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ABSTRACTS

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GA16- Development and Evaluation of D-Fluoroalanine and D-Fluoroalanine-d3 as PET Imaging Agents for Bacterial Infection

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Category: Infection
Abstract Body: Novel positron emission tomography (PET) imaging agents are needed to detect and diagnose deep-seated bacterial infections.[1] D-amino acids, which are selectively taken up by bacteria, are attractive targets for radiotracer development.[2] This has resulted in the synthesis and evaluation of several ^{11}C-labeled D-amino acids including D-Met,[3] D-Ala,[4] and D-Gln.[5] Given that D-alanine is an essential component of bacterial peptidoglycan, and in order to expand the studies to ^{18}F tracers which have a longer half-life than ^{11}C, D-FAla and D-FAla-d_3 were synthesized and evaluated in a soft-tissue infection model, laying the groundwork for the wider application of ^{18}F-labeled D-amino acids for bacterial imaging.
D-FAla and D-FAla-d_3 were synthesized using cyclic D-sulfamidate precursors involving a 2-step radiofluorination followed by acidic deprotection. Uptake experiments were performed with both Gram-negative (*Escherichia coli*) and Gram-positive (*Staphylococcus aureus*) bacteria, and a *S. aureus* Xen29 rat soft-tissue infection model was utilized for *in vivo* PET imaging. *In vivo* bioluminescent imaging was used to monitor the bacterial infection starting from the 2nd day post inoculation. Once a robust infection had developed, 90-min dynamic PET imaging was used to analyze the biodistribution of D-FAla (n=4) and D-FAla-d_3 (n=4), while the *ex vivo* biodistribution was evaluated at the conclusion of the PET imaging. Heat killed bacteria were used to generate an inflammatory response in the contralateral triceps to compare and contrast with radiotracer accumulation in the infected triceps. D-FAla and D-FAla-d_3 were prepared with radiochemical yields (decay corrected) of 19–21% and radiochemical purities of >98%. For D-FAla and D-FAla-d_3, the uptake in heat-killed *E. coli* was reduced to 2%−4% of the uptake in live *E. coli*, while the uptake in heat-killed *S. aureus* was decreased to 31–41% of that observed in live bacteria. The uptake of both tracers in bacteria was dose-dependently blocked by D-alanine. *In vivo* PET imaging was initiated when a strong bioluminescent signal was detected in the infected (right) triceps which *ex vivo* analysis of the tissue showed was due to ~10^7 colony-forming units (CFU)/ml of *S. aureus* Xen29. Based on the PET data, the uptake in the infected triceps at 15 min post injection of D-FAla and D-FAla-d_3 was 0.78 ± 0.07 %ID/cc and 0.64 ± 0.03 %ID/cc, respectively, which was ~2-fold higher than the uptake at the site of sterile inflammation.
The PET imaging data demonstrated that both D-FAla and D-FAla-d_3 can detect and localize bacterial infection. Subsequent studies will involve the evaluation of the radiotracers in models of prosthetic joint infection and endocarditis, and extending the studies to fungal infections. The future studies will support the clinical translation of D-FAla and D-FAla-d_3 for the management of infection.
Disclosures: The authors have no conflicts of interest to disclose.
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1) Polvoy, I.; Flavell, R. R.; Rosenberg, O. S.; Ohliger, M. A.; Wilson, D. M., Nuclear Imaging of Bacterial Infection: The State of the Art and Future Directions. J Nucl Med 2020, 61 (12), 1708–1716.
2) Miyamoto, T.; Homma, H., D-Amino acid metabolism in bacteria. J Biochem 2021, 170 (1), 5–13.

The results showed the highest LE% of 86.33 with 500 µg $SnCl_2$, 20 mg of tricine, and 5 mCi of ^{99m}Tc. ^{99m}Tc-HYNIC-FGF2 was purified with size exclusion chromatography to achieve 100% of LE.

In vitro binding assays on human keratinocytes expressing FGFR2c, showed that our radiopharmaceutical is able to bind to the specific receptor within minutes and demonstrating slow dissociation from the cells (Kd 3.36 x 10^{-9} M).

In vivo dynamic imaging showed rapid accumulation in lungs, liver and spleen in the first 10 min, followed by uptake in implanted tumors. Ex-vivo evaluation of radioactivity in tumors showed a tumor/blood ratio of %ID/g at 3h = 4.1 and at 24h = 26.1.

In conclusion, the high LE% and the high affinity of radiolabeled ^{99m}Tc-FGF2 to its receptor, confirmed the validity of these new radiopharmaceutical for imaging TAF.

Currently, there is no option to evaluate in vivo the abundance and expression of FGFR2c and this could be achieved by using the radiopharmaceutical developed in the present project.

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

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1) Ranieri D., et al., Cell Commun Signal. 2020, 18, 76.
2) Beenken A., et al., Nat Rev Drug Discov. 2009, 8, 235-53.
3) Bentivoglio V., et al., Biomolecules 2024, 14, 491.

Poster Presentation

LB176- Synthesis of Radiolabeled Poly(lactic-co-glycolic acid) (PLGA) Nanoparticles for Nano-Theranostic Use: In Vitro and Pre-clinical experiments

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Category: Oncology

Abstract Body: Poly(lactic-co-glycolic acid) (PLGA) is FDA and EMA-approved synthetic polymer for human use due to its high biocompatibility and easy biodegradability. PLGA-based nano-formulations are currently available for several types of cancer treatments as tumor-targeted drug delivery systems.

