RadOnc Annual Research Retreat, Friday, October 14, 2016

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Exosomes from the tumor microenvironment promote breast cancer progression and therapy resistance

Barzin Nabet, Minn Lab

Stromal communication with cancer cells can influence treatment response, making the elucidation of pathways used for interaction between these cell types an important goal. We show that stromal and breast cancer (BrCa) cells orchestrate chemotherapy and radiation resistance by utilizing both juxtacrine signaling and paracrine signaling that mimics events of an anti-viral response. After heterotypic interaction, exosomes are transferred from stromal to BrCa cells. Stromal-derived RNA within exosomes, which are largely non-coding transcripts regulated by RNA polymerase III, stimulates the BrCa RNA pattern recognition receptor RIG-I to activate STAT1-dependent anti-viral signaling. In parallel, stromal cells also activate NOTCH3 on BrCa cells. The paracrine anti-viral and juxtacrine NOTCH3 pathways converge as STAT1 amplifies the transcriptional responses to NOTCH3 and expands therapy resistant tumor-initiating cells. Analysis of primary human tumors and/or tumors from genetically engineered mouse models support the role of anti-viral/NOTCH3 pathways in stroma-mediated resistance. In mice, targeting these pathways abrogate stroma-mediated resistance and results in long-term tumor-free survival. Thus, stromal cells orchestrate an intricate cross-talk with BrCa cells by utilizing exosomes to transfer non-coding RNA and instigate anti-viral signaling. This expands BrCa subpopulations adept at resisting therapy and re-initiating tumor growth. Our work highlights how stromal exosomes and their non-coding RNAs can mimic salient features of a cellular response to viral infection to regulate how the tumor microenvironment influences BrCa therapy resistance.
A novel mouse model to study image-guided, radiation-induced intestinal injury and preclinical screening of radioprotectors

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Abstract
Radiation is an important treatment modality for gastrointestinal tumors, but intestinal injury is a common side effect in cancer survivors. We wanted to develop a physiologically-relevant model for studying the molecular determinants of radiation-induced intestinal damage and testing novel intestinal radioprotectors. Using minimally invasive surgery, we implanted a radiopaque marker onto the surface of the mouse (C57BL/6) jejunum to serve as a fiducial marker for precise targeting of radiation. One-week post-surgery mice were imaged with Cone-Beam CT (CBCT) to locate the marker and irradiated with 12 or 18 Gy to the marked area using the Small Animal Radiation Research Platform (SARRP®). Cohorts of mice were sacrificed at time points ranging from 1h to 4 months post-RT and phosphorylation of H2AX, EdU immunofluorescence and TUNEL assays were used to assess radiation damage. Intestinal lysates and plasma were also collected to assess inflammatory cytokine levels. Our results indicate that the IR-induced damage is acute but reversible and largely restricted to the area of the marker, leaving the surrounding tissues intact. Intriguingly, although whole gut irradiation with these doses causes lethal GI syndrome, irradiation of a 5mm portion of the intestine did not cause any lethality or weight loss. However, fibrosis and collagen deposition 4 months post-IR indicated chronic intestinal damage. A separate cohort of mice was treated daily with curcumin, a non-toxic radioprotector, three days prior and two weeks post-IR. Curcumin-treated mice showed significant decreases in both local and systemic inflammatory cytokine levels as well as in fibrosis suggesting it is effective as a radioprotector of the intestine. Our results indicate that this model, which emulates closely clinically relevant intestinal radiation-induced injury, can be used to assess radioprotectors prior to testing in the clinic.
Temporal DNA-PK activation drives genomic instability and radioresistance in glioma stem cells

Yanling Wang, Yi Fan

ABSTRACT

Cancer stem cells (CSCs) — a pluripotent tumor cell population known to be resistant to radiation and chemotherapy — play a fundamental role in cancer therapy failure and disease relapse and metastasis. Here, we unexpectedly reveal that glioma CSCs are hypersensitive to radiation, but a time-dependent DNA repair mechanism converts the intrinsic radiosensitivity of CSCs to genomic instability and radioresistance. Our transcriptome analysis by RNA-seq identifies DNA-PK as a predominantly expressed DNA repair enzyme in CSCs. Notably, DNA-PK activity is suppressed following X-ray irradiation when reactive oxygen species (ROS) induce the dissociation of DNA-PK with Ku70/80, resulting in delayed DNA repair and radiosensitivity; subsequently, after ROS clearance, the accumulated DNA damage and robust activation of DNA-PK induce genomic instability, leading to enhanced cell malignancy, CSC overgrowth, and radioresistance. Finally, we show a requisite in vivo role for DNA-PK in CSC-mediated radioresistance and glioma progression in mouse models. Collectively, these findings identify a time-sensitive mechanism controlling treatment resistance in CSCs, and provide evidence that targeted inhibition of DNA-PK may offer a selective and efficient strategy for eradicating CSCs in tumors.
TITLE: A methylimidazolium iodide compound induces DR5 dependent TRAIL synergy and selective activity against cancer stem cells

AUTHORS: Saad Sheikh, Xiaobing Tian, Deeksha Saxena, Bryan Manning, Xiangsheng Xu, Yi Fan, Gary D. Kao, Jay F. Dorsey

Management of Glioblastoma typically involves aggressive surgical resection followed by adjuvant chemotherapy and radiotherapy. This tri-modality treatment results in overall patient survival of only about 14.6 months [1]. Post-operative treatment strategies largely rely on inducing DNA damage, with progression free survival dictated by methylguanine methyltransferase (MGMT) promoter methylation [2]. However, most patients will have local or regional recurrence of disease. This necessitates the need for therapeutic agents that complement DNA damage pathways to induce cell death. One strategy is to target the integrated stress response (ISR) pathway in tumor cells. This mechanistic strategy has been clinically successful as evidenced by the use of small molecule protease inhibitor bortezomib to treat multiple myeloma, and more recently ONC201 [3]. By utilizing a cell-based death receptor luminescence reporter system and a comprehensive library of compounds, we identified a methylimidazolium iodide compound (MI) as an inducer of C/EBP homologous protein (CHOP). MI induction of ISR also leads to apoptosis in tumor cells at low micromolar concentrations. Additionally, the resulting modulation of CHOP leads to expression of death receptor DR5 in a p53 independent manner. Up-regulation of DR5 in turn allows for synergy with TNF related apoptosis inducing ligand (TRAIL) to enhance tumor cell death. This lead compound also demonstrates selective potency against glioblastoma cancer stem cells when compared to tumor cells. Our work points to an emerging strategy to treat a variety of aggressive tumors by targeting populations of cells that may be uniquely sensitive to ISR induction in combination with TRAIL.

References:
The Exploitation of Tumor Microenvironment for Monitoring Orthotopic Models of Pleural Cancer

Richard W. Davis IV, Joann Miller, Cassandra Houser, Elizabeth Browning, W. Tim Jenkins, Michael F. Beers, Theresa M. Busch

In animal studies of cancer therapy the use of orthotopic tumor models is important to understanding the interplay between the tumor and its surrounding environment. In the case of preclinical models of malignant pleural mesothelioma (MPM), tumor cells grow diffusely throughout the thoracic cavity and are entrenched in the rib cage. Thus, these studies require noninvasive yet sensitive, and quantitative measurements to follow tumor burden throughout the course of therapy. In this presentation, we discuss two approaches toward imaging of diffuse tumor burden in the murine thoracic cavity: optical imaging using activatable probes and computed tomography using native contrast. For initial studies, mice were administered 1 million cells (AB12 murine mesothelioma) approximately 1.5 centimeters above the edge of the rib cage and burden was allowed to develop a minimum of seven days before images were acquired. After imaging, mice were euthanized and the tumor burden removed and weighed. In the first modality, endogenous matrix metalloproteases (MMP’s) are detected using a commercially-available optical probe. This approach exploits the known overexpression of MMP’s in mesothelioma. These probes are optically silent until cleaved by MMP’s, at which time they fluoresce in the near-infrared spectrum. This modality was very sensitive, detecting tumor burden as low as 38 mg. However, the long incubation time (16 hours) and clearance time (96 hours) limit its use in short, repetitive timepoints. In addition, spectral unmixing was required in order to reduce signal from the liver. Therefore, we also assessed the use of cone beam computed tomography (CBCT) to detect increased fibrosis in tumors implanted in the thoracic cavity. Images were reconstructed using a custom workflow, and correlated strongly with tumor weights measured ex vivo. Moreover, these measurements were robust through multiple iterations. Tumor cells were detected at a range of weights from 48.9 mg to 279 mg, and no false positives were observed. Our ongoing investigation seeks to apply these methods towards the study of thoracic photodynamic therapy (PDT), allowing correlations to be determined between tumor regression and the PDT treatment parameters.
Title: From Big Data to Knowledge: Factors predicting a need for treatment re-planning with proton radiotherapy for lung cancer

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Purpose: In light of tumor regression and normal tissue changes, dose distributions can deviate undesirably from what was planned. As a consequence, re-planning is sometimes necessary during treatment to ensure continued tumor coverage or to avoid overdosing organs at risk (OARs). However, factors that predict re-planning are not identified. We investigated action thresholds for re-planning and identified dosimetric and non-dosimetric metrics that would predict a need for re-planning.

