblastoma by studying and deciphering biological pathways controlling intracellular radioresistance but also angiogenesis, hypoxia and invasion. We have first have shown that FGF2 controls radioresistance through the farnesylated form of RhoB and that integrins ▫v▫3 and ▫v▫5 control GBM radioresistance but also hypoxia and angiogenesis in vitro and in vivo through RhoB. More recently we demonstrated that FGFR inhibition by a specific FGFR inhibitor led to in vitro and in vivo GBM radiosensitization as well as inhibition of the expression of HIF-1▫. We also recently shown that irradiation as hypoxia induced HIF1▫ in GBM through ILK that we previously demonstrated to mediate ▫v▫3 and ▫v▫5 integrins- induced radioresistance and that inhibiting HIF-1▫ led to GBM radiosensitization. We then showed that inhibiting farnesylation of RhoB with the farnesyltransferase inhibitor Tipifarnib induced in vitro radiosensitization as well as oxygenation and vascularisation normalisation in vivo. Based on these preclinical studies we designed a Phase I-II clinical trial associating Tipifarnib with radiotherapy in newly diagnosed GBM patients, all the patients being followed by MRI spectroscopy as well as perfusion MRI. Expression of the proteins that we showed to control GBM radioresistance through RhoB were studied by immunohistochemistry in the tumor of all the patients included in the trial. This study allowed us to confirm in the patients the vascular normalisation after Tipifarnib and radiotherapy treatment and to show for the first time that expression of ▫3 integrin and FGFR1 were correlated with poor overall survival and shorter time to progression confirming that FGFR1 and ▫v▫3 integrin pathways are of interest to target in association with radiotherapy in the aim to radiosensitizing glioblastoma. Our team is pursuing this translational research including the study of the involvement of these pathways in GBM stem cells radioresistance.

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Potentiation of radiation response by a novel EGFR/DNA targeting molecule in a triple negative breast cancer model
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Purpose and objectives: Epidermal growth factor receptor EGFR is often overexpressed in human malignancies and it is associated with the activation of the AKT pathway leading to anti-apoptotic effects. This also includes the lack of sensitivity of some tumours to several existing cytotoxic therapies such as radio and chemotherapies. Therefore, it is of great importance to develop novel anti-cancer drugs effective against EGFR-overexpressing cancer cells.
ZRBA1 is a binary targeting molecule, which not only blocks EGFR at the TK domain but also induces DNA breaks. However, the binary property of this molecule can be limited by DNA repair mechanisms in cancer cells. Therefore to further increase the efficacy of treatment we combined ZRBA1 with ionizing radiation.
Methods: Using MDA-MB-468 breast cancer and 4T1 mouse mammary cancer cells, we performed colony forming assay to determine the radio-modulating effect of ZRBA1.The combined treatment was tested at multiple schedules (before radiation, concurrent and after radiation). Using Western blot analysis, flow cytometry and comet assay we have also evaluated the effect of each of the treatments alone and in combination on the level of apoptosis and cell cycle arrest as well as DNA damage induction. Finally, we have confirmed our *in vitro* data in a syngeneic breast cancer model by performing a tumour growth delay assay.
Results: Our colony forming assay showed a radiation dose enhancement factor (DEF) of 1.5 when ZRBA1 (22 uM) is combined with radiation. Moreover, our flow cytometry analysis showed a significant increase in G2/M cell cycle arrest when ZRBA1 and radiation are combined ($p<0.046$). Similarly, MDA-MB-468 cells treated with ZRBA1 and radiation showed increase in both single and double strand breaks. Western blot results demonstrated the highest level of cleaved PARP when radiation and ZRBA1 are combined as a late response. Importantly, our in vivo tumour growth delay assay strongly suggests that ZRBA1 potentiates the radiation response in our 4T1 breast cancer model. In addition, tumour growth delay was nearly doubled in combined treated group compared to irradiated only group (26 days in irradiated group vs. 47 days in combined treatment group) with a statistical significance of 0.0456 on day 31 post-treatment (radiation+ ZRBA1 vs. radiation alone).
Conclusion: Our results have shown that ZRBA1 potentiates the radiation response in a triple negative breast cancer model *In vitro* and *In vivo*. The higher potency of this combination is due to increased cell DNA damage, cell cycle arrest and apoptosis.

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Head motion correction in positron emission tomography using point source tracking system
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Aim: The motion of the head during brain positron emission tomography (PET) acquisitions has been identified as a source of artifact in the reconstructed image. In this study, a