Molecular Imaging of Cancer

Jonathan McConathy, M.D., Ph.D.
Assistant Professor of Radiology
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mcconathyj@mir.wustl.edu
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Outline

• Overview of molecular imaging in oncology

• Considerations for radiotracer development

• Examples of radiotracers targeting amino acid transporters for oncologic imaging
Hallmarks of Cancer

Sustaining proliferative signaling
Evading growth suppressors
Deregulating cellular energetics
Avoiding immune destruction
Resisting cell death
Enabling replicative immortality
Genome instability & mutation
Tumor-promoting inflammation
Inducing angiogenesis
Activating invasion & metastasis

Examples of PET Tracers in Human Oncologic Imaging Studies at Washington University

- $[^{18}\text{F}]\text{FDG}$
- $[^{11}\text{C}]\text{Choline}$
- $[^{18}\text{F}]\text{FDOPA}$
- $^{15}\text{O}-\text{PET}$ for aerobic glycolysis
- $[^{64}\text{Cu}]\text{ATSM}$
- $^{18}\text{F}$-labeled PARP-1 tracer
- $[^{89}\text{Zr}]\text{HER2-PET}$
- $[^{89}\text{Zr}]\text{trastuzumab}$

Clinical goals of oncologic imaging

- Diagnosis
- Staging
- Therapy planning
- Monitoring response to therapy
- Detection of recurrent disease

FDG-PET in lymphoma

Translational radiopharmaceutical development should focus on true unmet research and clinical needs

http://sweetclipart.com/multisite/sweetclipart/files/hammer_nail_outline.png
Examples of research goals using molecular oncologic imaging

- Biodistribution and pharmacokinetics of drugs
- Measurement of target engagement
- Patient selection for clinical trials
- Surrogate endpoints for clinical trials

- Many molecular imaging agents may be very useful for human research but will not be developed as clinical diagnostic agents

- Molecular agents used in clinical trials of therapeutics may be used as companion diagnostics
Key steps in PET tracer development in the United States for human research and clinical use

- Preclinical tracer development
- Clinical trials
- Routine clinical use
- eIND/IND
- NDA approval by FDA
- Coverage by CMS and insurers, clinical acceptance
The primary barrier to first in human studies for most PET imaging agents is financial (toxicity and manufacturing data)

- most PET agents do not have significant toxicity at tracers doses
- exploratory Investigation New Drug (eIND) application allows microdosing toxicity and can also allow multiple related tracers to be investigated
Key issues for translating novel molecular imaging agents

• Preparing and identifying the best lead compound
  – preclinical evaluation

• Competing molecular imaging agents
  – direct comparison can be challenging

• Competing modalities (e.g. CT and MRI)
  – preclinical comparison often not feasible

• Toxicity and other safety data for first-in-human studies is expensive
  – traditional funding is often not available

• Acceptance by referring physicians
Tracer development considerations

- Half-life of radionuclide is long enough for clinical use and appropriate for biological application
- Simple, high yield radiosynthesis
- Identification of the optimal compound for translation
- Acceptable metabolic stability
- Adequate selectivity for target
- High target to background ratio
- Adapt to unexpected results
Biological transporters are involved in the mechanisms of action for many agents used for oncologic imaging and therapy.

- $[^{18}\text{F}]$FDG
- Sodium $[^{123/124/131}\text{I}]$iodide
- $[^{123/131}\text{I}]$MIBG
- $[^{11}\text{C}]$choline and $^{18}\text{F}$-labeled derivatives
- $[^{11}\text{C}]$acetate
- $[^{18}\text{F}]$FLT and other nucleoside analogues
- Radiolabeled amino acids

Transporters can amplify signal.
Evolution of radiolabeled amino acids

Pancreatic imaging with $^{75}$Se selenomethionine (Blau and Bender, 1962)

Initial discovery of imaging properties of radiolabeled amino acids

$^{11}$C-methionine in an astrocytoma (Ogawa et al, 1996)

Radiohalogenated amino acids ($^{18}$F, $^{123}$I)

$^{18}$F-FDOPA-PET/MRI in a high grade glioma

anti-$^{18}$F-FACBC in recurrent prostate cancer (Schuster, 2007)
Selected amino acid transporter systems targeted with radiolabeled amino acids

