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# Clinical Molecular Imaging of Cancer: Why, When and How?

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## Personalized Medicine – Targeted Therapy



www.brandnovator.com



www.nature.com




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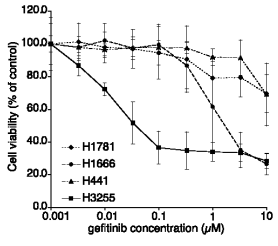
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## Targeted therapy of cancer

### Epidermal growth factor receptor (EGFR) mutations increase the sensitivity of lung cancer cells to gefitinib

Gefitinib (μM)	H441			H3255		
	0	0.1	10.0	0	0.1	10.0
p-EGFR						
EGFR						
p-ERK 1/2						
ERK 1/2						
p-AKT						
AKT						
	>10.0			.04		
	WT			L858R		



Cell viability (% of control)

gefitinib concentration (μM)

Legend: H1781 (diamonds), H1666 (squares), H441 (triangles), H3255 (circles)

Paez et al. Science (2004) 304:1497-1450, Figure 1, edited

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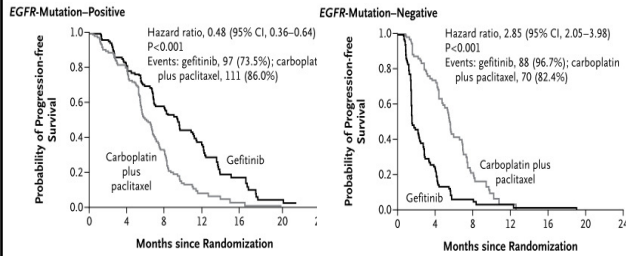
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## Treatment of lung cancer patients with the EGFR kinase inhibitor gefitinib



Mok et al. N Engl J Med (2009) 361:947-957, Figure 2 edited

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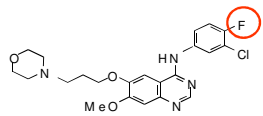
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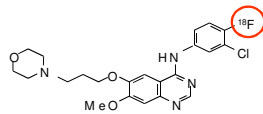
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## Gefitinib can be radiolabeled with fluorine-18 without changing its chemical properties

Gefitinib



[<sup>18</sup>F]Gefitinib



Seimbille et al. J Labelled Compd Radiopharm. 2005;48:819–27  
 Su et al. Eur J Nucl Med Mol Imaging, 2008 ;35:1089-1099.

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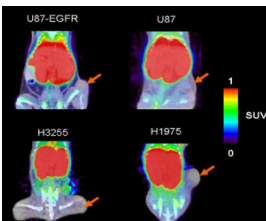
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## Distribution of [<sup>18</sup>F]gefitinib in tumor bearing mice



Tumor xenografts	BP <sub>T</sub> (two-compartment model)
H3255 <sup>a</sup>	1.14 ± 0.03
H1975 <sup>a</sup>	0.29 ± 0.02
U87 <sup>b</sup>	0.73
U87-EGFR <sup>b</sup>	0.69

