Radiopharmacy basics

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Radiopharmacy

“*The Preparation of high quality, radioactive, medicinal products for use in diagnosis and therapy.*”

- **Expertise**: Special licensure; Radiopharmacy normally allied to medical physics
- **Radioprotection**: of those working with the substances
- **Quality control**: ensuring the correct formulation and efficacy
- **Storage**: Decay, and other considerations
- **Correct usage**: liaise with other professions

➡ **Critical to the implementation of nuclear medicine**
Development of a radiopharmaceutical in oncology

Concept

Target
- ↑↑ Expression in cancer cells
- Hallmark of cancer

Probe
- Specific

Radiolabeling

Target

Concept

Probe

Radiolabeling
Radiolabeling: Radionuclide & Method

**Choice of Radionuclide**

- **Purpose:**
  - Therapy: $\beta^-$ vs $\alpha$
  - Imaging: SPECT ($\gamma$) vs PET ($\beta^+$)
- Physical/chemical characteristics
- Optimal tumor-to-nontumor ratios $\approx \text{Physical } t_{1/2} \text{ isotope}$
- Cyclotron ($^{18}\text{F}, ^{11}\text{C},...$) vs. generator ($^{99m}\text{Tc}, ^{68}\text{Ga}$)
- Availability and price

**Choice of method**

- Direct
- Indirect radiolabeling
  - Modification of precursor with a bifunctional chelator
  - Transchelation: low to high affinity
- Intravenous injection: aseptic techniques (sterile filtration)
- Protection of those preparing the drug
- Manual vs automatic vs kits
Radiolabeling: Quality controls

**Reception**
- Pakaging
- Documentation
- Swab/Wipe test swabbing potentially contaminated surface with a media capable of absorbing radioactivity.
  
  “Q-tips”, alcohol swabs and filter paper are all suitable media for a wipe test survey.

**Working place**
- Materials: conservation
- Machines: calibration and maintenance
- Clean working space
- LAF: Yearly maintenance and test

**Product**
- Physico-chemical properties
- Pharmacological properties
### Radiolabeling: Quality controls

**Appearance**
- Powder
- Solution
- Particles in solution
- Color
- Clear
- Homogenous

<table>
<thead>
<tr>
<th><strong>pH</strong></th>
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<tbody>
<tr>
<td><strong>pH indicator strips:</strong></td>
</tr>
<tr>
<td>+ Easy, single use, little sample</td>
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**Equipment:** indicator strips/paper desired pH

1. Immerge in sample or place a drop on pH paper
2. Read the color code

**pH meter:**

**Equipment:** pH meter with electrode

- + refined, adjusting possible

1. Immerge electrode
2. Read the measurement
# Radiolabeling: Quality controls

<table>
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<tr>
<th>Type of purity</th>
<th>Definition</th>
<th>methods</th>
<th>Effect of impurity</th>
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<td>Radionuclidic</td>
<td>radioactivity desired radionuclide / the total radioactivity of the source</td>
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Radiolabeling: Quality controls

**Radionuclide purity**

- **Energy spectrum**: “fingerprint of the radioisotope
- **Decay** (eg. $^{68}$Ga 68 min vs $^{68}$Ge 270d)

**Equipment:**

- **Isotope Calibrator**: ionisation chamber
- **Gamma counters**: sodium iodide scintillation
  - small amounts of radioactivity
  - 'counts per minute'
  - automated → many samples in succession
  - clinical samples: blood or urine,
  - QC: TLC strips cut up into several pieces
  - swabs used for wipe tests
- **Beta counters**: liquid scintillation detectors
  - beta radiation: $^{14}$C, $^{3}$H and $^{32}$P, that emit
  - auger electrons: $^{51}$Cr and $^{125}$I.
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<td>Increased Radiation Dose, Poor Image Quality</td>
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<td>Colorimetric or HPLC</td>
<td>Poor Image Quality</td>
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<tr>
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<td>desired radiolabelled species/total radioactivity</td>
<td>TLC or radio-HPLC</td>
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Radiolabeling: Quality controls

