PET/CT Imaging of Angiogenesis

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Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is essential for tumor growth and progression.

Inhibition of angiogenesis has been shown to prevent tumor growth and even to cause tumor regression in various experimental models.

The ability to non-invasively visualize and quantify $\alpha_v\beta_3$ integrin expression levels may provide new opportunities to document tumor integrin levels; more appropriately select patients for treatment; and monitor treatment efficacy in integrin-positive lesions.
Due to the higher sensitivity of PET (10^{-11}-10^{-12} M) compared with other imaging modalities, the development of probes for PET imaging of integrin expression has been the focus of many research projects.

Because arginine-glycine-aspartic acid (RGD) peptides strongly bind to integrin \( \alpha_v\beta_3 \), many of the probes developed for imaging of integrin expression are based on this RGD peptide sequence.

These compounds exhibit high \( \alpha_v\beta_3 \) affinity \textit{in vitro} and receptor specific tumor uptake \textit{in vivo}. 
a) Dormant

b) Perivascular detachment and vessel dilation

c) Onset of angiogenic sprouting

d) Continuous sprouting; new vessel formation and maturation; recruitment of perivascular cells

e) Tumour vasculature

18F-RGD K5

18F-AH111585 (18F-Fluciclatide)

18F-FPPRGD2

18F-AIF-NOTA-PRGD2 (18F-Alfatide)
Noninvasive Visualization of the Activated αvβ3 Integrin in Cancer Patients by Positron Emission Tomography and [18F]Galacto-RGD


- 18F Galacto-RGD can safely be administered to patients and is able to delineate certain tumors that are integrin positive.

- 18F Galacto-RGD PET standard uptake value (SUV) analysis is likely related to tumor vessel density (CD31 staining).

- The tumor expression of αvβ3 integrins and glucose metabolism are not closely linked in malignant lesions.
a) Patient with malignant melanoma stage IV and multiple metastases in liver, skin, and lower abdomen (arrows): marked uptake of $^{18}$F FDG in the lesions (left), but no uptake of $^{18}$F Galacto-RGD (right).

b) Patient with malignant melanoma stage IIIb and a solitary lymph node metastasis in the right axilla (arrow): intense uptake of both $^{18}$F FDG (left) and $^{18}$F Galacto-RGD (right).

Phase I Trial of the Positron-Emitting Arg-Gly-Asp (RGD) Peptide Radioligand $^{18}$F-AH111585 in Breast Cancer Patients

- $^{18}$F-AH111585 is stable and can detect integrin positive primary and metastatic breast tumors
- $^{18}$F-AH111585 is only minimally metabolized in vivo in humans, and activity is rapidly cleared from blood
- Other than in the liver, the tissue-binding kinetics of $^{18}$F-AH111585 in tumors, compared with normal tissues, are consistent with high-affinity receptor interaction
$^{18}$F-AH111585 PET of metastatic lesions and corresponding CT images showing increased signal in periphery of lesions in patient with lung and pleural metastases (a), intrallesion heterogeneity of uptake within pleural metastasis in PET image, which was not demonstrated as necrosis on corresponding CT section (b), and liver metastases imaged as hypointense lesions because of high background signal (c). High uptake in spleen is possibly due to blood pooling.

Successive whole-body PET/CT scans were obtained after intravenous injection of $^{18}$F RGD K5 in 3 rhesus monkeys and 4 healthy humans.

$^{18}$F-RGD K5 is stable and the biodistribution in monkeys and humans was similar, with increased uptake in the bladder, liver, and kidneys.

There was rapid clearance of $^{18}$F-RGD-K5 through the renal system.

Both whole-body effective dose and bladder dose can be reduced by more frequent voiding.
Decay corrected MIP images from a healthy female volunteer after $^{18}$F RGD K5 administration
9 patients with a primary diagnosis of lung cancer were examined by both static and dynamic PET imaging with $^{18}$F-alfatide, and 1 tuberculosis patient was investigated using both $^{18}$F-alfatide and $^{18}$F-FDG PET.

$^{18}$F-Alfatide is stable and identified all tumors, with mean standardized uptake values of 2.90 ± 0.10.