Su et al. Eur J Nucl Med Mol Imaging, 2008 ;35:1089-1099, Figure 5, Table 2

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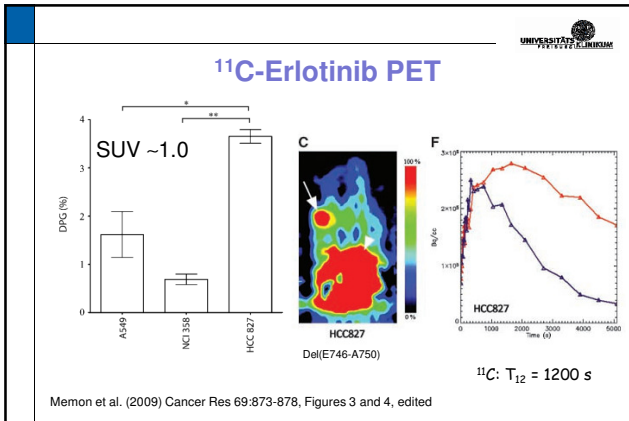
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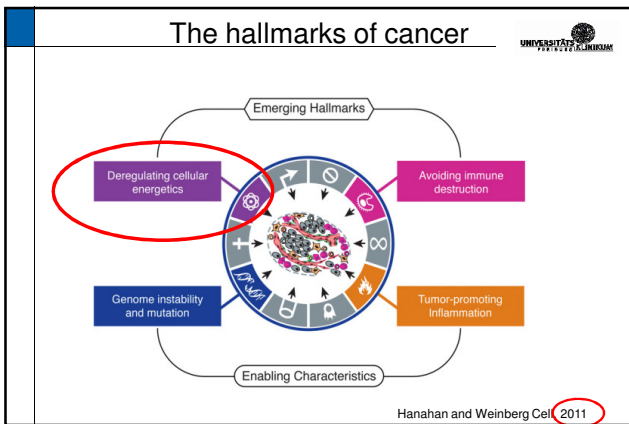
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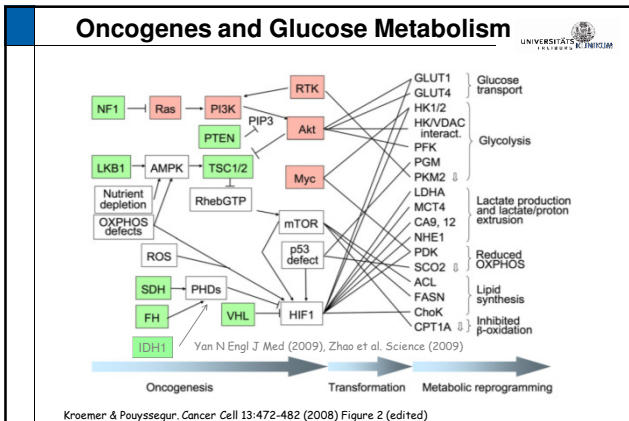
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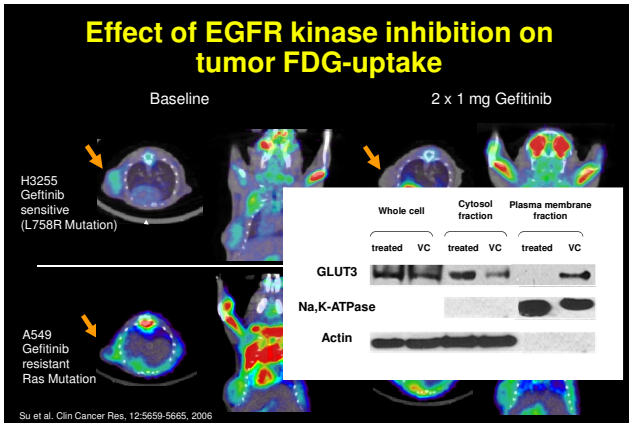
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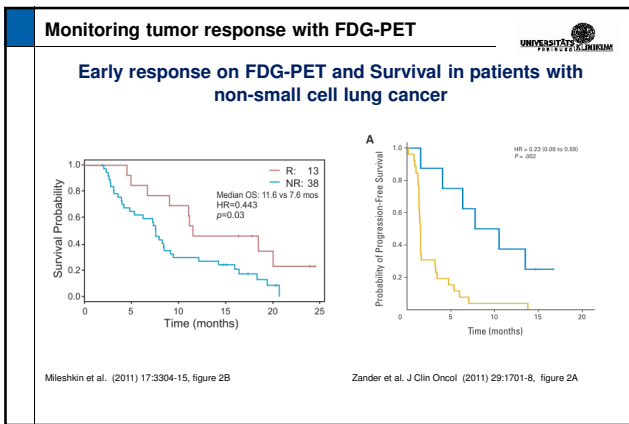
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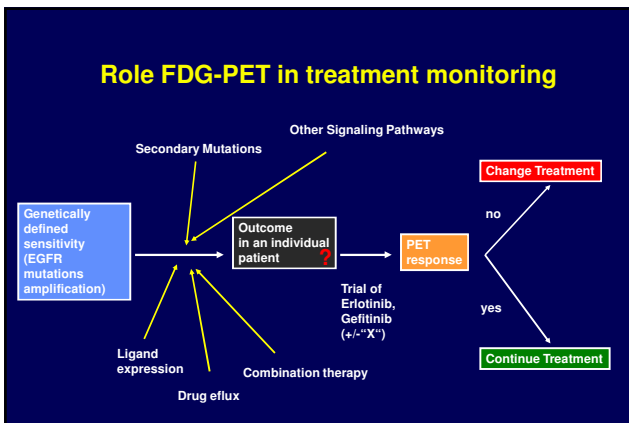
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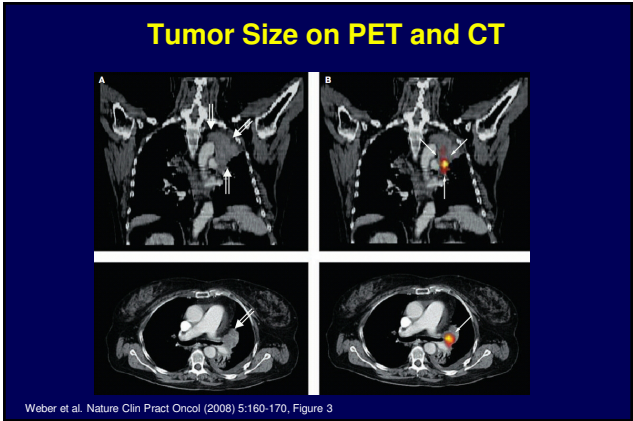
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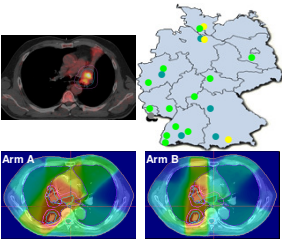
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### PET-Plan Study

