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ABSTRACTS

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GA101- Immunomodulatory Photoacoustic Nanoparticle-engineered Macrophages for Solid Cancer Immunotherapy and Longitudinal Monitoring

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Category: Oncology

Abstract Body:
Background: Reinforcing antitumor functions of macrophages, phagocytosis of cancer cells and secretion of inflammatory cytokines, can be a potent approach to treat solid tumors. Several strategies including CAR-macrophages and phagocytosis-enhanced macrophages (engineered via anti-CD47 antibody treatment) have been recently reported and have shown promise in preclinical models [1, 2]. However, these approaches lack mechanisms for monitoring transferred macrophages and assessing their therapeutic efficacy against tumors, limiting the ability to implement longitudinal therapeutic interventions throughout the treatment. Integrating imaging and contrast agents offers a possibility for real-time and non-invasive tracking of macrophages within the tumor microenvironment. Specifically, labeling macrophages with imaging contrast agents allows for longitudinal visualization of their migration, infiltration, and persistence in tumors, which could serve as an indicator of therapeutic response. Photoacoustic (PA) imaging is a technique that combines ultrasound and optical imaging by leveraging the light-to-sound conversion under laser irradiation of optical absorbers with high-intensity nanosecond laser pulses. PA imaging offers a powerful tool for real-time and noninvasive tracking of adoptively transferred cells. Here, we propose a macrophage engineering strategy for PA image-guided cancer immunotherapy. A nanoparticle formulation with both PA contrast and immunomodulatory effects is synthesized. Macrophages labeled with the formulated nanoparticles demonstrated strong antitumoral phenotypes and allowed longitudinal PA imaging. Our work provides perspectives on engineering macrophages for image-guided cancer immunotherapy.
Methods: Macrophages were derived from murine bone marrow cells. Bone marrow cells were extracted from the femur and the tibia from 5 - 8 weeks old mice. The cells were cultured with 20 ng/mL M-CSF for differentiation into macrophages. The hyperbranched gold nanoconstructs (HBGNCs) were synthesized via surface-blocker assisted seeded growth. Briefly, the surface of 35 nm-sized gold nanospheres was partially blocked during the seeded growth to yield the hyperbranched structure with a construct dimension of 100 nm.
For PA imaging, macrophages were labeled with HBGNCs. Afterwards, cells were washed with PBS and collected. The cell solution was embedded in gelatin phantom. The phantom was submerged in water and imaged under Vevo2100/LAZR imaging system.
The effect of particle labeling on key cellular functions, such as viability, migration, and antitumoral functions (CD80, CD87, MHCII, and CD206 expression), was investigated by confocal microscopy and flow cytometry.
Results: Photostable HBGNCs with high optical absorption efficiency, ~90% in the near-infrared I (NIR I) region, were synthesized. The enhanced optical absorption was attributed to the hyper-branched structure. Due to the enhanced optical responses at NIR I region, the HBGNCs produced robust photoacoustic (PA) responses at corresponding wavelengths, offering high sensitivity in PA imaging. When macrophages were labeled with HBGNCs, the size and the granularity of the cells increased as the particles were internalized. The labeling did not affect the viability of the cells. HBGNC-labeled macrophages embedded in tissue-mimicking phantoms yielded high PA signal.
The migration ability of the labeled macrophages was evaluated. Compared to IFNg-primed macrophages that are known to migrate at a high rate, macrophages labeled with either HBGNCs or HBGNC-Gs displayed a superior migration ability.
The phenotype of macrophages became more strongly anti-tumoral when labeled with IFNg-conjugated HBGNCs (HBGNC-Gs) compared to HBGNC and IFNg alone. This was supported by the increased expression of costimulatory receptors CD80 and CD86, MHCII, and the decreased expression of pro-tumoral marker CD206.
Conclusion: In the current study, a new strategy of macrophage engineering for cancer immunotherapy was introduced. Labeling macrophages with HBGNC-Gs have enabled PA imaging of macrophages and, at the same time, enhanced their migration ability and antitumoral phenotype. Results suggest that HBGNC labeling approach can provide insights into developing strategies for macrophage-based cancer immunotherapy.
Disclosures: The authors have no conflicts of interest to disclose.
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Disclosures: The authors have no conflicts of interest to disclose.
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Poster Presentation

GA160- Development and Implementation of Physics-Informed Segresnetunet for Brain Tumor Segmentation Using BRATS2020 Dataset

