Des radioisotopes pour la santé

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H (Dwingeloo 25m)
IR (IRAS)
VIS (ESO)
X (ROSAT)
$a_511$ keV (INTEGRAL)
$\gamma^{26}\text{Al}$ (COMPTEL)

H (MRI)
IR
VIS
X
PET (FDG)
$\gamma^{99m}\text{Tc-MDP}$
The Nuclear Medicine Alphabet

Bone metastases

- planar or SPECT scan for bone metastases
- differentiate between local and generalized disease
- decide on treatment options: surgery or radiation therapy versus systemic therapy
- Bone: 35% of NM procedures in Europe
Ischemic heart disease

- diagnose by ECG and cardiac stress test with SPECT
- treatment by medication, angioplasty or bypass surgery
- 26% of NM procedures in Europe

Thyroid scintigraphy

Thyroid: 12% of NM procedures in Europe

\[ {^{123}}I, {^{131}}I \text{ or } {^{99m}}\text{TcO}_4^- \]

AJ Bauer. CH Philadelphia.
Positron Emission Tomography


\(^{99m}\text{Tc-MDP planar}\)  \(^{99m}\text{Tc-MDP SPECT}\)  \(^{18}\text{F- PET}\)
Rhenium skin cancer therapy

non-melanoma skin cancer:

- basal cell carcinoma and squamish cell carcinoma
- in the Alps (UV!) 20-30% lifetime risk to develop skin cancer

Cancer and efficiency of treatments

<table>
<thead>
<tr>
<th>At time of diagnosis</th>
<th>Primary tumor</th>
<th>With metastases</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed</td>
<td>58%</td>
<td>42%</td>
<td>100%</td>
</tr>
<tr>
<td>Cured by:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>22%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery+radiation therapy</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other treatments and combinations incl. chemotherapy</td>
<td></td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Fraction cured</td>
<td>69%</td>
<td>12%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Over one million deaths per year from cancer in EU.
⇒ improve early diagnosis
⇒ improve systemic treatments

Comparison of Therapies

Macroscopic tumors: ≥ 5mm (> $10^7$ cells)
Microscopic tumors: < 5mm (1 – $10^7$ cells)

Cell kill after Chemotherapy: only about 3 logarithmic steps (ordinate)

(Molls, TU München; according to Tannock: Lancet 1998, Nature 2006)
The principle of targeted therapies

- “attractive” vector > high uptake by the target
- transportable
- good in-vivo stability
- warriors “not visible”
- delayed uptake > suitable half-life
- limited space > high specific activity
- optimum arms
- specific

Metabolic targeting

**Thyroid cancer**

- $^{123}$I or $^{99m}$TcO$_4^-$ for imaging
- $^{131}$I for therapy

**Bone metastases**

- 1.5 million patients world-wide

- $^{99m}$Tc-MDP for SPECT imaging
- $^{18}$F for PET imaging

**Therapy**

- $^{153}$Sm-EDTMP (Quadramet)
- $^{89}$Sr$^{2+}$ (Metastron)
- $^{223}$Ra$^{2+}$ (Xofigo/Alpharadin)
Immunology approach

Multidisciplinary collaboration to fight cancer

Nuclear medicine and medical physics
Structural Formula of DOTA-TOC/TATE

1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate

\[ IC_{50} (\text{Y}^{III}) = 1.6 \pm 0.4 \text{ nM} \]


Male
36 years of age
Small cell pancreatic neuroendocrine tumour
Liver metastases
Ki-67 index 10-15% (liver biopsy)
4 cycles with \(^{177}\text{Lu}\)-octreotate and capcitabine
Partial remission

**What success does PRRT offer?**

- CR+ PR + MR in about 50% of patients: **YES**
- Reduce symptoms and improve quality of life: **YES**
- Increase survival time: **YES**
- Safety and tolerability: **YES**


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**Lymphoma therapy: RITUXIMAB+^{177}Lu**