Methods: All consecutive lung cancer patients (n = 188) who received definitive proton radiotherapy and had more than three evaluation CT scans at the Roberts Proton Therapy Center (Philadelphia, USA) from 2011 to 2015 were included in this study. The cohort included a variety of tumor sizes, locations, histology, beam angles, as well as radiation-induced tumor and lung change. Dosimetric changes during therapy were characterized by changes in the dose volume distribution of PTV, ITV, and OARs (heart, cord, esophagus, brachial plexus and lungs). Tumor and lung change were characterized by changes in sizes, and in the distribution of Hounsfield numbers and water equivalent thickness (WET) along the beam path. We involved our lung clinicians to give retrospective re-planning decisions and applied machine learning tools to identify dosimetric and non-dosimetric metrics that predicted the re-planning decisions.

Results: Preliminary data showed that clinical indicators were highly correlated; thus, only a few metrics may be necessary to predict re-planning decisions. We used the random-forest method to identify the most important predictors and proposed a decision tree to help guide an online workflow for re-planning decisions.

Conclusions: We identified the most important metrics for predicting a treatment re-planning for proton therapy for lung cancer.
Fig 1: (a) Auto-correlation matrix between clinical indicators. (b) Cross-correlations between changes in tumor density (i.e., average CT number of the original GTV volume) with changes in clinical indicators. Clinical indicators included are (1-6) D95%, Dmin, Dmean of PTV and ITV, (6-12) D0.03cc, Dmax, Dmean of Cord and Cord+5MM, (13-22) Dmax, Dmean, V5, V10, V20, V25, V30, V45, V50, V60 of Heart, (23-28) Dmax, Dmean, V35, V50, V55, V70 of Esophagus, (29-36) Dmax, D3cc, D1cc, D0.3cc of R- and L- Brachial Plexus, and (37-54) Dmax, Dmean, V5, V20, V20, V25, V60 of R-, L-Lung and Total-Lung minus GTV.

Fig 2: Decision tree reduces the number of dosimetric metrics to simple branch points, predicting clinical re-planning decisions.
Prompt gamma imaging for \textit{in vivo} proton range verification of pencil beam scanning proton therapy

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\textbf{Purpose:} To report the first clinical experience and value assessment of prompt gamma imaging (PGI) for \textit{in vivo} proton range verification in pencil beam scanning (PBS) mode.

\textbf{Methods and Materials:} A standalone, trolley-mounted, prototype prompt gamma camera, utilizing a knife-edge slit collimator design was used to record the prompt gamma signal emitted along the proton tracks during delivery of the proton therapy treatment for a brain cancer patient. The recorded prompt gamma depth detection profiles of individual pencil beam spots were compared to the expected profiles simulated from the treatment plan.

\textbf{Results:} In 6 treatment fractions recorded over three weeks, the mean range shift aggregated over all spots in 9 energy layers could be verified with an accuracy of $0.47 \pm 0.69$ mm for the lateral field, $2.61 \pm 0.40$ mm for the right-superior-oblique field, $0.26 \pm 0.51$ mm for the vertex field.

\textbf{Conclusions:} This study demonstrates the feasibility and illustrates the distinctive benefits of prompt gamma imaging for the PBS treatment mode. Accuracy in range verification was found in this first clinical case to be lower than the uncertainty accounted for in the treatment planning range uncertainty margin. These first results encourage additional efforts towards deeper integration of the system in order to further reduce residual uncertainties for optimal clinical application.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{The average spot shift in the Bragg peak position for each proton iso-energy layer in the lateral field.}
\end{figure}
**Title:** Can Equivalent Uniform Dose (EUD)-based optimization lead to dose painting and dose guidance?

**Presenter:** Dimitris Mihailidis, PhD., Perelman Ctr for Advance Medicine

**Introduction:** Presently, acceptable IMRT plans can be generated by most radiation therapy planning systems using dose-volume (D&V) objectives based optimization. For complex plans that include many structures with D&V objectives, the objective function becomes complex and difficult to be managed by the optimizer. On the other hand, an objective function based on generalized equivalent uniform dose (gEUD), firstly, becomes simpler with fewer parameters and secondly generates plans with at least the same coverage for the target volumes as D&V-based plans and higher sparing for the organs at risk (OARs). This potentially leads to “dose sculpting” or “dose painting”. The purpose of this proposed study (pilot) is to show that, for the same or better target coverage, gEUD-based optimization is capable of providing higher sparing of OARs, with less number of objectives compare to D&V-based optimization, when applied to head and neck (H&N) and postmastectomy chest wall (CW) treatment sites.

**Methods and Materials:** A number of H&N and CW patients were planned first, with in-house physician-set objectives (in-house protocol with D&V objectives-phys) then, with gEUD-based objectives for the OARs and physical (D&V) objectives for the target volumes (PTVs) and finally, with multiple and more stringent D&V-based objectives for every OAR and PTV. For the latter case, the doses for 50%V, 30%V and Dmax were defined for every OAR and the same weight of importance as in the gEUD plan, were used for every OAR respectively. Six or 7 coplanar intensity modulated 6 MV fields where inversely optimized and delivered via step-and-shoot mode. The gEUD allows the reduction of a dose distribution into a single biologically relevant quantity for target volumes and OAR alike, with a single adjustable parameter, $\alpha$ ($\alpha>0$ for OAR and normal tissues and $\alpha<0$ for tumors). Thus, one can use a single objective per OAR with a specific $\alpha$ as oppose to multiple D&V objectives. gEUD-based objectives for all OARs and D&V-based objectives for PTVs were used in order to control the hot spots and improve the dose distribution inhomogeneities within the PTVs. Comparisons between the gEUD-based, D&V-based and the phys-set objectives (phys) plan will be made.

**Results:** For all patients in this study and both treatment sites, we have seen that the gEUD-based plans allow greater sparing of the OAR keeping good target coverage. For the H&N cases, gEUD lead to lower doses for critical structures such as parotid and sub-mandibular glands, spinal and vocal cords (Fig. 1 medium solid lines). On the other hand, multiple D&V objectives for every OAR might lead to the same DVH as in the gEUD case but with considerable trial-and-error effort and longer computation time. In the CW plan the D&V plan (not shown) gave almost the same DVHs as the gEUD plan, for all structures except, the ipsilateral lung where the gEUD plan gave better sparing. The 1-2 Gy dose clouds, are constricted closer to the target with gEUD, resulting better sparing of heart, ipsilateral lung and uninvolved normal tissues (fig. 2). Overall, the gEUD optimized plans allowed better control of the lower doses sculpting them around OARs.

**Conclusions:** gEUD-based optimization results in better normal tissue sparing for various treatment sites and similar or better target coverage compare to the D&V-based one. gEUD requires a smaller number of parameters for optimization and a larger space of solutions becomes available. Thus, gEUD optimization can be used to search for or evaluate plans of different DVHs but the same gEUDs. With gEUD being a quantity in the dose domain makes it easier for the user to set the objectives for optimization as oppose to other dose-response indices such as TPC and NTPC, for example. A disadvantage of gEUD-based optimization is that, due to the limited number of parameters controlled by the user, details of dose distributions cannot be fine-tuned. gEUD can potentially be used as a dose-guidance tool.