- FDOPA
- MeAIB
- MeFAMP
- AFETP
- FACBC
- 5-FASu
- FET
- MET
- 4-FGln
- 4-FPGlu

Extracellular

- L
- A
- CAT
- ASC
- Xc^-

AA

AA Na^+

Intracellular amino acid pool

mTOR signaling

4-FGln
4-FPGlu

Glutathione metabolism
• Session 1: New Radiofluorination. Synthesis of L-4-[\(^{18}\text{F}\)]fluorotryptophan starting from isotopic exchange. Ermert, Johannes (Forschungszentrum Jülich, Germany)

• Session 2: New Radiolabeling Chemistry
• for Radiotracers. Stereoselective synthesis of L-[4-\(^{11}\text{C}\)]-asparagine via a cyclic sulfoamidate precursor. Xu, Youwen (Brookhaven National Laboratory, USA)

• Session 6: Radiopharmacology/Radiopharmacy. Development of PET Tracers Targeting ASCT2 for Cancer Imaging. Schulte, Michael (Vanderbilt University, USA)

• Session 7: Wiley Award Presentations: Evaluation of novel carbon-11 labeled tissue transglutaminase inhibitors. van der Wildt, Berend (VU University Medical Center, The Netherlands)
Mechanism of transport affects amino acid uptake in mouse DBT tumors and normal brain.

Decreasing transport by system L.
Clinical applications of radiolabeled amino acids

Brain tumors

- **MET**
  - \( \text{H}_2\text{N} \xrightarrow{\text{CO}_2\text{H}} \text{S}^{11}\text{CH}_3 \)
  - [\(^{18}\text{F}\)]FACBC for prostate cancer
  - Schuster et al, 2007

- **FET**
  - \( \text{H}_2\text{N} \xrightarrow{\text{CO}_2\text{H}} \text{O}^{18}\text{F} \)
  - [\(^{18}\text{F}\)]FDOPA for neuroendocrine tumors
  - Pauleit et al, 2009

- **FDOPA**
  - \( \text{H}_2\text{N} \xrightarrow{\text{CO}_2\text{H}} \text{OH}^{18}\text{F} \)
  - Haug et al, 2009
Radionuclides with longer half-lives generally give higher patient dose.

Longer-radionuclides are more amenable to batch synthesis and remote distribution.

\[^{18}\text{F}\]FDOPA-PET/MRI in optic pathway gliomas.
High yield radiosyntheses: cyclic sulfamidate precursors for selective system A transport substrates

60-80% yield, ~90 min total production time


High yield radiosyntheses: click reaction for lead compounds for cationic amino acid transport

Boc-\(\text{NH-CO}_2\text{tBu}\)  \(\text{N}_3\) \(^1\text{H}_2\text{N-CO}_2\text{H}\)  
\(\text{N}_3\) \(\text{N}^2\text{N}\)  \(\text{N}_3\) 
\(\text{N}_3\) \(\text{N}^2\text{N}\)  \(\text{N}_3\) 

Solid phase reaction, room temperature click reaction

50-60\% yield, ~60 min total production time

**Amino acid transport: System L**

**System L** (leucine preferring, large neutral AAs like Leu, Phe, Tyr)
- Established utility in tumor imaging, LAT1 over-expressed in many tumors
- Not directly concentrative = lower tumor to normal tissue ratios
- Active at the normal blood brain barrier (BBB)

Extracellular compartment

LAT1 (SLC7A5): exchange, heterodimer
LAT2 (SLC7A8): exchange, heterodimer
LAT3 (SLC43A1): facilitated
LAT4 (SLC43A2): facilitated

Intracellular amino acid pool
High LAT1 levels are associated with decreased overall survival in many human cancers.

**Stage I non-small cell lung cancer**

- LAT1 negative (n = 137)
- LAT1 positive (n = 104)

**Prostate cancer**

- Pathologic T3 + T4 stage

**Glioblastoma**

- Grade IV astrocytoma
  - Low LAT1 (n=35)
  - High LAT1 (n=14)

**Gastric carcinomas**

- Stage IB or II

**Triple negative breast cancer**

- LAT1+/CD98+ (n=21)
- Others (n=29)

**Mesothelioma**

- LAT1-negative (n=11)
- LAT1-positive (n=10)
Substrate-based vs. immunoPET for system L
Substrate-based vs. immunoPET for system L