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Category: Computational & Data Science

Abstract Body:
Background: Accurate brain tumor segmentation is crucial for effective diagnosis and treatment planning in brain cancer cases. Traditional segmentation methods often fall short in capturing the complex nature of tumors. This study presents the Physics-InformedResNetUNet model, a deep learning framework that integrates a physics-informed layer simulating realistic tumor growth dynamics into U-Net's segmentation capabilities and ResNet's residual learning. The physics-informed component models thectumor growth using simplified diffusion equations, reflecting how tumors evolve spatially over time, thereby enhancing the network's understanding of tumor morphology.
Methods: Data Preprocessing: For model training, the Physics-Informed ResNetUNet model, preprocessing steps include: Normalization (scaling pixel values to 0–1 for consistency), resizing (standardizing image dimensions to match model input).
Data Augmentation: Techniques like random cropping, flipping, intensity normalization, and random intensity adjustments have been applied to increase data diversity and improve model robustness.
Model Architecture (Physics-Informed ResNetUNet): encoder (uses ResNet-based residual blocks for feature extraction), bottleneck (a deeper residual block captures complex features), decoder (3D transpose convolutions upsample and reconstructfeature maps), dropout (mitigates overfitting). The architecture is illustrated in figure 1.
Physics-Informed Layers: simulates tumor growth using an anisotropic diffusion equation, factoring in oxygen levels and necrosis.
Training Process: this includes batch processing, Dice loss calculation, and gradient updates. Physics-informed inputs simulate tumor growth to guide segmentation predictions.
Validation: Evaluated post-epoch with Dice scores for different tumor regions (core, whole tumor, enhancing tumor), and the best model was saved based on their performance. Key metrics tracked were learning rate adjustments, training and validation loss, and Dice scores according tumor region.
Results: Over the last five epochs, the Physics-Informed ResNetUNet achieved the following scores: Mean Dice of 0.6975, TC Dice of 0.6763, WT Dice of 0.7180, ET Dice of 0.6983, and a training loss of 0.3420 with an average time of 52.44 seconds per epoch. In comparison, SegResNet recorded a Mean Dice of 0.4150, TC Dice of 0.6608, WT Dice of 0.5689, ET Dice of 0.0154, and a training loss of 0.8876 with an average time of 81.53 seconds per epoch. Finally, U-Net achieved Mean Dice of 0.0511, TC Dice of0.0197, WT Dice of 0.1133, ET Dice of 0.0204, and a training loss of 0.9418 with an average time of 41.36 seconds per epoch. Table 1 shows the performance of ResNetUNet and SegResNet in comparison with traditional UNet. Figure 2 shows the performance of the model on training and testing dataset showing the segmented tumor region.
Conclusion: The results demonstrate that the Physics-Informed ResNetUNet outperformed both SegResNet and U-Net in segmentation accuracy, particularly for the Whole Tumor and Enhancing Tumor regions. The incorporation of tumor growth dynamics as an additional layer allows the model to better reflect the physical processes underlying tumor development, leading to a more reliable and precise tool for clinical applications in brain tumor segmentation.
Disclosures: The authors have no conflicts of interest to disclose.
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Poster Presentation

GA161- Physics-informed UNETR: A Brain Tumor Segmentation Combining UNETR Architecture and Physics Constraints Using Brats2021 Dataset and Insights for Molecular Imaging

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Category: Computational & Data Science

Abstract Body:
Background: This Physics-Informed UNETR model incorporates both learned features from MRI scans and the physical constraints of tumor dynamics, offering a more holistic and accurate segmentation. By integrating reaction-diffusion equations, which govern tumor expansion, the model aims to provide more accurate segmentation results, especially in complex cases with irregular tumor boundaries. The problem, therefore, lies in how to effectively combine state-of-the-art deep learning techniques with well-established biological models to improve the accuracy and reliability of brain tumor segmentation. This study seeks to address this gap by developing a novel approach that leverages both

data and physics, providing a more informed and robust solution to the brain tumor segmentation problem. The physics models incorporated could allow us gain molecular insights into brain tumors especially cell metastatic processes via diffusion and cell transport.