**Fig. 1:** H&N plans, EUD-thin solid, D&V-dash, phys-thick lines. **Fig. 2:** CW site, phys-plan (Right) and EUD-plan (Left), the extend of 2 Gy dose cloud (orange) is controlled better with EUD.
Intestinal microbiome modulates antitumor immune response and impact RT effectiveness.

Stavros Rafail, Mireia Uribe-Herranz, Ioannis Verginadis, Stefano Pierini, Costas Koumenis and Andrea Facciabene

Abstract:

Radiotherapy (RT) is an established curative and palliative cancer treatment regimen, with approximately half of all cancer patients with solid tumors receiving RT some time during their disease. Despite substantial improvements in the spatial delivery of radiation, the majority of irradiated solid tumors recur locally or distally. Published reports over the past couple of decades, have demonstrated that high-dose RT delivered to primary or metastatic lesions exerts potent immune modulatory effects. These effects include immunologically active tumor cell death, Tumor-Associated Antigen (TAA) cross priming and anti-tumor CD8 T cell elicitation. Several studies in animal models have connected in vitro cytotoxic T cell activity with in vivo antitumor efficacy. Nonetheless, these therapies are only effective in a minority of patients raising the question of whether there are other important regulators of T cell function relevant to tumor control. Compelling evidence has shown that the cell-mediated immune mechanisms described above, can be influenced by the gut microbiome. Importantly experiments linking gut microbiome with atherosclerosis, arthritis, autism and inflammation have demonstrated that the commensal gut bacteria impact the function of T cells and other immune cell subsets within the gut-associated lymphoid tissue (GALT), and well beyond. Furthermore, the mechanism of action of some of the most effective chemotherapies, such as doxorubicin and cyclophosphamide have been shown to involve the immune system, and also be influenced by the gut microbiota. Our overall hypothesis is that microbiota-regulated systemic immune responses play an important role in the RT induced anti-cancer immune response and thereby impacts the effectiveness of RT. We thus challenged animals with TC1 or B16-Ova cells in either flank and treated them per os with antibiotics targeting gram positive bacteria (vancomycin), we chose established antibiotic treatment that are known to have local effects only and are not found in the periphery. After 11 days, we irradiated one tumor per animal. We demonstrated that:

(a) Vancomycin caused a significant enhancement of the tumor inhibitory effect of targeted radiation.

(b) Vancomycin treatment increased the presence of overall tumor infiltrating T cells and cytotoxic CD8+ cells in tumors from mice treated with RT/vancomycin combination compared to RT alone.

(c) Vancomycin enhanced the ability of RT to increase the expression of IFN-γ in CD8+ infiltrating T cells and antigen presentation in the draining lymph nodes.

(d) The observed synergy between vancomycin and RT in eliciting an anti-tumor immune response and inhibiting tumor growth was abrogated in IFNγ KO animals or by CD8+ T cell depletion.

We conclude thus that the effects of antibiotic treatment in RT impact antigen presentation and require the production of IFNg for the effectiveness of the effectors CD8+ T cells.
Avoiding skin creams just before radiation: Good advice or much ado about nothing?

Brian C. Baumann, Ioannis I. Verginadis, Chuan Zeng, Carolyn Vachani, Timothy D. Solberg, Costas Koumenis, James M. Metz

Purpose/Objectives:
Radiation dermatitis is common & often treated with topical creams. Patients are traditionally advised to avoid lotions for several hours before radiotherapy (RT) based on concern that creams might increase skin dose. With modern RT’s improved skin sparing, this recommendation may be irrelevant. We hypothesize that applying either metallic or non-metallic creams before treatment would have minimal effect on skin dose.

Methods/Materials:
We conducted an online, 24-question anonymous survey of patients and providers to determine current skin cream practices. To evaluate the dosimetric effect of creams, we delivered 200 MU at 100 cm SSD & measured the dose at the surface and 2 cm depth in a tissue equivalent phantom with optically stimulated luminescent dosimeters (OSLDs), with and without two common skin creams, a topical emollient & silver sulfadiazine. We assessed the effect of various photon & electron energies, cream thicknesses & beam incidence on dose. The effect of creams on skin dose was also evaluated in C57BL/6 mice using γ-H2AX IHC staining. Mice were shaved and irradiated to 2 or 4 Gy in a single fraction in the presence or absence of thin and thickly applied emollient. Each mouse served as its own control. Skin was harvested 1 hour after RT & stained for γ-H2AX. Quantification of γ-H2AX foci was performed using ImageJ.

Results:
57 of 66 surveyed cancer patients (86%) & 44 of 47 providers (94%) either received or gave the advice to avoid applying creams prior to RT treatments. Measurements showed no difference in dose at the surface or 2 cm depth with or without a 1-2 mm application of either cream when using enface 6 or 15 MV photons. The same application of cream had no effect on surface dose as a function of beam incident angle from 15-60°, except for a 7% increase at 60° with the silver cream. Surface dose for 6 and 15 MV beams were significantly increased with a thicker (≥3 mm) layer of cream. For 6 MV, the surface dose was 105 cGy (emollient), 102 cGy (silver cream) & 88 cGy (controls). For 15 MV, the doses were 70, 60 & 52 cGy, respectively. With 6 & 9 MeV electrons, there was only a 2-5% increase in surface dose with use of creams. There were no dose differences at 2 cm depth. Irradiated skin in mice treated to 2 Gy and 4 Gy showed no significant difference in γ-H2AX positive foci with or without creams (p>0.05). There was also no significant difference in γ-H2AX positive foci based on differences in the applied cream thickness (p>0.05).

Conclusions:
Our findings suggest that thin or moderately applied creams, even if applied just prior to RT, have minimal impact on skin dose, regardless of beam energy or beam incidence. Applying very thick amounts of cream just prior to RT increased surface dose and should be avoided. Pre-clinical results confirm that skin creams have minimal effect on the surface dose. Use of creams prior to radiation can be liberalized, which may improve patient quality-of-life.
Androgen Deprivation Therapy and Risk of Dementia

Kevin T. Nead, Greg Gaskin, Cariad Chester, Samuel Swisher-McClure, Nicholas J. Leeper Nigam H. Shah

Introduction: Androgen deprivation therapy (ADT) is a mainstay of treatment for prostate cancer. While most individuals return to normal testosterone levels following treatment, 20% to 30% have prolonged androgen suppression. Concerningly, androgens have been shown to aid in neuron growth and axonal regeneration with multiple studies showing an association between ADT and cognitive dysfunction. In the current analysis we utilize an informatics approach using electronic medical record data from more than 1.2 million patients to examine the association of ADT with the subsequent development of dementia among men with prostate cancer.

Methods: We used a previously validated and implemented text-processing pipeline to analyze electronic medical record data in a retrospective cohort of patients. We extracted International Classification of Diseases-9th (ICD-9) revision diagnosis and Current Procedural Terminology codes, medication lists, and positive-present mentions of drug and disease concepts from all clinical notes. New-onset dementia was defined using terms from clinical notes and ICD-9 diagnostic codes 290.0-290.9, 331.0-331.2 or 294.1-294.21. We then tested the effect of ADT on risk of dementia using 1:5 propensity score–matched and traditional Cox proportional hazards models. Traditional models were adjusted for age at prostate cancer diagnosis, race, smoking status, use of antiplatelet, anticoagulant, antihypertensive, and statin medications, and a history of cardiovascular disease, diabetes, or malignancy. We also tested whether the duration of ADT use was association with dementia risk.

Results: There were 9,501 men with prostate cancer meeting all study criteria with 1,921 (20.2%) receiving ADT. During a median follow-up period of 4.6 years (interquartile range, 0.9-7.1 years) 297 patients were diagnosed with dementia. Propensity score–matched analysis (hazard ratio, 1.64; 95% CI, 1.20 to 2.23; $P = 0.002$) and traditional multivariable Cox regression analysis (hazard ratio, 1.81; 95% CI, 1.39 to 2.37; $P < 0.001$) both supported a statistically significant association between ADT use and dementia risk. We also observed a statistically significant increased risk of dementia with increasing duration of ADT ($P$ for trend < 0.001) with individuals undergoing ADT for greater than 1 year having the highest risk (hazard ratio, 1.96; 95% CI, 1.38 to 2.78; $P < 0.001$) in propensity score–matched models.