Optimization of radiotherapy planning of patients with inoperable locally advanced non-small-cell lung cancer with F-18-FDG  
Prospective randomized multicenter therapy optimizing trial  
21 Centers, 396 Patients, start: Nov. 2009



- Arm A: CT based target volume delineation
- Arm B: PET based target volume delineation
- Dose escalation study.
- Dose limitation: tolerance of normal tissue
- End point: Local tumor control

Ursula Nestle, Freiburg, Deutsche Krebshilfe

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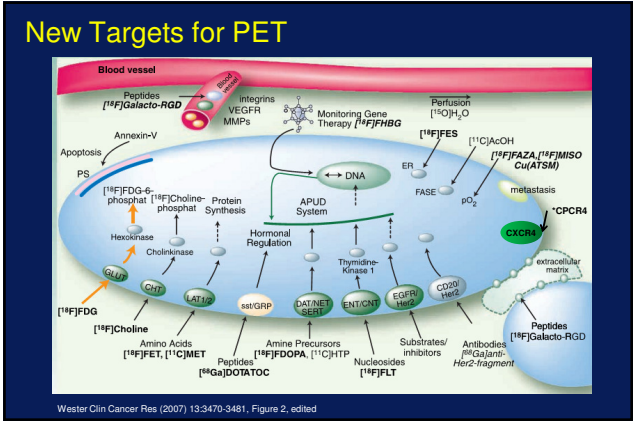
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## Why peptides as radiopharmaceuticals?

Peptide hormone receptors are **excellent targets**

- Expression on the cell surface
- Peptide hormones bind to these receptors with high affinity and specificity -> **the receptors have a characteristic structure that can be recognized by an imaging agent**
- Peptide hormones can serve as starting points for tracer development

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## Why peptides as radiopharmaceuticals?

Peptides labeled with radiometals can be used for **diagnostic and therapeutic purposes.**

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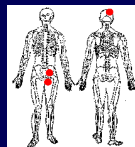
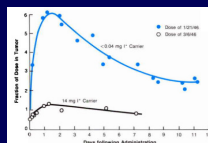
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## Nuclear Medicine is more than Molecular Imaging

**Radioactive Iodine Therapy: Effect On Functioning Metastases of Adenocarcinoma of the Thyroid**  
Seldin, Marinelli, Oshry.  
JAMA 1946

„This paper is a report of successful therapy of a case of metastatic adenocarcinoma of the thyroid treated by the **principle of specific internal radiation** with radioactive iodine.“



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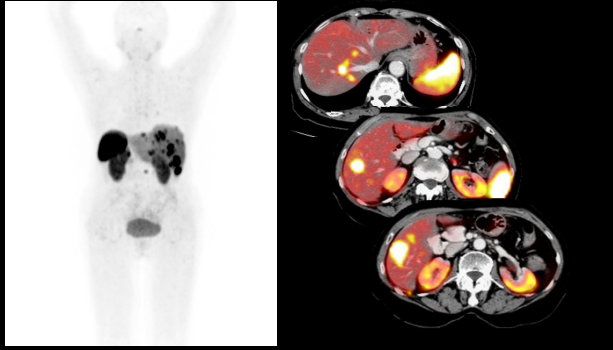
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Somatostatin receptors as a target for imaging and therapy  
**Metastatic NET before Therapy**




