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Design of Theranostic Radiopharmaceuticals For Enhanced Drug Delivery

KARAZIN UNIVERSITY
CLASSICS AHEAD OF TIME

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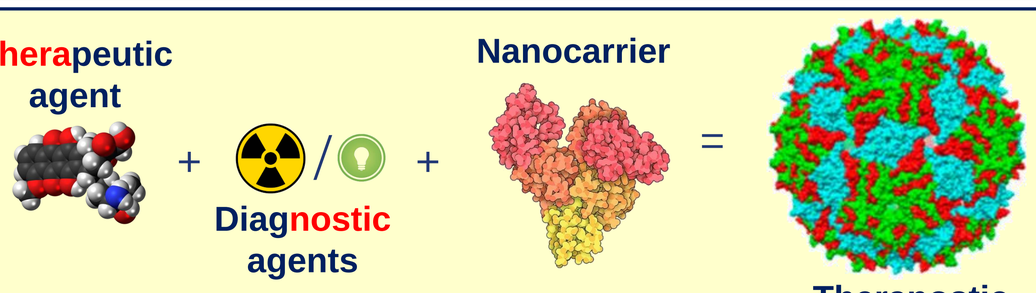
BACKGROUND

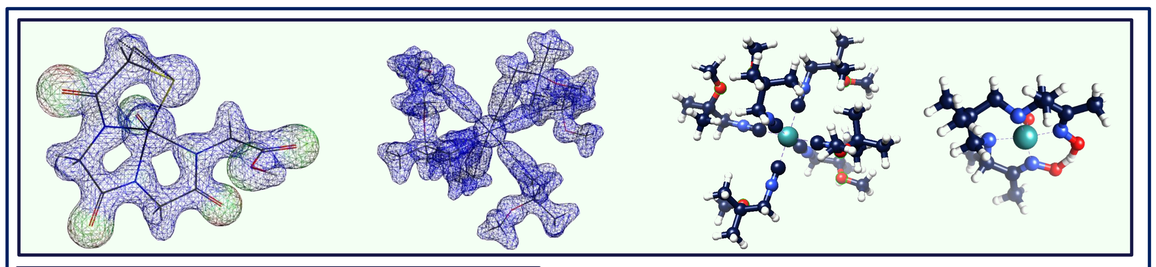
- The field of **nuclear medicine** is undergoing rapid advancements, driven by the need for more precise and effective diagnostic and therapeutic tools.
- **Targeted radiopharmaceuticals** have become a cornerstone strategy in oncology, significantly improving both diagnostic accuracy and therapeutic efficacy.
- **Technetium-99m (99m-Tc)** has emerged as one of the most widely used radionuclides in medical imaging due to its **ideal nuclear properties**, such as its short half-life, which minimizes radiation exposure while providing high-quality imaging.
- Recent breakthroughs in nuclear medicine have focused on the development of **theranostic radiopharmaceuticals**, a novel class of compounds that integrate both **therapeutic** and **imaging** capabilities within a single molecular framework.
- **Theranostic radiopharmaceuticals** are expected to play a crucial role in the future of nuclear medicine, providing more **effective**, **safer**, and **patient-specific** solutions for diagnosing and treating complex diseases such as cancer.

THERANOSTIC PLATFORMS

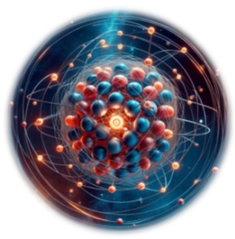


Design of protein-based delivery platforms for Tc RPhs with multimodal imaging modalities