Conclusion: Our results support an association between the use of ADT in the treatment of prostate cancer and an increased risk of dementia in a general population cohort. Future prospective studies are needed to confirm this finding.
Dosimetry study of PHOTOFRIN-mediated photodynamic therapy in a mouse tumor model

Haixia Qiu, Michele M. Kim, Rozhin Penjweini, and Timothy C. Zhu

It is well known in photodynamic therapy (PDT) that there is a large variability between PDT light dose and therapeutic outcomes. An explicit dosimetry model using apparent reacted $^1O_2$ concentration ($[^1O_2]_{rx}$) has been developed as a PDT dosimetric quantity to improve the accuracy of the predicted ability of therapeutic efficacy. In this study, this explicit macroscopic singlet oxygen model was adopted to establish the correlation between calculated reacted $[^1O_2]_{rx}$ and the tumor growth using Photofrin-mediated PDT in a mouse tumor model. Mice with radiation-induced fibrosarcoma (RIF) tumors were injected with Photofrin at a dose of 5 mg/kg. PDT was performed 24h later with different fluence rates (50, 75 and 150 mW/cm²) and different fluences (50 and 135 J/cm²) using a collimated light applicator coupled to a 630nm laser. The tumor volume was monitored daily after PDT and correlated with the total light fluence and $[^1O_2]_{rx}$. Photophysical parameters as well as the singlet oxygen threshold dose for this sensitizer and the RIF tumor model were determined previously. The result showed that tumor growth rate varied greatly with light fluence for different fluence rates while $[^1O_2]_{rx}$ had a good correlation with the PDT-induced tumor growth rate. This preliminary study indicated that $[^1O_2]_{rx}$ could serve as a better dosimetric predictor for predicting PDT outcome than PDT light dose.

Keywords: photodynamic therapy, macroscopic singlet oxygen model, Photofrin, explicit PDT dosimetry
Postoperative whole-breast radiotherapy has an essential role in suppressing the recurrence of cancer and improving long term patient outcomes. Because of breast proximity to the lung and heart, some patients develop radiation related pulmonary and cardiovascular complications after receiving left anterior oblique (LAO) single field RT. At the same time, avoiding the heart and lung may compromise the dose coverage within the target breast. Dose inhomogeneity can result in hotspots within the target breast, and may lead to tissue toxicity and cosmetic complications. The intention of this project was to evaluate proton modulated arc therapy (PMAT) as a treatment modality for left-sided breast cases. Our hypothesis was that PMAT could potentially reduce the dose to organs at risk, while improving the dose conformity in the target.

We present a method of proton arc therapy treatment planning where the target breast is segmented into multiple sub-targets, with each sub-target having the same angular spread (2°) in the transverse plane of the breast. Each segment is targeted by an individual single beam of the arc, and the dose calculation from each beam is used as a control point for the dose optimization process. The objective of our method is to use single energy-layer beams throughout the arc in order to be able to continuously rotate the gantry without having to stop to switch energy between angles. The range of the proton each beam was calculated and subsequently normalized to the most distal beam through the insertion of a physical wedge to compensate for the change in range throughout the arc. The wedge thickness at every beam angle was calculated as follows (see Figure 1): to force every beam to travel an estimated water depth equivalent to the single largest estimated water depth output by an initial, pre-wedge, dose calculation. The range output from the pre-wedge calculation provides the data for the thickness of the wedge outwards from the interior ellipse. This wedge thickness was determined at an angle tangential to the target segment. This angle corresponds to the angle of beam travel for the target segment. After wedge construction, a second calculation was run. The range for each beam was manually overridden to the determined midrange from the multi-beam wedge calculation. Additionally, the SOBP of each beam was manually set to 0 to remove any intra-layer switching time to allow for continuous gantry rotation. For the breast cases analyzed, two mono-energetic arcs with different beam energy were used to achieve conformity.

PMAT and single field PBS plans were compared for 6 left-sided breast cancer patients scanned with breath hold. The results indicate that with a single field approach, only 95% of the prescribed dose was deliverable to 95% of the PTV before producing large hotspots as a difference to the 98% deliverable to the same volume of the PTV with PMAT. This improvement comes with no significant increase in hotspots delivered to the target volume, indicated by the analysis of relative volume received 107% dose in Table 1. PMAT also significantly reduces the mean dose delivered to the heart and left anterior descending artery. Doses distributions to the ipsilateral lung are comparable for PMAT and PBS treatment modalities. PMAT also offers a potential improvement in dose conformity and provides homogeneity comparable to that seen in PBS treatment.

Our results illustrate a significant biological advantage for PMAT through calculated LET distribution to OARs. Maximum LET distributed to all of the observed OARs was significantly less for PMAT than PBS treatment. Additionally, PMAT resulted in a reduction in average LET distributed to the ipsilateral lung. These results indicate that by treating the breast tangentially through PMAT, it is possible to reduce the delivery of biologically relevant dose to OARs without a reduction of homogenous coverage. In the LAO proton field approach, a single field carries all the dosimetric weight with the potential risk of making the plan not robust and prompt to large dosimetric variations due to range uncertainties and setup errors. By targeting the breast tangentially, it is possible to avoid delivering high LET directly into the lung and other OARs.

In conclusion, the potential to reduce dose to OARs for left-sided breast patients without a reduction in the homogeneity and conformity of dose delivered to the target itself makes PMAT an interesting treatment modality for further study. We believe improving the treatment planning system’s ability to properly implement and optimize an arc therapy treatment would further expand the benefits of PMAT.
Figure 1: Target breast segmentation and example of single beam dose tangential to target segment

Single Field PBS  PMAT

Figure 2: Dose distribution

Figure 3: Dose-volume histogram
Table 1: Dose distribution averages to target breast and OARs for 6 patients. HI: homogeneity index, is a measure of the maximum dose seen within the target structure. CI: conformity index, is a measure of the volume of the target coverage by 95% of the isodose line.

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<th>LUNG</th>
<th>LAD</th>
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<td>V20G Gy</td>
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Table 2: The average mean and maximum LET distributions to the target breast and OARs for 6 patients.

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Impact of Prophylactic Cranial Irradiation on Overall Survival in Extensive-Stage Small Cell Lung Cancer: A Propensity Score Matched Analysis

Sharma, Sonam; McMillan, Matthew T; Doucette, Abigail; Simone, Charles B II; Shabason, Jacob

ABSTRACT

Purpose: Patients with small cell lung cancer (SCLC) have a high propensity for brain metastases and are, therefore, often treated with prophylactic cranial irradiation (PCI). The role of PCI in patients with extensive stage (ES) SCLC is controversial. We utilized the National Cancer Database (NCDB) to assess survival of patients with metastatic SCLC treated with PCI.

Methods: We identified 4,257 patients with metastatic SCLC without brain metastases. To minimize bias of PCI delivery, we excluded patients with an overall survival < 6 months. We conducted propensity score matching to account for factors that predicted for receipt of PCI and overall survival (OS). We examined the impact of PCI on OS using unadjusted Kaplan Meier analyses and log-rank statistics.

Results: In our final cohort, 473 patients (11.1%) received chemotherapy and PCI and 3,784 patients (88.9%) received chemotherapy alone without PCI. With a median follow up of 30.4 months, there was a significant survival benefit for patients who received PCI, with a median survival of 13.9 vs 11.1 months (p <0.0001), 1-year OS 61.2% vs. 44.0% (p <0.0001) and 2-year OS 19.8% vs. 11.5%, (p <0.0001). This survival benefit remained after excluding patients who survived < 9 months to further minimize bias (15.3 vs. 12.9 months, P <0.0001). On multivariable analysis, predictors of receipt of PCI were Caucasian race, younger age, and lower Charlson/Deyo comorbidity score.