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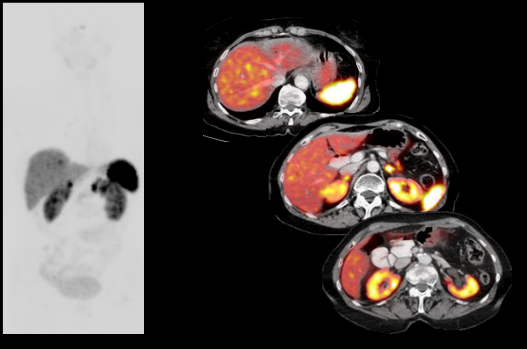
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Metastatic neuroendocrine tumor  
**After three cycles <sup>177</sup>Lu-DOTA-TATE**




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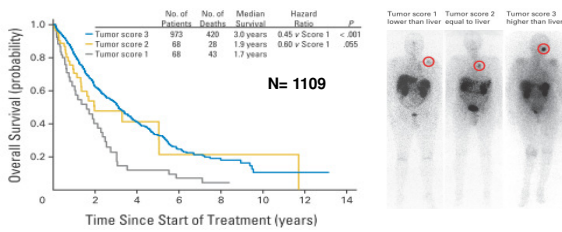
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**Radionuclide therapy with <sup>90</sup>Y-DOTA-TOC**



**Response rate: 34%**

Imhof et al. J Clin Oncol (2011) 29:2416-2423, Figures 2 and 3

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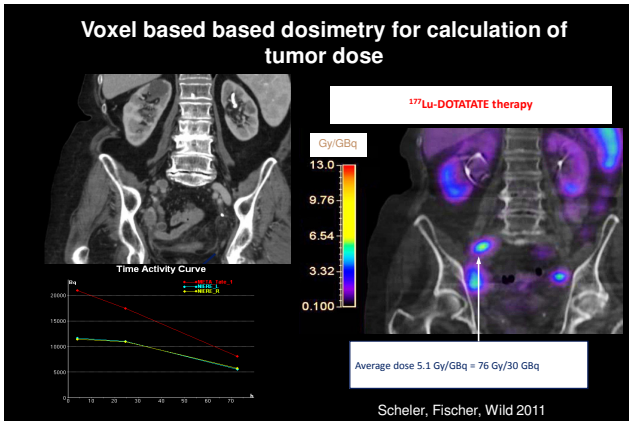
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### The bombesin receptor family

**Bombesin: 14 aa, found in toad bombina bombina**  
 $Glp-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2$

**GRP: Gastrin releasing peptide 27 aa, human counterpart**  
 $.....-Arg-Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met-NH_2$

*Bombina bombina*

**Bombesin receptors**

- BB1 receptor (neuromedin B receptor)
- **BB2 receptor (gastrin-releasing peptide receptor)**
- BB3 receptor (orphan bombesin receptor)
- BB4 receptor (only amphibians)

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### GRP receptor expression in human prostate cancer

**Histology**       **Autoradiography**

GRP receptors are expressed in PIN (prostate intraepithelial neoplasia) and prostate cancer, but not in normal prostate or hyperplasia (n=36)

Markwalder & Reubi. *Cancer Res* (1999) 59:1152-1159

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## The bombesin receptor family



**Bombesin based radioagonists were studied in preclinical models and patients**

### Problems encountered

- Limited metabolic stability
- High uptake in the gastrointestinal tract
- Side effects like nausea, vomiting, cramps in clinical studies
- Potential mitogenic effects

### Bombesin Antagonists as an Alternative?

- Promising preclinical and clinical results with somatostatin antagonists
- Bombesin antagonists are being developed for anticancer therapies
- Less/no side effects of bombesin antagonists expected

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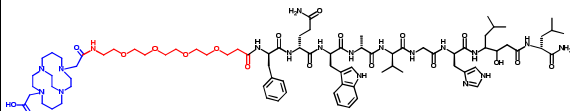
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## GRP receptor antagonist CBC-AR-06



**CBC** (stable chelator for  $^{64}\text{Cu}$ )      **Spacer** (PEG<sub>4</sub>)      **Statin-based bombesin antagonist** (active group)

- $^{64}\text{Cu}$  half-life 12.7 h → PET imaging for several hours to allow for urinary clearance of the peptide
- **IC<sub>50</sub> CBC-AR-06 =  $5.5 \pm 1.3$  nmol/L** (assessed by in-vitro GRP receptor autoradiography using  $^{125}\text{I}$ -Tyr<sup>4</sup>-Bombesin)