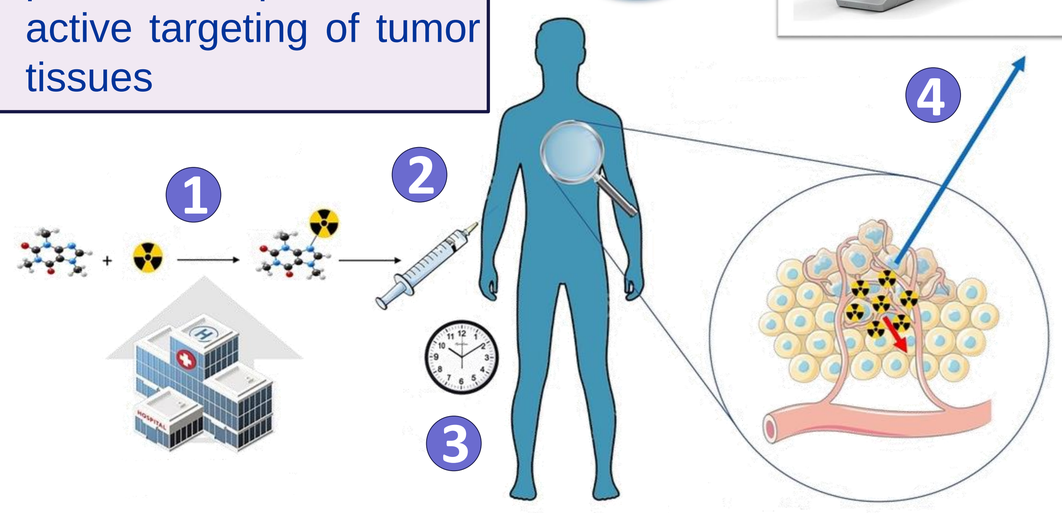
TECHNETIUM RPhs



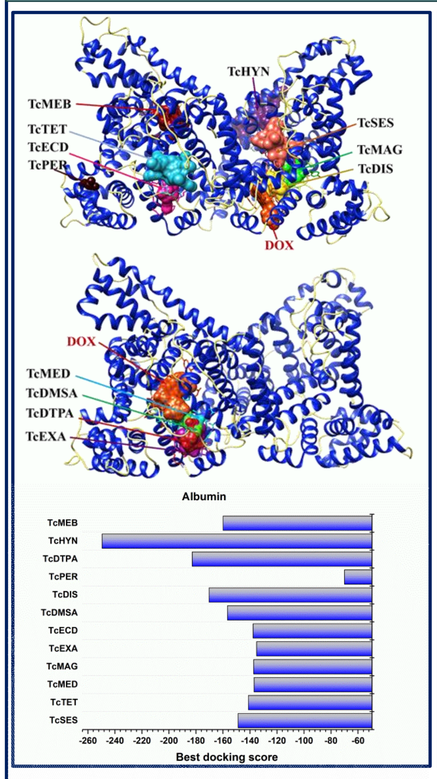
- ✓ prolonged circulation time
- ✓ enhanced permeability and retention effect
- ✓ potential for passive and active targeting of tumor tissues



PET/CT scan



RESULTS



Molecular docking studies revealed that most Tc RPhs bind to domain I of HSA, specifically in the region between LEU115 and LYS190. This common binding site suggests a potential competitive binding scenario among these Tc RPhs, which could impact their pharmacokinetics when administered together. Interestingly, TcHYN, which contains a specific peptide sequence, demonstrated the highest affinity for HSA and bound to domain III, partially overlapping with Sudlow site II. This finding highlights the potential of peptide conjugation as a strategy to enhance the albumin-binding properties of radiopharmaceuticals, potentially improving their in vivo stability and target tissue accumulation.