Conclusion: Utilizing a large, modern population-based data set, we show that patients with ES-SCLC treated with PCI have significantly improved OS. This study, the largest in this population to date, helps substantiate prior prospective data addressing this question. We also identified racial disparities in receipt of PCI.
A Tumor Mitochondria Vaccine Protects against Experimental Renal Cell Carcinoma

Stefano Pierini, PhD
Facciabene Lab

Mitochondria provide energy for cells via oxidative phosphorylation. Reactive oxygen species, a byproduct of this mitochondrial respiration, can damage mitochondrial DNA (mtDNA), and somatic mtDNA mutations have been found in all colorectal, ovarian, breast, urinary bladder, kidney, lung, and pancreatic tumors studied. The resulting altered mitochondrial proteins or tumor-associated mitochondrial Ags (TAMAs) are potentially immunogenic, suggesting that they may be targetable Ags for cancer immunotherapy. In this article, we show that the RENCA tumor cell line harbors TAMAs that can drive an antitumor immune response. We generated a cellular tumor vaccine by pulsing dendritic cells with enriched mitochondrial proteins from RENCA cells. Our dendritic cell-based RENCA mitochondrial lysate vaccine elicited a cytotoxic T cell response in vivo and conferred durable protection against challenge with RENCA cells when used in a prophylactic or therapeutic setting. By sequencing mtDNA from RENCA cells, we identified two mutated molecules: COX1 and ND5. Peptide vaccines generated from mitochondrial-encoded COX1 but not from ND5 had therapeutic properties similar to RENCA mitochondrial protein preparation. Thus, TAMAs can elicit effective antitumor immune responses, potentially providing a new immunotherapeutic strategy to treat cancer.
**Liposome-encapsulated Doxorubicin is a promising adjuvant to increase the efficacy of mTERT DNA-vaccine**

Mireia Uribe Herranz - Stavros Rafail - Stefano Ugel - John Facciponte - Stefano Pierini Andrea Facciabene

Challenging the notion that chemotherapy negatively modulates the immune system of tumor-bearing hosts, recent evidence on the contrary indicates that some cytotoxic drugs control tumor growth in part by facilitating an anti-tumor immune response. The precise mechanism(s) that controls this phenomenon have not been elucidated. Chemotherapy, especially at low doses, may modify the host’s immune system by either augmenting antigen-specific effector cells by rendering tumor cells immunogenic or eliminating immune-suppressive cell populations that limit the anti-tumor immune effect. Doxil (pegylated liposomal doxorubicin) possesses specific immunomodulatory properties such as inducing immunogenic tumor cell apoptosis. Mice were injected intraperitoneally (i.p.) with 5 x 10^6 ID8 cells. For chemotherapeutic treatment, mice received a single i.p. injection of either 50 mg/m^2 of Doxil (doxorubicin HCl liposome injection) or 50 mg/m^2 of Doxorubicin. DNA immunization (mTERT-LTB) was performed according to commonly used protocols: 50 micrograms of plasmid DNA was injected into mice quadriceps and then electroporation was carried out with a BTX electroporator intramuscularly at the injection site. For NK cell depletion, tumor-free and ID8 tumor-bearing mice were treated with anti-Asialo GM1. Here we characterize how Doxil treatment is able to improve both the tumor-free and tumor-bearing host immune system by expanding Natural Killer (NK) cell populations after 5 days from the time of drug administration. Moreover, NK cells isolated from Doxil-treated mice produce greater amounts of interferon (IFN)-γ compared to isolated NK cells from untreated mice, promoting selective Th-1 polarization of naïve CD4+ T cells. These immune modifications mediated by chemotherapy, ameliorates the capability of a DNA-vaccine to select and expand an antigen-specific CD8+ T cell population. This synergistic effect between chemotherapy and vaccination was completely mediated by NK cell expansion; in fact, the in vivo depletion of this cell subset totally abrogated the Doxil immune adjuvant activity. We combined Doxil with a DNA-vaccine encoding mouse telomerase reverse transcriptase (TERT). TERT is an attractive target antigen for cancer vaccine because its expression is reactivated in tumors of different histology such as ovarian cancer. We verified different vaccination schedules in ID8 ovarian tumor-bearing mice and only combinations that resulted in significant tumor growth inhibition were related to a specific anti-TERT CD8+ T cell response. This data demonstrates “Chemo-immune adjuvancy” of a conventional drug and highlights the importance to define the precise time window between treatments to improve their therapeutic synergism.
Target Wnt/β-catenin to de-transform tumor vasculature and block glioma progression

Menggui Huang, PhD and Yi Fan, MD PhD

Department of Radiation Oncology, University of Pennsylvania

Aberrant vascularization is a hallmark of cancer progression and treatment resistance. Newly formed tumor blood vessels deliver oxygen and nutrients and produce paracrine factors to tumor microenvironment, fueling tumor growth, progression and metastasis. Targeting endothelial cells (ECs) has emerged as a fundamental strategy for cancer treatment. However, inefficient eradication of tumor-associated ECs remains a major barrier for current anti-vascular therapy. Here, we show that ECs transformed to mesenchymal stem cell (MSC)-like cells, leading to EC chemoresistance in glioblastoma multiforme (GBM).

Our analysis with human patient-derived ECs showed that GBM-associated ECs are resistant to treatments with chemodrugs including temozolomide (TMZ), etoposide and doxorubicin. Likewise, utilizing EC lineage tracing in a genetic murine GBM model, we show that EC-originated cells exhibit robust resistance to temozolomide (TMZ) chemotherapy in vivo. Transcriptome analysis by deep sequencing revealed a global change in RNA expression of human brain ECs treated with glioma-conditioned medium, with over 25% of total detected genes altered. Interestingly, robust increases in the expression of mesenchymal genes including S100A4 (FSP-1) and ACTA2 (α-SMA), PDGFRs and stemness-associated genes including c-Kit, ANPEP (CD13) and THY1 (CD90) suggested transformation of ECs to MSC-like cells. The MSC-like features were validated by increased expression of MSC markers Stro-1 and Sca-1 and by enhanced Sox2 transcriptional activity in those treated ECs. Additionally, FSP-1 expression correlated with EC chemoresistance to TMZ, suggesting a role of this transformation for chemoresistance in tumor ECs.

Furthermore, bioinformatic analysis of whole transcriptome expression revealed potential Wnt/LEF1 transcriptional activity. In vitro studies showed that HGF induced β-catenin nuclei translocation and stimulated LEF1 transcriptional activity. Pretreatment of ECs with HGF/c-Met inhibitor SU11274 abrogated glioma-CM-induced TMZ chemoresistance. These results suggest that HGF/c-Met activated Wnt signaling, leading to EC transformation to MSC-like cells and chemoresistance.

Finally, we tested the in vivo role of Wnt signaling in EC chemoresistance, using a genetic GBM mice model. Combined treatment with pharmacological Wnt inhibitor XAV939 and TMZ chemotherapy, but not XAV939 alone, dramatically extended mouse survival and abrogated GBM progression.

These findings illustrate a novel mechanism controlling therapy resistance in tumor-associated ECs, and suggest that de-transformation of ECs may provide an efficient strategy for anti-vascular and vessel normalization therapies in GBM, and possibly other malignant tumors.
Glioblastoma-derived circulating tumor cells are cancer stem cell-like cells

Tianrun Liu, Menggui Huang, Deeksha Saxena, Gary D. Kao*, Jay F. Dorsey*, and Yi Fan*

*co-senior author

Department of Radiation Oncology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA.

Circulating tumor cells (CTCs), tumor cells from a primary tumor that intravasate and enter circulation, play a fundamental role in cancer metastasis and recurrence. As a potential clinical biomarker, the detection of CTCs may correlate with poor prognosis, diminished treatment response, or rapid tumor recurrence in patients with glioblastoma (GBM); however, the biological functions of CTCs remain largely unknown. Here, we report that GBM-derived CTCs acquire a cancer stem cell (CSC)-like phenotype, likely contributing to GBM recurrence after treatment.

We developed two virus-based systems that genetically labeled CTCs and CSCs, using vectors that have the human telomerase (TERT) promoter and Sox2/ETn (a cancer stem cell marker) promoter to drive mCherry and GFP expression, respectively. Utilizing a transgenic mouse GBM model, we observed that TERT-mCherry-positive CTCs express Sox2/ETn-GFP. Moreover, immunofluorescence analysis showed that TERT-mCherry-positive CTCs robustly expressed CD133 and Olig2, two well-established markers of glioma CSCs. Finally, quantitative real time- (RT)-PCR consistently revealed robust expression of stemness-associated transcriptional factors including Sox2 and Oct4. Likewise, quantitative RT-PCR assay confirmed high expression of Sox2, Oct4, and Nanog in GBM patient-derived CTCs, compared with astrocytes and CTCs from early-stage lung cancer patients. These results together suggest that GBM-derived CTCs are CSC-like cells.