Radiochemical Purity

**Thin-layer chromatography (TLC):**
- Differential distribution liquid (mobile) phase vs solid (stationary) support
- Mostly consisting of silica gel, normally bound to glass-fibre sheets. (ITLC).
- **Equipment:** Beaker & lid, TLC plate, solvent
  1. Line on the TLC plate
  2. Drop product on TLC plate
  3. Plate into beaker containing solvent, cover
  4. Let solvent reach almost top
  5. Analyze:
     - Cut into pieces and count in γ-counter
     - Autoradiography

**High Pressure Liquid Chromatography (HPLC):**
- Separation down a column by elution with a suitable mobile phase
- Can be performed using a very efficient separation mode
- **Equipment:** radio-HPLC, column, mobile phase
  1. Pre-conditioning column with mobile phase
  2. Injection onto the column
  3. Run
  4. Analyze graphs
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## Radiolabeling: Quality controls

### Sterility

No micro-organisms in the preparation?
- Most iv administration → sterile
- working in a clean environment
- aseptic transfer techniques

**Equipment:**
LAF, bacterial culture media, 37°C incubator
- Under aseptical conditions

1. Transfer sample into bacterial culture in duplicate
2. Incubate for 10-14d at 37°C
3. Visual inspection of media
   → Clear ✓

### Pyrogenicity

No bacterial endotoxin?
- fragments of the bacteria → pyrogenic response (chills, fever, myalgia,...)
- IV 2.5 EU/kg, IT 0.2 EU/kg (PhEur )
- Method A. The gel-clot technique
- Method B. The turbidimetric technique
- Method C. The chromogenic technique

**Equipment:** Endosafe, endotoxin-free water, LAL cassette (contains LAL, standard)

1. Turn Endosafe on, add cassette
2. Add sample
3. Run test
4. Read results
   → < 0,5EU/mL ✓
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Development of a radiopharmaceutical in oncology

**Target**
- Expression in cancer cells
- Hallmark of cancer

**Probe**
- Specific

**Radiolabeling**
- Choice of radioisotope
- Choice of the method
- QC: Conform
**In vitro** biological properties

**Models:** cells overexpressing the particular target

**Knowledge:** tracer properties + maintenance of specific characteristics

**How:** binding/internalization study

- Gamma counter or Autoradiography
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In vitro
- Model: cells (target)
- Binding/Internalisation
**Models:**
Small animal expressing the desired target
- Inoculation of a cancer cell lines
- Genetic modification
- Patient tumor graft (PDX)

**Knowledge:**
- targeting properties
- biodistribution
- pharmacokinetics

**How:**
- ex vivo dissection
- ex vivo autoradiography
- in vivo imaging studies

**In vivo imaging studies:** facilitates extrapolation from animals to human studies
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**Preclinical**

- **In vitro**
  - Model: cells (↗↗ target)
  - Binding/Internalisation

- **In vivo**
  - Model: animal (↗↗ target)
  - Imaging & ex vivo (distribution, PK,...)
Imaging of the radiotracer in patients

- Imaging = Translational!

**Regulatory steps:**
- IMPD
- FAMHP & FANC
- Ethical committee

**Knowledge:**
- Targeting properties
- Biodistribution
- Pharmacokinetics
- Dosimetry

**How:**
- In vivo imaging studies
- Blood samples

➤ **Ultimate test of the quality of a radiopharmaceutical:**
  biological behavior and the distribution in the patient

18F-FDG  89Zr-Trastuzumab

Dr. Geraldine Gebhart (5/10/17)
Development of a radiopharmaceutical in oncology

**Concept**

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**Radiolabeling**
- Choice of radioisotope
- Choice of the method
- QC

**In vitro**
- Model: cells (↗↗ target)
- Binding/Internalisation

**In vivo**
- Model: animal (↗ target)
- Imaging & ex vivo (distribution, PK,...)

**Preclinical**

**In patients**
- Regulatory steps: IMPD FAMHP, FANC, ethical committee
- Imaging & distribution, PK,...
Radiolabeling

- $^{68}$Ga-DOTATATE (NET-PET) 03/10/17
- $^{177}$Lu-DOTATATE (NET-PRRT) 05/10/17
- $^{89}$Zr-trastuzumab (HER2-PET) 06/10/17
- $^{68}$Ga-PSMA (PSMA-PET)
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