Extracellular compartment

Amino acid

Intracellular compartment

LAT1
CD98hc

LAT2
CD98hc

LAT3

LAT4
Substrate-based vs. immunoPET for system L

Amino acid

Extracellular compartment

CD98hc

LAT1

Intracellular compartment

H₂N-\text{CO}_2\text{H}

LAT2

LAT3

LAT4

\text{H}_2\text{N}-\text{CO}_2\text{H}^{18}\text{F}
Substrate-based vs. immunoPET for system L

Extracellular compartment

CD98hc
LAT1

CD98hc
LAT2

LAT3

LAT4

Intracellular compartment

$^{89}\text{Zr}$
Substrate-based vs. immunoPET for system L

- LAT3
- LAT2
- CD98hc

- LAT1
- CD98hc

- Extracellular compartment
- Intracellular compartment

$^{89}$Zr
$^{89}$Zr-Ab2 demonstrates high and specific uptake in HCT-116 colorectal cancer xenografts.

Ikotun, O. F. et al., 2013. Imaging the L-type amino acid transporter-1 (LAT1) with Zr-89 immunoPET, PloS one. 8: e77476.
anti-3-[^{18}F]FACBC

- Non-natural amino acid analogue of the C-11 amino acid, 1-aminocyclobutane-1-[^{11}C]carboxylic acid

Advantages of non-natural amino acids
- often metabolically stable
- can label with longer lived radionuclides (F-18, I-123)
- structural modifications can facilitate labeling and targeting of specific transporters
[\textsuperscript{18}F]FACBC-PET/CT detection of local recurrence in the prostate bed.

Slides courtesy of David Schuster MD, Emory University.
[\textsuperscript{18}F]FACBC detection of lymph node metastasis in recurrent prostate cancer

Alternative MI agents:
- $[\textsuperscript{11}C]$choline and fluorinated analogues
- $[\textsuperscript{11}C]$acetate
- Small molecule PSMA ligands

Slides courtesy of David Schuster MD, Emory University
Radiation necrosis: a diagnostic dilemma in neuro-oncology

Patient 1
T1 post Gd contrast
fusion
FDG-PET

Patient 2

Patient 3
Clinically relevant applications: (R)-MeFAMP for distinguishing radiation necrosis from viable tumor

BrVAIB facilitates delayed imaging of DBT brain tumors due to the 16 hour half-life of $^{76}\text{Br}$

BrVAIB-PET/CT, 1 hour after injection

$\text{H}_2\text{N}-\text{CO}_2\text{H}$

$^{76}\text{Br}$

(S)-$[^{76}\text{Br}]\text{BrVAIB}$

3 hours after injection

24 hours after injection

Burkemper et al, manuscript in preparation
Clinically relevant applications: FDOPA-PET/MRI to monitor response to bevacizumab in recurrent pediatric brain tumors

- FDOPA-PET and MRI performed simultaneously on a Siemens mMR system
- No sedation used
- No DOPA decarboxylase inhibitors administered
- Dynamic PET scan from time of injection to 45-60 min after injection

Collaboration with Josh Rubin MD, PhD, Karen Gauvain MD, and Amy Barone MD
Change in FDOPA-PET metabolic tumor volume (MTV) at 2 weeks after initiation of bevacizumab predicts overall survival (OS)

Example 1

- 9 yo with right-sided small cell astrocytoma
  - Good initial response to radiation+ TMZ
  - Continued on TMZ+CCNU
8 year old with recurrent small cell glioma

33% decrease in MTV (1.5 tumor/brain threshold)

Tumor challenging to measure on MRI

Increasing left-sided weakness and left visual field loss after 2nd maintenance cycle
Example 2

- 10 year old boy with recurrent pilocytic astrocytoma involving the optic chiasm
  - debulked 2 years ago followed by carboplatin and vincristine and then lenalidomide
  - low vision status with slow progression based on MRI led to treatment with bevacizumab and irinotecan
10 year old with recurrent pilocytic astrocytoma

No residual tumor above 1.5 ratio

4 weeks bevacizumab

stable to slight interval increase in tumor size on MRI 2 months after FDOPA-PET/MRI
Conclusion

- Translational radiopharmaceutical research has great potential but faces significant challenges.

- Development of novel MI agents should begin with real clinical issues and the end user in mind.

- Radiolabeled amino acids are a promising class of oncologic imaging agents for a variety of applications.
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