We have furthermore established a system to culture CTCs. Our in vitro data indicate that CTCs possess a robust ability to form neurospheres and are more resistant to radiation and temozolomide. To test the CTCs’ tumorigenic ability in vivo, these cells were subcutaneously injected into mice. Whole-body bioluminescence analysis indicated that cultured CTCs have a superior tumor-forming capability, compared with matched glioma cells.

Collectively, this study demonstrates that GBM-derived CTCs are CSC-like cells, and suggests that targeting CTCs may offer novel therapeutic opportunities for inhibiting GBM recurrence after treatment.
Role of IL-6 in macrophage-mediated glioma immunity

Qirui Wang PhD and Yi Fan MD PhD

Department of Radiation Oncology, University of Pennsylvania School of Medicine

Spatiotemporal regulation of tumor immunity remains largely unexplored. Here we identify a vascular niche that controls alternative M2 macrophage polarization in glioblastoma (GBM). We identify most of tumor-associated macrophage undergo M2 polarization in GBM. Our data shows that tumor-promoting M2-type macrophages are spatially proximate to endothelial cells (ECs) in human GBM, permissive for angiocrine-induced macrophage polarization. We identify ECs as a major source for interleukin (IL)-6 expression in GBM microenvironment. Furthermore, we reveal that colony stimulating factor-1 (CSF-1) and angiocrine IL-6 induce robust arginase-1 expression and macrophage M2 polarization, mediated through peroxisome proliferator-activated receptor (PPAR)-γ-dependent transcriptional activation of hypoxia-inducible factor (HIF)-2α. Finally, utilizing a genetic murine GBM model, we show that EC-specific knockout of IL-6 inhibits macrophage M2 polarization and improves survival in the GBM-bearing mice. These findings illustrate a vascular niche-dependent mechanism for macrophage polarization and cancer progression, and suggest that targeting endothelial IL-6 may offer a selective and efficient therapeutic strategy for GBM, and possibly other solid malignant tumors.
Toward Detection of Circulating Tumor Cells from Non-Small Cell Lung Cancer Patients: Validating a Digital PCR-Based Approach

Rodrigo Gier, Bruna Bittencourt, Deeksha Saxena, Louise Aguarin, Phillip Cheng, Charles B. Simone, Jay F. Dorsey, Gary D. Kao

Department of Radiation Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Abstract

Mutational analyses can help guide treatment selection for patients with non-small cell lung cancer (NSCLC), predicting, for example, the efficacy of EGFR inhibitors for patients with exon 19 deletions or the exon 21 mutation L858R. Fast and reliable detection of these genetic alterations via circulating tumor cells (CTCs) found in the peripheral blood could enable testing that avoids repeated invasive and costly surgery. Analyzing the small amounts of DNA available in rare CTCs is technically challenging, however, and whole genome amplification may introduce unwanted artifacts. Here, we report a new assay designed to incorporate targeted PCR pre-amplification of single viable CTCs before genotyping by chip-based digital PCR (dPCR). The assay was extensively validated in blinded spiked blood experiments, demonstrating complete sensitivity and specificity, as well as the ability to accurately detect variations in the molecular heterogeneity of small populations of less than ten cells. For example, in ten different mixed populations of wild-type and mutant cells, we detected a corresponding and significant difference in the presence of mutant alleles in each case. These results suggest that the power of dPCR to quantify specific DNA sequences with great speed and precision may be usefully harnessed to reliably detect either of these two druggable EGFR alterations in CTCs from NSCLC patients who could then benefit from appropriate targeted therapy. Additionally, a live-CTC dPCR assay could potentially be used to monitor tumor heterogeneity, providing special insight throughout the evolution of an individual patient’s disease, and perhaps complementing analyses of circulating tumor DNA.
“Genome-wide transcriptome analysis identifies a spliced isoform of *EIF2B5* which represses translation under hypoxic stress”

Lauren K Brady, Vladimir Popov, Hejia Wang, Caleb Radens, Milan Radovich, Amit Maity, Christina Ivan, Mircea Ivan, Yoseph Barash, Constantinos Koumenis

Hypoxia is a physiological stress which occurs naturally during development, but is also a major feature of the tumor microenvironment. The level of hypoxia in solid tumors is negatively correlated with response to therapy and overall survival for many cancers. Cellular adaptation to hypoxia is marked by widespread changes in expression of genes that mediate angiogenesis, metabolism and cell survival. Here, by performing RNaseq analysis of hypoxic and normoxic head and neck cancer cells and examining individual isoform levels, we identified mRNA splicing as a major component of the hypoxia-mediated gene expression program. We uncovered >1,000 changes in alternative splicing (AS), and observed a relative enrichment for three types of AS which occurred near the 3’ end of genes, including a significant increase in intron retention. Our data revealed that hypoxia-induced intron retention in the major translation initiation factor *EIF2B5*, creates a pre-termination codon and subsequent truncated 65kDa isoform of eIF2Bε. We provide evidence that 65kDa eIF2Bε acts in opposition to the full-length isoform to inhibit translation under stringent hypoxic conditions. Moreover, this retained intron is present in solid cancers and is overexpressed in head and neck cancer in a stage-dependent manner compared to normal tissues. These results underscore the importance of AS as a mechanism to fine-tune gene expression under hypoxia through regulation of stress-induced isoforms involved in cellular adaptation to hypoxia.
Identifying novel regulators of UPR by utilizing genome-scale CRISPR-Cas9 knockout screens

Nektaria M. Leli, Koumenis Lab

Development and growth of a tumor as well as its ability to metastasize involves a complex relationship with the tissue microenvironment. A proliferating tumor encounters several stress conditions from the microenvironment such as hypoxia, lack of nutrients and acidosis. To cope with these conditions, cancer cells have developed several elaborate cytoprotective mechanisms which provide them with distinct advantages to thrive. These mechanisms constitute a complex of homeostatic signaling pathways and are collectively known as the Integrated Stress Response (ISR). Thus, deciphering the signaling pathways which get activated in the tumor microenvironment has been paramount to develop new therapeutic strategies for treatment. The Unfolded Protein Response (UPR) in response to tumor microenvironment involves translational and transcriptional activation of regulated signaling pathways designed to relieve cellular stress and block cancer cell death. Central to that program is a master transcriptional regulator ATF4 which upregulates genes including CHOP which are central to the decision of conferring survival or apoptosis depending on the nature and duration of the stress. However, CHOP cannot alone explain the balance between survival and apoptosis following UPR activation.

As a result, a comprehensive analysis to determine critical regulators of UPR is of utmost importance. Using a functional CRISPR mediated genetic knockout screen, we wanted to determine novel regulators of UPR and furthermore we will investigate the mechanism by which the regulators control cellular fate following chronic ER stress. To address the abovementioned question we delivered a lentiviral genome-scale CRISPR-Cas9 knockout (GeCKO) library to Sq20B cells (human squamous head and neck carcinoma) and A375 (human melanoma) cells. The library is targeting 18,080 genes with 64,751 unique guide sequences and enables both negative and positive selection screening We used the GeCKO library to identify genes essential for triggering the UPR in response to thapsigargin and tunicamysin, known activators of the ER stress. Our highest-ranking candidates include Survivin, a well-studied molecule that acts as an inhibitor of apoptosis and is highly expressed in cancer cells and EIF-6 a translation factor whose overexpression increases motility and invasiveness of cancer cells. So far, our preliminary results indicate that loss of Survivin enhances sensitization of cells to ER stress. Our current goals focus on the utilization of functional screens to identify genes that confer to radioresistance.
Nelfinavir: the physiological mechanisms behind its therapeutic enhancement of radiation

Intae Lee¹, Pavlina Todorova², Clementina Mesaros³, Sergey A. Vinogradov⁴, Ian Blair³, Sandeep Burma², Fiona Simpkins⁵, Lilie Lin¹, Constantinos Koumenis¹, Alexander Lin¹, and Amit Maity¹

¹Department of Radiation Oncology, ³Department of Pharmacology, ⁴Department of Biochemistry & Biophysics, ⁵Department of Obstetrics/ Gynecology, University of Pennsylvania, Philadelphia, PA 19104-6069, USA; ²University of Texas Southwestern Medical Center, Dallas, TX95390, USA

Purpose: To further study nelfinavir (NFV), an HIV protease inhibitor, as a potential radiation sensitizer, we investigated the physiological effects of NFV in vivo, specifically its influence on tumor oxygenation and radiation response.