E.B., 1941 (m): UPN 6

1. **18FDG PET**
2. **177Lu-Scan**
3. **18FDG PET**

- 1.9.2002
- 13.9.2002
- 15.11.2002
- 15.9.2009

Still in CR

## Radionuclides for RIT and PRRT

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>$E_{\text{mean}}$ (keV)</th>
<th>$E_{\gamma} \text{ (B.R.)}$ (keV)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y-90</td>
<td>64 h</td>
<td>934 $\beta$</td>
<td>-</td>
<td>12 mm</td>
</tr>
<tr>
<td>I-131</td>
<td>8 days</td>
<td>182 $\beta$</td>
<td>364 (82%)</td>
<td>3 mm</td>
</tr>
<tr>
<td>Lu-177</td>
<td>7 days</td>
<td>134 $\beta$</td>
<td>208 (10%) 113 (6%)</td>
<td>2 mm</td>
</tr>
<tr>
<td>Tb-161</td>
<td>7 days</td>
<td>154 $\beta$ 5, 17, 40 $e^-$</td>
<td>75 (10%)</td>
<td>2 mm</td>
</tr>
<tr>
<td>Tb-149</td>
<td>4.1 h</td>
<td>3967 $\alpha$</td>
<td>165...</td>
<td>25 $\mu$m</td>
</tr>
<tr>
<td>Ge-71</td>
<td>11 days</td>
<td>8 $e^-$</td>
<td>-</td>
<td>1.7 $\mu$m</td>
</tr>
<tr>
<td>Er-165</td>
<td>10.3 h</td>
<td>5.3 $e^-$</td>
<td>-</td>
<td>0.6 $\mu$m</td>
</tr>
</tbody>
</table>

Modern, better targeted bioconjugates require shorter-range radiation $\Rightarrow$ need for adequate (R&D) radioisotope supply.

### Matched pairs for theranostics

Terbium: a unique element for nuclear medicine

Folate-receptor positive cancers

Frequent overexpression of folate receptor in cancer of:
- ovaries
- cervix uteri
- lung
- kidney
- brain
- colon
- breast
- leukemia

folic acid = vitamine B9

Tumor Tageting Agent for Tb-Coordination
Chemical Structure with 3 Functionalities

**Characteristics:**
- stable coordination of Tb-isotopes
- high affinity to the folate receptor
- prolonged blood circulation time


Theranostics with terbium isotopes

The Tordesillas meridian

The Tordesillas meridian of radioisotope production
Cumulative use of diagnostic isotopes in Europe

- **99mTc**
- **201Tl**
- **131I**
- **123I**
- **PET**
- **Other**


**99Mo/99mTc generator**

- simple
- reliable
- portable
- self-shielded
The traditional supply chain of $^{99}\text{Mo}/^{99m}\text{Tc}$

From the producers to the users ... No time to lose ...
The rising star for therapy

The highest neutron flux in Western Europe

\[1.5 \times 10^{15} \text{ n.cm}^{-2}\text{s}^{-1}\]
“Clean” production route to $^{177}$Lu

- Free of long-lived isomer
- Non-carrier-added quality
- Requires high-flux reactor and advanced radiochemistry

New automated irradiation system at ILL
Production of radioisotopes in 2005

The diameter of the white circles is proportional to the thermal neutron flux in the irradiation positions.

Production of innovative radioisotopes in 2020

The diameter of the white circles is proportional to the thermal neutron flux in the irradiation positions.
Production of innovative radioisotopes in 2020

high flux reactor
70 MeV p cyclo.
40 MeV d LINAC
MEDICIS-CERN
$^{224}\text{Ra}/^{212}\text{Pb}$

The diameter of the white circles is proportional to the thermal neutron flux in the irradiation positions.

Which radionuclides will we need for medicine in 2030?
Today 30 million clinical applications per year!

The New York Patent Group has carefully studied the information available relative to the above-identified item. The AEC does not present desire to prepare a patent application on this item for the following reason:

"The method of producing carrier-free molybdenum-99 from fission products is disclosed in U. S. Patent Application S.N. 732,108, Green, Powell, Samos & Tucker (BNL Pat No. 58-17). It is noted that molybdenum-99 may be separated from its radioactive daughter, technetium-99, by absorption of a solution of molybdenum-99 on alumina and subsequent elution of its daughter with 1 nitric acid. While this method is probably novel, it appears that the product will probably be used mostly for experimental purposes in the laboratory. On this basis, no further patent action is believed warranted."

believe that this attitude is significant. We are not aware of a potential market for technetium-99 great enough to encourage one to undertake the risk of patenting in hopes of successful and rewarding licensing. We would recommend against filing on the Tucker, Greene and Murrenoff separation process."

Questions
The economy of the aviation industry and of nuclear medicine

- **19%** “Fuel” sourcing
  - Reactor: 0.11% (0.26€)

- **5%** “Fuel” refinement
  - Mo processing: 0.67% (1.64€)
  - Generator: 0.14% (0.34€)

- **17%** Equipment
  - (amortization, maintenance, leasing, chartering)

- **31%** Personal costs
  - CH 2009: 760 €
  - US 2014: 909 €
  - Total 245.61€

*OECD-NEA, 2008

Air France KLM, financial reports 2007-2012

2013: **99Mo production capacity and demand**

Circle diameter proportional to annual reactor capacity (blue) and demand (red).
2017: $^{99}$Mo production capacity and demand

Diameter of circles proportional to annual reactor capacity and demand.

