Imaging for Target Engagement in Oncology

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Disclosures (None relevant to lecture)

• Patents: unrelated to lecture content
  • MR-US fusion biopsy system
  • Computer aided diagnosis
  • Photoimmunotherapy
  • Various devices for measuring radioactivity
  • Method to measure GFR with Gadolinium chelates

• Cooperative Research Agreements:
  • Philips, Aspyrian, General Electric, Scan Med
Imaging for Target Engagement in Oncology

• Past mistakes and lessons learned (Antibodies)
• Current use of molecular imaging (FDG)
• Leading edge developments (Small Molecules)
• Opportunities and Challenges
• Kidney as a target for molecular imaging
Molecular Imaging PET Agent Anatomy

- Beacon
- Carrier or Bifunctional binder
- Targeting Moiety
Chelating agent
In-Trastuzumab AntiHER2 imaging Breast cancer

A problem of Target to Background
Lessons Learned

• High affinity is not enough
• Target to background ratio is critical (TBR)
• TBR is determined by
  – High affinity
  – Fast clearance
• Affects diagnostic imaging
• Affects therapeutic targeted therapy
Tumors use aerobic glycolysis: Warburg Physiology

Warburg

2-deoxyfluoroglucose: FDG

Fatty Acid Synthesis

Amino Acid Metabolism
PET/CT Fusion Imaging

Metastatic Breast Cancer
FDG: Transformational

Robotic GMP Synthesis

PET/CT Equipment

Delivery and Distribution

PET/CT Equipment

Image Courtesy of Philips
New Oncologic PET Probes Entering Practice

PET tagged somatostatin receptor ligands for neuroendocrine tumors

PET tagged PSMA binding ligands for prostate cancers

Hallmarks:
High sensitivity and specificity for cancer
Revealing completely new aspects of natural history
Fibroblast activating protein (FAPI) PET

AdenoCa Lung-
Size of Probe

(a) scFv, Diabody, Minibody, scFv-Fc, Intact

VH, VL

CH1, CH2, CH3

Ck

\( \sim 5\text{nm} \)

(b) Tumor uptake and Blood activity

ID/g (%) vs. Time (h)

Intact Ab

(Wu AM, Nature Biotech. 2005)
New Small Molecule Platforms

Knottin

Antibody

ADAPT

DARPin

Affibody

sdAb / Nanobody

FN3 / Adnectin

Molecular Imaging: Opportunities in the field

Small Molecule Platforms

The Surfaceome-targets

Novel Molecular Imaging Agents

Animal Models and Organoids

Expanded use of EM Spectrum
A few words about MI of the kidney

• Challenge: Most small molecules are excreted thru the kidney so TBR will be a problem.
  • By tweaking PK, one can get small molecules to be hepatically excreted.

• Challenge: Kidney is a high blood flow, dynamic organ, subject to changes in hydration, cardiovascular status etc.
  • Careful control of imaging conditions will be necessary

• Huge opportunities for developing MI for the kidney:
  • Need to solve an important and actionable problem
  • Good cell surface or interstitial targets (high abundance, accessible target)
  • Modify excretory route
Conclusions

• Molecular Imaging in Oncology is poised to make dramatic gains in the next decade
  • Rewrite the natural history of many cancers
  • and lead to earlier interventions

• The major breakthrough is in small molecule chemistry where
  • High affinity ligands with high clearance rates lead to high TBR
  • New platform technologies exist to further this effort

• Huge opportunities in Nephrology
  • Need to find viable targets with meaningful endpoints
  • Same strategy of small molecules but tweak the excretory route
How to Screen All These People?

*Imaging or Blood-Urine testing?*
Which is more practical?
Radiolabeled Antibodies

- Very high affinity (nM) even after labeling
- >30 approved human monoclonal Abs
- But...
  - Slow clearance
  - Delayed Imaging

Examples: Breast Zr-89
Zr-89 Trastuzumab

Right internal iliac (3 mm) and presacral (5 mm) lymph nodes – SUVmax 12.2 and 45.3

Status post prostatectomy (Gleason 9)
Rising PSA = 0.39 ng/mL

✓ 18F-DCFPyL PET imaging was able to detect positive findings at range of low PSA values ( < 0.5 ng/mL)

Ravi Madan
James Gulley
GUMB

Right internal iliac (3 mm) and presacral (5 mm) lymph nodes – SUVmax 12.2 and 45.3