Experimental Design: HeLa human cervical tumor xenografts were grown in athymic nude mice. NFV (10 mg/kg) was administered via intravenous (IV) or oral gavage in single or multiple doses. To assess the levels of NFV accumulation in tumors we used a mass spectroscopy method. The effect of NFV on hypoxia was measured using two different methodologies, direct measurements of pO₂ with the OxyLite probe and phosphorescence pO₂ probes. We studied the effect of NFV on tumor hypertension by measuring changes in tumor interstitial fluid pressure (TIFP) by a wick-in-needle method.

Results: Using a mass spectroscopy method, we measured the levels of NFV in tumors after administration via IV or oral gavage. % ID (Injected Dose) of NFV per gram of tissue in tumors (n=3) was 2.52 ± 0.60 for IV and 0.65 ± 0.37 for oral gavage (daily administration for 3 days). We observed that detectable levels of NFV in tumors were accompanied by significant decreases of hypoxia. After three daily IV administrations of NFV, the pO2 levels increased from 14.2 mm Hg to 23.6 mm Hg (p < 0.01). Non-invasive phosphorescence pO₂ was measured up to 7 days post-treatment of NFV. Multiple (3 days or more) oral gavages of NFV significantly increased tumor pO₂ from day 3 to day 7 post-treatment (p < 0.05), but the levels became saturated after day 3 and the pO₂ levels became held constant.
NFV + RT significantly retarded tumor growth compared to RT alone in HeLa human cervical carcinoma xenografts and B16F10 murine melanoma tumors grown in mice (NFV alone had no effect compared with control). To investigate whether changes in hypoxia contributed to the increased efficacy of NFV + RT in retarding tumor regrowth, we assessed DNA damage by measuring 53BP1 foci counts per nucleus in cells taken from tumors removed from mice 15 minutes after in vivo irradiation. The prediction would be that improved oxygenation would lead to increased initial DNA damage following radiation. The average foci count per nucleus was significantly increased from 1.21 ± 0.14 (control) to 17.85 ± 1.35 for NFV + RT vs. RT (p < 0.001).

In order to understand how NFV might be decreasing tumor hypoxia, we examined the effects of the drug on tumor O2 consumption (QO2) in vitro using the Clark electrode method. We observed that NFV decreased tumor QO2 by 30-40% (p < 0.01). We also examined the effects of NFV on TIFP in vivo. NFV significantly reduced TIFP 7 days after the end of treatment (p=0.01) although it did not result in an immediate reduction of TIFP after treatment with NFV.

**Conclusion:** We observed a therapeutic concentration of NFV in tumors grown in mice after multiple oral doses. NFV decreased hypoxia within tumors, which may contribute to its radiosensitizing effect in vivo, as we were able to show increased DNA damage 15 minutes after radiation. The mechanism by which NFV reduces tumor hypoxia may include both a reduction in QO2 as well as decreased TIFP.
Tumor Interferon Signaling Regulates a Multigenic Resistance Program to Immune Checkpoint Blockade

Joseph Benci, Minn Lab

Blocking the PD1 pathway results in significant tumor responses but resistance is common. Prolonged interferon (IFN) signaling can orchestrate PDL1-dependent and PDL1-independent resistance to immune checkpoint blockade (ICB) and to combinations such as radiation plus anti-CTLA4. Persistent type II IFN signaling in tumors is sufficient to instigate a resistance-related epigenome and a program of interferon-stimulated genes and multiple T cell inhibitory receptor (TIR) ligands. Both type I and II IFNs maintain this multigenic program, and crippling tumor IFN signaling genetically or pharmacologically interferes with ligand availability, allows preferential expansion of distinct populations of PD1\textsuperscript{high}Eomes\textsuperscript{*} T cells despite high co-expression of multiple TIRs, and renders tumors that are resistant to multi-agent ICB responsive to ICB monotherapy.
The visible signal responsible for proton therapy dosimetry using bare optical fibers is not Čerenkov radiation

Arash Darafsheha, Reza Taleeb, Alireza Kassaee, and Jarod C. Finlay

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Proton beam dosimetry using bare plastic optical fibers has emerged as a simple approach to proton beam dosimetry. The source of the signal in this method has been attributed to Čerenkov radiation. The aim of this work was a phenomenological study of the nature of the visible light responsible for the signal in bare fiber optic dosimetry of proton therapy beams. Plastic fiber optic probes embedded in solid water phantoms were irradiated with proton beams of energies 100, 180, and 225 MeV produced by a proton therapy cyclotron. Luminescence spectroscopy was performed by a CCD-coupled spectrometer. The spectra were acquired at various depths in phantom to measure the percentage depth dose (PDD) for each beam energy. For comparison, the PDD curves were acquired using a standard multilayer ion chamber device. In order to further analyze the contribution of the Čerenkov radiation in the spectra, Monte Carlo simulation was performed using FLUKA Monte Carlo code to stochastically simulate radiation transport, ionizing radiation dose deposition, and optical emission of Čerenkov radiation. The measured depth doses using the bare fiber are in agreement with measurements performed by the multilayer ion chamber device, indicating the feasibility of using bare fiber probes for proton beam dosimetry. The spectroscopic study of proton-irradiated fibers showed a continuous spectrum with shape different from that of Čerenkov radiation. The Monte Carlo simulations confirmed that the amount of the generated Čerenkov light does not follow the radiation absorbed dose in a medium. We showed that the source of the optical signal responsible for the proton dose measurement using bare optical fibers is not Čerenkov radiation. It is intrinsic fluorescence of the plastic material of the fiber.

Figure 1: (a) Series of spectra obtained from the bare fiber irradiated with 100 MeV proton beams. A continuous spectrum with a peak at $\lambda \sim 410$ nm was observed. (b) Relative depth dose measurements by using the fiber compared with that measured with a multilayer ionization chamber for 100 MeV proton beam. (c) Comparison between a typical experimental spectrum from the PMMA fiber and theoretical spectra of Čerenkov radiation. Two theoretical spectra of Čerenkov radiation with different intensities are presented for comparison. (d) Simulation results for Čerenkov radiation and absorbed dose in the fiber as a function of depth in phantom for a proton beam of 100, 180, and 225 MeV energy, respectively. The maximum value of dose was normalized to 1 in all panels. The maximum value of Čerenkov signal was normalized to 1 for the 225 MeV case. Solid and dashed curves are dose and Čerenkov signal, respectively.
Proton therapy dosimetry by using intrinsic fluorescence of silica fibers

Arash Darafsheh, Alireza Kassaee, and Jarod C. Finlay

In this work we proposed a fiber dosimeter based on using a bare silica glass fiber. We performed optical spectroscopy and showed that the visible emission from the silica fiber can be used for proton beam dosimetry with minimal impact form the ionization quenching effect provided that spectral filtering is performed. The spectrum of the fiber shows two distinct peaks at 460 and 650 nm. The intensity of the peak at 650 nm correlates with the absorbed dose with minimal effect of ionization quenching whereas that of the 460 nm peak does not follow the absorbed dose and is affected by the quenching effect manifested as under-response to the radiation dose. In practice, a band pass filter and a photomultiplier tube or photodiode can be used as an alternative to the spectrometer. Our experimental results show that the Čerenkov radiation cannot be responsible for such phenomenon. The origin of the observed spectral peaks at 460 and 650 nm is connected to the oxygen-deficiency center (ODC) and non-bridging oxygen hole center (NBOHC) in the silica, respectively. The fact that the ratio of the signal peak intensities at 460 and 650 nm varies with depth suggest a dependency on the linear energy transfer (LET) of the beam and can be exploited for LET sensing. This phenomenon, however, requires further study.