Tumor-to-muscle and tumor-to-blood ratios were 5.87 ± 2.02 and 2.71 ± 0.92, respectively.
Lung cancer patient imaged after $^{18}$F Alfatide administration
Inhibition of $^{125}$I-echistatin binding to $\alpha_v\beta_3$ integrin on U87MG cells by $^{19}$F-galacto-RGD and $^{19}$F-FPPRGD$_2$. These data show that FPPRGD$_2$ has higher binding affinity that galacto-RGD.

Small-animal PET images of U87MG tumor-bearing mice. Decay-corrected whole-body coronal images at 30 min, 1 h, and 2 h after injection of about 3.7 MBq of $^{18}$F galacto-RGD or $^{18}$F FPPRGD$_2$ demonstrate more intense accumulation of $^{18}$F FPPRGD$_2$ than $^{18}$F galacto-RGD in the tumor (arrows).

Data courtesy of Dr Chen
Temporal Variability

A

0 hr 0.5 hr 1 hr 2 hr 3 hr

Time after injection, Subject 2

Courtesy of Erik Mittra, MD, PhD
Inter-Subject Variability

Subject Number, 1 hr post-injection

Courtesy of Erik Mittra, MD, PhD

MIPS
Molecular Imaging Program at Stanford

Stanford University
School of Medicine
Department of Radiology
Materials and Methods

- Prospective phase I study enrolled 15 GBM and 4 NSCLC patients

- 5 GBM and 2 NSCLC patients had {\textsuperscript{18}}F FPPRGD\textsubscript{2} PET/CT scans done before and at 1 week after starting bevacizumab

- Uptake in lesions and normal background was semiquantitatively assessed at 45-60 minutes after the i.v. radiopharmaceutical administration
$^{18}$F FPPRGD$_2$ Pre-Therapy Uptake (GBM)
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- Lesion: 2.58
- Cerebellum: 0.17
- Resection Cavity: 0.58
- Liver: 2.53
- Muscle: 0.53
- Aortic Arch: 1.15
Pre-Therapy Uptake (GBM)

- SUVmax FDG (pre):
  - Mean: 11.07
  - Range: 2.50

- SUVmax FPPRGD2 (pre):
  - Range: 2.50
Pre-Therapy Uptake (GBM)

FPPRGD2 at 45' (n=5) | FDG at 60' (n=4)

Lesion | Background

0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100%
18F FPRGD2 Pre-Therapy Uptake (NSCLC)

- Lung lesions
- Pleural lesions
- Lymph nodes
- Other
- Benign nodules
- Aortic arch
- Liver

Time points: 15 min, 30 min, 45 min, 60 min, 120 min
Pre-Therapy Uptake (NSCLC)

Lung lesions (FDG pre) 14.28
Lung lesions (FPRGD2 pre) 6.53
Metastases (FDG pre) 12.60
Metastases (FPRGD2 pre) 3.57
$^{18}\text{F FPPRGD}_2$ Post-Therapy Uptake (NSCLC)
76 year-old woman with right lung NSCLC, treated with carboplatin, pemetrexed and bevacizumab, scanned before starting bevacizumab and 1-week after starting bevacizumab
Materials and methods

✓ Prospective study (Dec 2010 – Jan 2011) of 8 women with newly diagnosed/recurrent breast cancer

✓ The patients were 44-67 year-old (average: 53.7 ± 9.3)

✓ $^{18}$F FPPRGD$_2$ and $^{18}$F FDG PET/CT scans were sequentially performed within a 2 weeks interval for each patient

✓ A direct comparison for each detected lesion was performed among the scans
$^{18}\text{F} \text{ FPPRGD}_2$ Uptake (Breast Cancer)

- Breast lesions
- LN metastases
- Other metastases
- Benign lesions
- Aortic arch
- Liver

Time:
- 15 min
- 30 min
- 45 min
- 60 min
- 120 min
$^{18}$F FPPRGD$_2$ Uptake (Breast Cancer)

- Breast lesions: 4.78
- LN metastases: 3.18
- Other metastases: 3.04
- Benign lesions: 1.26
- Liver: 2.45
- Aortic arch: 1.13
Conclusions

- $^{18}$F FPPRGD$_2$ has stable kinetics for imaging $\alpha_v\beta_3$ integrin expression as a biomarker for angiogenesis at multiple time points.

- Early assessment of response to anti-angiogenesis treatment is feasible and shows encouraging results in patients with GBM.

- $^{18}$F FPPRGD$_2$ may not offer advantages over $^{18}$F FDG in NSCLC.
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