TCC	HSA-TCC interface residues	Types of interactions
TcSES	TYR_{150A*}, GLU_{153A}, PHE_{156A}, PHE_{157A}, ARG_{160A}, GLU_{188A}, ALA_{191A}, SER_{192A}, LYS_{195A}, GLN_{196A}, LYS_{199A}, ARG_{218A}, ARG_{222A}, HSD_{288A}, GLU_{292A}	Hydrophobic interactions, hydrogen bonds
TcTET	ASN_{109B}, ARG_{114B}, LEU_{115B}, ARG_{145B}, LYS_{190B}, GLU_{425B}, ARG_{428B}, GLU_{520B}, ILE_{523B}	Hydrophobic interactions, hydrogen bonds
TcMED	LEU_{115A}, ARG_{117A}, TYR_{138A}, ILE_{142A}, HSD_{146A}, PHE_{149A}, LEU_{154A}, PHE_{157A}, TYR_{161A}, LEU_{182A}, ASP_{183A}, LEU_{185A}, ARG_{186A}, ASP_{187A}, GLY_{189A}	Hydrogen bonds
TcMAG	ASP_{107A}, ASP_{108A}, ASN_{109A}, ARG_{145A}, HSD_{146A}, PRO_{147A}, TYR_{148A}, LYS_{190A}, ALA_{191A}, SER_{193A}, ALA_{194A}, ARG_{197A}, GLU_{425A}, ASN_{458A}, GLN_{459A}	Hydrogen bonds, salt bridges
TcEXA	LEU_{115A}, VAL_{116A}, ARG_{117A}, PRO_{118A}, MET_{123A}, PHE_{134A}, LYS_{137A}, TYR_{138A}, LEU_{139A}, GLU_{141A}, ILE_{142A}, ARG_{145A}, TYR_{161A}, PHE_{165A}, LEU_{182A}	Hydrophobic interactions, hydrogen bonds
TcECD	LEU_{115B}, ARG_{117B}, PRO_{118B}, MET_{123B}, PHE_{134B}, LYS_{137B}, TYR_{138B}, GLU_{141B}, ILE_{142B}, TYR_{161B}	Hydrophobic interactions, hydrogen bonds, salt bridges
TcDMSA	LEU_{115A}, VAL_{116A}, ARG_{117A}, PRO_{118A}, MET_{123A}, TYR_{138A}, ILE_{142A}, HSD_{146A}, PHE_{149A}, LEU_{154A}, PHE_{157A}, TYR_{161A}, LEU_{182A}, LEU_{185A}, ARG_{186A}	Hydrogen bonds, salt bridges
TcDIS	ASN_{109A}, PRO_{110A}, LEU_{112A}, ARG_{114A}, LEU_{115A}, ARG_{145A}, HSD_{146A}, ARG_{186A}, LYS_{190A}, PRO_{421A}	Hydrophobic interactions, hydrogen bonds
TcPER	TYR_{30B}, HSD_{67B}, THR_{68B}, PHE_{70B}, GLY_{71B}, LEU_{74B}, GLU_{95B}, ARG_{98B}, ASN_{99B}, PHE_{102B}	Hydrogen bonds
TcDTPA	LEU_{115A}, VAL_{116A}, ARG_{117A}, PRO_{118A}, MET_{123A}, PHE_{134A}, LEU_{135A}, LYS_{137A}, TYR_{138A}, GLU_{141A}, ILE_{142A}, TYR_{161A}	Hydrogen bonds, salt bridges
TcHYN	GLU_{383A}, LEU_{387A}, ASN_{391A}, LEU_{394A}, LEU_{407A}, VAL_{409A}, ARG_{410A}, TYR_{411A}, LEU_{430A}, LEU_{453A}, GLU_{492A}, SER_{489A}	Hydrogen bonds, π-stacking, salt bridges
TcMEB	GLU_{188B}, LYS_{195B}, TRP_{214B}, ARG_{218B}, GLN_{221B}, ARG_{222B}, GLU_{292B}, VAL_{293B}, GLU_{294B}, ASN_{295B}, LYS_{436B}, HSD_{440B}, LYS_{444B}, PRO_{447B}, CYS_{448B}, ALA_{449B}, ASP_{451B}, TYR_{452B}	Hydrophobic interactions, hydrogen bonds, salt bridges

CONCLUSIONS

The results showed that when the binding sites for Tc RPhs and DOX do not overlap, DOX binds to a specific region in domain I of HSA. However, when Tc RPhs and DOX binding sites overlap, DOX binds to an alternative site containing residues from ASP107 to GLN459. The results of the study demonstrate the suitability of albumin as a nanocarrier for DOX with radionuclide imaging capabilities. The findings provide valuable insights into the interactions between HSA, various ^{99m}Tc radiopharmaceuticals, and DOX, which can guide the development of more effective radiopharmaceutical delivery systems. These advancements have the potential to enhance both diagnostic accuracy and therapeutic efficacy in nuclear medicine applications, ultimately improving patient care and treatment outcomes.