Figure 1: (a-c) A set of spectra acquired from the fiber probe at various depths in phantom irradiated with 100, 180, and 225 MeV energy proton beams, respectively. Two distinct intensity peaks are observed at 460 and 650 nm wavelengths. (d-f) Depth dose plots measured from the fiber and a standard ion chamber array for 100, 180, and 225 MeV energy proton beams, respectively. Shaded area shows the spectral region over which the optical power was integrated. Only signal corresponding to the second peak, i.e. \( \lambda \sim 610-705 \) nm is proportional to the dose.
Proton Radiography Using Pencil Beam Scanning and a Novel, Low-Cost Range Telescope
Derek Dolney, Mark Macerato, Leland Muller, Godwin Mayers, David Weiss, Evan Meekins, Maura Kirk, Robert Lustig, Richard Maughan, Mitch Newcomer, Timothy Solberg, Robert Hollebeek

Aim: To develop a low-cost approach to proton radiography to reduce the beam range uncertainty of proton therapy.

Background: While proton beams can be designed to penetrate any given depth of water very precisely, there is uncertainty in the stopping power of proton beams penetrating a given patient. To improve the precision of proton therapy, we propose a methodology for direct measurement of the integral proton stopping power using a novel imaging detector. Our approach to proton radiography is novel in two respects: 1) our approach takes advantage of proton pencil beam scanning (PBS), and 2) our prototype radiography system is based on a novel, multilayer detector technology that the authors have developed specifically for the PBS-radiography application.

Methods: Proton PBS imaging fields were delivered using an IBA clinical proton therapy system. The position-sensitive monitor chambers in the IBA proton delivery nozzle provide the beam entrance position. We obtained a proton radiograph using a multi-layer Micromegas range telescope positioned downstream of an anatomical head phantom (Figure 1). The radiograph was used to correct the Hounsfield Unit to proton relative stopping power calibration (Figure 2).

Results: At high dose, we have measured spatial resolution as good as 20 μm with our PBS+Micromegas approach. At lower doses (2 cGy), spatial resolution is 300 μm. WET resolution is 0.02% RMS (60 μm out of 31 cm total WET).

Discussion: Looking forward to clinical use, we have explored the spatial resolution that can be realized in practice given the need to limit patient dose. Sub-millimeter resolution can be achieved with only 2 cGy additional dose to the patient per radiograph. Faster instrumentation and a lower minimum MU/spot threshold could lower the patient dose to 1 mGy per image, while still achieving sub-mm spatial resolution (see Table). WET resolution is determined to be 60 μm in homogeneous media, and so in heterogeneous media we expect that the spatial resolution limitation will be of order 1 mm, as imposed by range mixing. Table 1 demonstrates the clinical significance of 1-2 mm range uncertainty.

Conclusion: Proton radiography using PBS and Micromegas can deliver high spatial and WET resolution and thereby provide a high-resolution correction to the proton beam range per patient.

Figure 1: First proton radiograph (left) of an anatomical head phantom compared with DRR (right)

![Figure 1](image1)

Figure 2: Difference between measured and Monte-Carlo determined range through the head phantom in Figure 1 for 14,641 spot positions using Penn clinical HU to proton stopping power calibration (red) and a derived, phantom-specific calibration.

![Figure 2](image2)

<table>
<thead>
<tr>
<th>Range Uncertainty</th>
<th>5 mm</th>
<th>2 mm</th>
<th>1 mm</th>
</tr>
</thead>
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<tr>
<td>TCP</td>
<td>68%</td>
<td>72%</td>
<td>80%</td>
</tr>
<tr>
<td>Brainstem NTCP</td>
<td>6%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Table 1: Potential improvement in mean tumor control probability for skull base chordomas given reduced beam range uncertainty. Probabilities were assessed by replanning 12 patients.
Comparison of Dosimetric Robustness between Proton Therapy and IMRT Plans Following Tumor Regression for Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

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Purpose: In the light of tumor regression and normal tissue changes, dose distributions can deviate undesirably from what was planned. As a consequence, replanning is sometimes necessary during treatment to ensure continued tumor coverage or to avoid overdosing organs at risk (OARs). Proton plans are generally thought to be less robust than photon plans because of the proton beam’s higher sensitivity to changes in tissue composition, suggesting also a higher likely replanning rate due to tumor regression. The purpose of this study is to compare dosimetric deviations between forward-calculated double scattering (DS) proton plans with IMRT plans upon tumor regression, and assesses their impact on clinical replanning decisions.

Methods: Ten consecutive locally advanced NSCLC patients whose tumors shrank > 50% in volume and who received four or more CT scans during radiotherapy were analyzed. All the patients received proton radiotherapy (6660 cGy, 180 cGy/fx). Dosimetric robustness during therapy was characterized by changes in the planning objective metrics as well as by point-by-point root-mean-squared differences for the entire PTV, ITV, and OARs (heart, cord, esophagus, brachial plexus and lungs) DVHs.

Results: Sixty-four pairs of DVHs were reviewed by three clinicians, who requested a replanning rate of 16.7% and 18.6% for DS and IMRT plans, respectively, with a high agreement between providers. Robustness of clinical indicators was found to depend on the beam orientation and dose level on the DVH curve. Proton dose increased most in OARs distal to the PTV along the beam path, but these changes were primarily in the mid to low dose levels. In contrast, the variation in IMRT plans occurred primarily in the high dose region.

Conclusions: Robustness of clinical indicators depends where on the DVH curves comparisons are made. Similar replanning rates were observed for DS and IMRT plans upon large tumor regression.
Innovation/Impact: This innovative method allows comprehensive plan robustness analysis following tumor regression.

Dosimetric deviation is computed as the root-mean-squared-distance (RMSD) between planning CT and evaluation CTs. Values shown in the table and the figure below are the differences in RMSD between DS and IMRT plans. Positive numbers are color coded in red, indicating more change in DS than in IMRT plans. Negative numbers are color coded in blue, indicating less change in DS than in IMRT plans.

Table 1: Differences in Dosimetric Deviation between DS and IMRT Plans at the Metrics of Planning Objectives

<table>
<thead>
<tr>
<th>Case ID</th>
<th>PTV_6660</th>
<th>CORD</th>
<th>CORD_5MM</th>
<th>ESOPHAGUS</th>
<th>ESOPHAGUS</th>
<th>HEART</th>
<th>HEART</th>
<th>BRACHIALP</th>
<th>BRACHIALPL</th>
<th>LUNG_TOT</th>
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<td>0.08</td>
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<td>0.22</td>
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<td>1.08</td>
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</table>

mean   -0.25  1.54  2.33  0.01  1.09  1.09  1.17*  -0.02  0.33  0.54*  1.49*  1.53*  
signrank_p 0.19335938 0.375 0.27539063 0.43164063 0.07421875 0.19335938 0.00585938 1 1 0.0019531 0.00585938 0.00195313

IMRT is more robust  
DS is more robust

Figure 1: Population Average of the Difference in DVH Deviations between DS and IMRT Plans
MediBoost: a Patient Stratification Tool for Interpretable Decision Making

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** Department of Radiation Oncology, University of California San Francisco
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Abstract

In disciplines such as medicine, where errors can have a serious consequence, machine learning algorithms have provided valuable contributions in medical diagnosis. However, there is currently a tradeoff between accuracy and interpretability among state-of-the-art methods. The use of decision trees for stratifying patients has become extensive throughout medicine. Unfortunately, decision trees are consistently outperformed in accuracy by other less interpretable machine learning models such as, ensemble methods. We introduce MediBoost, a novel framework for constructing decision trees that retain interpretability while having accuracy similar to ensemble methods. By comparing the performance of our framework to that of conventional decision trees, we found that Mediboost significantly outperformed current decision tree algorithms in 11 out of 13 medical problems, giving accuracy comparable to ensemble methods. The 13 medical problems used for comparison consist of a variety of datasets associated to acute inflammation of the bladder, nephritis, arrhythmia, breast cancer, diabetic retinopathy, fertility, hepatitis, mammographic mass, Parkinson’s disease, Pima people diabetes, heart disease, cardiac SPECT and thoracic surgery. Thus, the main advantage of Mediboost decision trees for clinical practice is their improved accuracy. Therefore, our algorithm gives the best of both worlds: it grows a single, highly interpretable tree that has the high accuracy of ensemble methods.