Targeted radionuclide therapies in the clinic

- **Thyroid:** $^{131}$I
- **Lymphoma:** Zevalin® ($^{90}$Y-mab)
- **Bexxar® ($^{131}$I-mab)**
- **Bone metastases:** Metastron® ($^{89}$SrCl$_2$)
- **Quadramet® ($^{153}$Sm-EDTMP)**
- **Xofigo® ($^{223}$RaCl$_2$)**
- **Neuroblastoma:** $^{131}$I-MIBG
- **Neuroendocrine (GEP-NET):** $^{177}$Lu-peptides (II)
- **$^{90}$Y-peptides**
- **Liver (HCC):** Theraspheres® & SIRspheres® ($^{90}$Y)
- **$^{188}$Re-Lipiodol (II)**
- **$^{166}$Ho-microspheres**
- **Colon & rectum:** $^{131}$I-mab (II)
- **Prostate:** $^{177}$Lu-mab (II)
- **Kidneys (RCC):** $^{90}$Y/$^{177}$Lu-mab (I)
- **Brain:** $^{90}$Y-mab, $^{131}$I-mab (I/II), $^{211}$At-mab (I), $^{213}$Bi-pept. (I)
- **Lymphoma, myeloma:** $^{90}$Y-mab, $^{212}$Bi-mab (II)
- **Medullary Thyroid:** $^{131}$I-mab (II)
- **$^{90}$Y-pept.**
- **Breast:** $^{90}$Y-mab, $^{90}$Y-pept.
- **$^{212}$Pb-mab (I)**
- **Lung (SCLC):** $^{177}$Lu-mab (II)
- **Pancreas:** $^{90}$Y-mab (II)
- **Ovary:** $^{212}$Pb-mab (I)
- **$^{90}$Y/$^{177}$Lu-mab**
- **Melanoma:** $^{213}$Bi-mab (II)
Bibliography

- Nuclear Physics for Medicine, NuPECC 2014
- Lectures on Theranostics by Richard Baum:
  https://www.youtube.com/watch?v=Z0TlXH2dVi8
  https://www.youtube.com/watch?v=S74LNxXOaSw
- (Free) medical review papers from: http://pubmed.gov
- Information on on-going clinical trials: http://clinicaltrials.gov

Comment trouver des essais cliniques en cours

3. Cocher “Include only open studies” pour ceux qui recrutent des patients.
5. Descendre pour voir les détails
6. Description détaillé,
7. critères d’éligibilité et critères d’exclusion,
8. puis les adresses des hôpitaux et contact des médecins.
Purpose

Lung cancer is currently the leading cause of cancer death in both men and women in Europe, with an estimated 256,000 new cases diagnosed in 2007. The continued poor outcome of patients indicates that the current recommended regimens are falling short. In addition, many of the commonly used chemotherapeutic agents are associated with severe nonhematologic toxicities that are often cumulative and irreversible and impair quality of life in this essentially palliative setting. Therefore, agents with novel mechanisms of action and superior safety profiles should be investigated. More than 50% of lung cancer shows carcinoembryonic antigen (CEA) expression and anti-CEA radiomunotherapy (RAIT) may be used. The investigators group showed that pretargeted RAIT (PRAIT) using bispecific antibody (bsAb) can deliver a higher radiation dose than a directly radiolabeled anti-CEA antibody, and shows improved anti-tumor efficacy. This clinical trial is designed to assess, using an entirely new recombinant anti-CEA bsAb and a 177Lu-labeled peptide for the treatment of CEA-expressing small cell lung cancer (SCLC) or CEA-expressing Non Small Cell Lung Carcinoma (NSCLC).
Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Inclusion Criteria:

- Patients with histologic diagnosis of SCLC who are in partial response or who have failed at least two lines of standard radiation and/or chemotherapy. Outside formal contra indication, patients must have received at least one prior platinum-based chemotherapy or
- Patients with histologic diagnosis of NSCLC (without activating mutation of EGFR gene) who have failed at least one line of chemotherapy (platinum in combination with a third generation drug or combination of 2 third generation drug +/- bevacizumab in case of preeminence of non-squamous tumor)
- Age ≥ 18 years
- At least 4 weeks after the previous treatment and have recovered from previous radio- or chemotherapy
- Women of child-bearing potential must have a negative pregnancy test.
- Karnofsky performance status ≥ 90 or ECOG performance status 0-2
- Karnofsky
- Minimum life expectancy of 3 months
- Positive CEA or immunohistology or plasma CEA ≥ 10 ng/mL
- At least one measurable lesion by CT
- At least one abnormal focus by FOG-PET
- Imaging studies must be performed within 1-4 weeks before PRAIT study to document extent of disease.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT01221675

Locations

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