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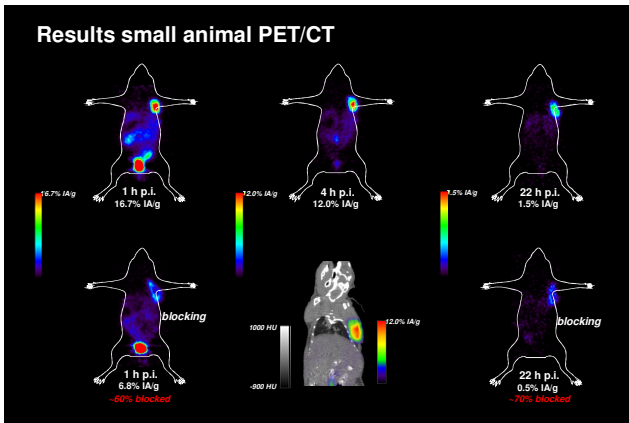
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## Results small animal PET/CT




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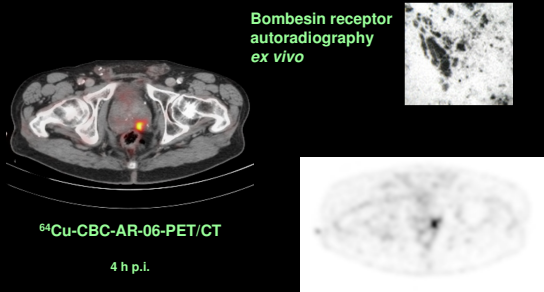
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### Imaging of bombesin receptors in prostate cancer



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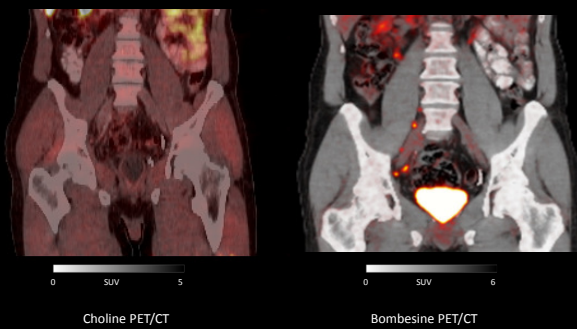
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### Bombesine and Choline PET/CT in a patient with PSA recurrence



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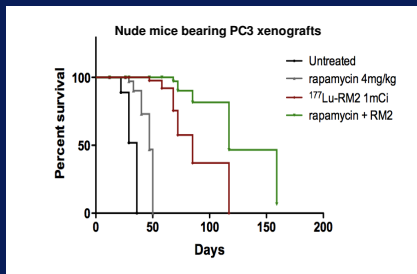
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### Combination therapy with the bombesin receptor antagonist $^{177}\text{Lu}$ -RM2 and rapamycin



Dumont, Mansi, et al. WMIC 2011

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## PET imaging in oncology

### Research

- Proliferation
- Hypoxia
- Apoptosis
- Receptors  
(Integrins, Bombesin, CXCR4, Folate)
- Metabolism  
(Glucose, amino acids, lipids, ...)



### Regulatory approval

- Glucose metabolism (FDG)
- Described 1980, approved 2000, reimbursed (in Germany) ????

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## They all fly, but do they need the same regulations?




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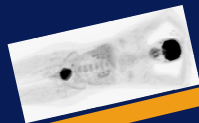
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## Where to invest?



210,000 NSCLC/year in the US  
 ~ 40,000 resections  
 w/o PET: ~17,000 not curative  
 w PET: ~8,000 not curative

No reported side effects of PET  
 Radiopharmaceuticals in 81,801 applications  
 Silberstein et al. J Nucl Med (1998)

\*extrapolation of the data of the  
 PLUS study (van Tinteren 2002)

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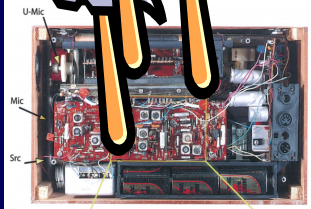
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## Can biologists/physicians



Y Lazebnik. Cancer Cell (2002) 2:179-182, Figures 1 and 2

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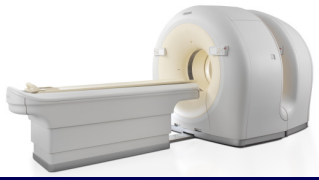
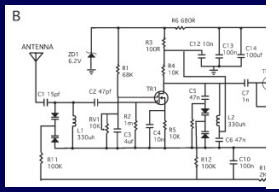
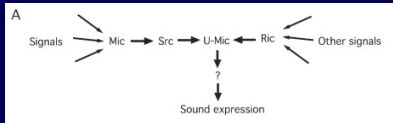
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## Systems Biology and Molecular Imaging



Y Lazebnik. Cancer Cell (2002) 2:179-182, Figure 3

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