We focused our research on the validation of a new nano-radiopharmaceutical based on the use of PLGA nanoparticles (PLGA-NPs) loaded with high amounts of radioactive isotopes. In preliminary studies, pharmacokinetics of fluorescent PLGA-NPs was determined in vivo at 2, 6, 24, 48, 72, 96, 168 and 240h, by optical imaging with a Kodak FX station (Figure 1). At the end of acquisition, animals were sacrificed, and organs collected for ex-vivo imaging. Regions of interest (ROIs) were drawn to calculate target-to-background ratios. Tumor targeting studies were performed in a syngeneic mouse model obtained by subcutaneous injection in the right thigh of 106 J774a.1 cells (reticulum sarcoma cell line) in Matrigel: Medium (50:50).

^{99m}Tc-PLGA-NPs were synthetized and radiolabeled in our laboratory with an innovative microfluidic technique, which allows for high quality NPs in terms of size, encapsulation efficiency (EE%) and batch-to-batch reproducibility. Eighteen different formulations were tested and characterized for particle size, zeta potential, polydispersity index, labelling efficiency, and in vitro stability. From these analyses, the two best formulations were selected and analyzed in BALB/c mice for biodistribution studies. After each time point (1, 6, 24h) three mice per group were sacrificed and major organs collected and counted in a single-well γ-counter. The percentage of injected dose per organ (%ID) and percentage of injected dose per gram (%ID/g) were calculated.

In vivo pharmacokinetic studies of fluorescent PLGA-NPs showed maximum tumor uptake at 72h post injection, with a high tumor to background ratio.

Physical characterization of native and radiolabeled NPs showed an increase in particle size after radiolabeling probably due to the incorporation of the isotope into the PLGA-NPs shell. ITLC results showed a high encapsulation efficiency for all batches analyzed, ranging from 73 to 99%. ^{99m}Tc-PLGA-NPs of 60 and 100nm showed a difference in biodistribution, with different uptake from RES tissues.

In conclusion, the innovative microfluidic technique allows to synthetize and encapsulate the isotope inside NPs with high reproducibility in terms of size, charge, PDI and encapsulation efficiency. The research sets the stage for the development of a new theragnostic radiopharmaceutical based on PLGA-NPs to detect and treat aggressive and undifferentiated tumors.

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

References:

1) Varani M. et al., J Clin Med. 2020, 9, 1750.
2) Varani M. et al., Pharmaceutics. 2021, 13, 1769.

Poster Presentation

LB179- Development of Physics-Informed Neural for Computational Magnetic Resonance Imaging of Noradrenergic Neurons

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Category: Computational & Data Science

Abstract Body: Recently, magnetic resonance imaging (MRI) method has been applied to a transgenic model of Alzheimer's disease demonstrating its potential use in neuroradiology . Since a decline in locus coeruleus (LC) neuron numbers is associated with aging, dementia, Aβ plaque load, and the progression of Alzheimer's disease, MRI of Noradrenergic (NA) neurons has been proposed to play an increasing role in translational biomedical research of neurodegenerative diseases. MRI methods are currently being explored for testing whether NA imaging is related to disease progression in neurodegenerative diseases. Characterization of the relationship between MRI measures and neuropathology would be crucial in this direction. This study proposes a characterization method using MR relaxometry and physics-informed neural network. T_1 and T_2 relaxation times have been known to be fundamental diagnostic feature in MRI assessment. Since noradrenergic neurons have abundant water protons interacting with paramagnetic ions in active cells and molecules, the spin dynamics must be consistent with the Bloch NMR flow equation. Under transient condition, the Bloch NMR flow equation is given as eqn (1). Subject to eqn (2), an analytical solution to eqn (1) is given in eqn (3). This equation has been used to generate training and testing data for a NetChain model using Wolfram Mathematica programming. In the traditional neural network, a simple net class with net function that takes 4 arguments (1 input, 1 outputs, 100 hidden neurons per layer, and 4 layers). The final model was then implemented and tested with relaxometric data presented in table 1. Other parameters used are: $C1 = C2 = -0.01$, $M0 = 50A/m$, $\omega = 28Hz$.

Physics-informed neural networks (PINNs), also referred to as Theory-Trained Neural Networks, are a type of universal function approximators that can embed the knowledge of any physical laws that govern a given data-set in the learning process, and can be described by differential equations. The structure and training process for the PINN model developed in this study are shown in figure 1. Using the relaxometric data in table 1, the PINN model has been implemented as a graphic user interface with comparison to results from exact solutions.

As shown in figure 2, the PINN model did not perform badly even on unseen data (figure 2B-2D). The model was able to mimic the MR signal profile but slightly underestimates the transverse magnetization values. Figure 2A was perfect because the parameters for this figure were used to train the original PINN model. However, the models (exact and PINN) were able to show contrasts between A2 and LC cell groups. A finetuned version of this model can open opportunities for robust computational molecular imaging of noradrenergic neurons. With a PINN-based simulator, assessing the decline in LC neuron numbers as often seen in aging and dementia may become much easier. This will also make rooms for repetitive studies on translational biomedical research of neurodegenerative diseases. It is important to note that this model may be modified slightly for use in computational magnetic resonance spectroscopy of noradrenergic neurons.

With hyperparameter tuning, the PINN model can be improved upon so they could perform much better on any set of T_1 and T_2 pair. Specifying a range of values for the relaxation times could also help in overcoming this challenge. It is noteworthy that the model is easily interpretable.

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

Figure LB179-01:

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Poster Presentation

LB186- High Throughput Macrophages Respond to the Glioma Immune Microenvironment to Identify White Matter Micro-Infiltrates

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Category: Neuroscience