Methods: The primary dataset used for this study is the BraTS 2021 dataset. For data processing, normalization (MRI intensity values are normalized to a standard range to ensure consistency across images) and resampling (images are resampled to a uniform voxel size of 128×128×128 to standardize the input dimensions and facilitate effective training) were done. UNETR with Physics integrates the UNETR model with a reaction-diffusion mechanism for enhanced tumor segmentation. Once the model is instantiated, the training begins with the configuration of the optimizer, loss function, and the learning rate scheduler. By carefully choosing these configurations and incorporating the reaction-diffusion model, the model effectively learns to segment brain tumors while taking into account the physical growth dynamics of the tumor. The modified model was then implemented for real-time image segmentation.

Results: Key performance metrics included Dice scores for Tumor Core (dice_tc), Whole Tumor (dice_wt), and Enhancing Tumor (dice_et), as well as the average Dice score, training loss, and training/validation times. The model achieved a dice_tc of 0.7035, dice_wt of 0.7813, dice_et of 0.7764, and an average Dice score of 0.7538 (implemented as shown in figure 1). The final training loss was 0.3870, with an average training time of 859.87 seconds per epoch, and a final validation time of 793.93 seconds (as illustrated in figures 2). The physics-informed UNETR demonstrated improved segmentation accuracy compared with standard UNETR. Specifically, the proposed model achieves a dice coefficient of 77%, a 4% improvement over the baseline UNETR (73%); improvements are also observed in precision, recall, and F1-score as shown in Table 1. Visual inspection of the segmentation results confirms that the physics-informed UNETR better captured tumor boundaries, particularly in complex cases where traditional methods struggle. This has been demonstrated in figure 1.

Conclusion: These results show that the Physics-Informed UNETR model outperforms the U-Net in brain tumor segmentation, particularly in Whole Tumor and Enhancing Tumor areas. The addition of tumor growth dynamics improves the model's accuracy and reliability, making it a valuable tool for clinical applications in brain tumor diagnosis. Furthermore, molecular-based tumor spread could be predicted with this model. This implies the model could be used for predicted the spread of metastatic cells through molecular diffusion and cell transport.

Disclosures: The authors have no conflicts of interest to disclose.

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Poster Presentation

GA166- Molecular Imaging-Guided Evaluation of Indazole-Based Immunotherapy Targeting Tumor-Associated Macrophages

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Category: Oncology

Abstract Body:

Background: Immunological modulation of the tumor microenvironment has recently emerged as a critical paradigm in anticancer drug development. Extensive research is being conducted on immune checkpoint inhibitors and immune enhancers, alongside growing interest in cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs). In this study, we explored the potential of reprogramming intratumoral TAMs for application as a form of immunotherapy. Previous studies have demonstrated that various indazole-based small molecules, including Sulfanilamidoindazole (SAI), can induce inflammatory responses in macrophages. Based on these findings, we investigated whether SAI and its derivatives could serve as effective immuno-oncology therapeutics.

Methods: Indazole compounds and derivatives were produced by combining sugars, and were evaluated using molecular imaging techniques to confirm whether they could modulate immunity and control tumors intracellularly and extracellularly

Results: We first confirmed through in vitro experiments that treatment with SAI and its derivatives effectively polarized macrophages toward the M1 phenotype. Notably, this polarization was observed not only in RAW264.7 cells but also in THP-1 macrophages, showing a response comparable to lipopolysaccharide (LPS) treatment. Similarly, a tendency toward M1 polarization was observed in both TAMs treated in vitro with SAI and its derivatives, which were isolated from 4T1 tumors, and in TAMs analyzed from tumors isolated from mice after oral administration of SAI or its derivatives. Additionally, pharmacokinetic studies and in vivo distribution studies of the drug were studied using DESI imaging to use this agent as an immunotherapy anticancer agent, and it was observed that cancer could be specifically targeted using the lipid based formulation.

In vivo molecular imaging demonstrated approximately 30% tumor growth inhibition following treatment with SAI and its derivatives. Furthermore, flow cytometry (FACS) analysis of the treated tumor models revealed immunological alterations in the tumor microenvironment. While the levels of regulatory T cells (Tregs) remained unchanged, notable increases were observed in NKT cells, $CD8^+$ T cell ratios, and IFN-γ expression.

Conclusion: This study effectively demonstrated the immunotherapeutic potential of SAI and its derivatives using molecular imaging and other analytical approaches. Our findings suggest that such molecular imaging strategies may be effectively leveraged in the development and evaluation of novel anticancer therapies

Disclosures: The authors have no conflicts of interest to disclose.

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