Agenda

- PET characteristics
- Manufacturing of radiopharmaceuticals
- Good Manufacturing Practice
- Radiopharmaceutical Production Site — process management and design
- Applications
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Contemporary diagnostics modes

<table>
<thead>
<tr>
<th>Anatomy</th>
<th>Physiology</th>
<th>Metabolic</th>
<th>Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray</td>
<td>MRI USG</td>
<td>PET</td>
<td></td>
</tr>
</tbody>
</table>

RTG CT USG MRI PET
Some definitions

Radiotracer - chemical compound consists of:

**Radioisotope**: a radionuclide with physical data suitable for external measurement

**Linker**: a molecule with suitable pharmacokinetics, and high concentrations in the target organ or process
PET Characteristics

• 3D imaging mode with β-isotopes

Linear resolution in clinical imaging [mm]:

- CT: 0.5-1.0
- MRI: 0.2-
- USG: 0.1-1
- PET: 3-6
**PET Characteristics**

**Linear resolution in clinical imaging (mm):**

- CT: 0.5-1.0
- MRI: 0.2-
- USG: 0.1-1
- PET: 3-6

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**Coupling PET with anatomic imaging modes**

PET + CT = PET/CT
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PET Radioisotopes

Useful radionuclides

- $^{18}$F - half-life 110 min.
- $^{11}$C - half-life 20 min.
- $^{15}$O - half-life 2 min.
- $^{13}$N - half-life 10 min.

Radionuclide scissors

- Shorter half-life — radiation exposure
- Longer half-life — clinical availability
Isotopes production

Cyclotrone

Cyclotron IBA 18/9

Cyclotron GE PETrace 8

Targets

Target for liquids

Target for gases
**18F Production**

Production $^{18}$F:
Reaction: $^{18}$O(p,n)$^{18}$F
Target: $\text{H}_2^{18}$O c, 95%$^{18}$O
Product: $^{18}$F–

Target for liquids

---

**18F Production**

Production $^{18}$F:
Reaction: $^{18}$O(p,n)$^{18}$F
Target: $^{18}$O g, 95%$^{18}$O
Product: $\text{F}_2(^{18}$F$^{19}$F)

Target for gases
**11C Production**

Production $^{11}\text{C}$:

Reaction: $^{14}\text{N}(p,\alpha)^{11}\text{C}$

Target: 99.6% $^{14}\text{N} (0.1-5\% \text{H}_2)$

Product: HCN, CH$_4$ or $^{14}\text{N} (\text{O}_2)$

**Target for gases**

**15O Production**

Production $^{15}\text{O}$:

Reaction: $^{14}\text{N}(d,n)^{15}\text{O}$

Target: 99% $^{14}\text{N}_2 + 1\%^{16}\text{O}_2$

Product: $^{15}\text{O}^{16}\text{O}$

**Target for gases**
Radiopharmaceuticals manufacturing

Dispensing

Radiopharmaceuticals manufacturing

[Image of dispensing equipment]

[Image of syringe and container]

[Image of medical scan]
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**GMP**

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<td>Reactor Production</td>
<td>Chemical synthesis</td>
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<td>Cyclotron Production</td>
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<td>Processing</td>
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## Manufacturing regulations

Radiopharmaceutical site structure

1. Isotope production
2. Synthesis
3. Final sterility
4. Quality control

Cleanrooms

<table>
<thead>
<tr>
<th>Clean room classes by PIC:</th>
</tr>
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<tbody>
<tr>
<td>Class</td>
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<td>-------</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
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Cleanrooms

<table>
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<th>Microorganisms</th>
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<tr>
<td>Fingertip</td>
<td>20-100/cm²</td>
</tr>
<tr>
<td>Hand</td>
<td>1000-6000</td>
</tr>
<tr>
<td>Saliva</td>
<td>10⁵-10⁹/ml</td>
</tr>
<tr>
<td>Nasal discharge</td>
<td>10⁶-10⁷/ml</td>
</tr>
<tr>
<td>1 x Sneezing</td>
<td>10⁴-10⁶</td>
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</table>
Isolator safety features

Dispensing unit
Quality control

1. Isotope production
2. Synthesis
3. Final sterility
4. Quality control

Quality control

FLUDEOXYGLUCOSE (18F) INJECTION
Fludeoxyglucosi (18F) solutio injectabilis

DEFINITION
Fludeoxyglucose (18F) injection is a sterile solution of 2-[18F]fluoro-2-deoxy-D-glucose (2-[18F]fluoro-2-deoxy-D-glucose) for diagnostic use. The injection contains not less than 90.0 per cent and not more than 110.0 per cent of the declared fluorine-18 radioactivity at the date and time stated on the label. Not less than 95 per cent of the radioactivity corresponds to fluorine-18 in the form of 2-[18F]fluoro-2-deoxy-D-glucose and 2-[18F]fluoro-2-deoxy-D-glucose, with the 2-[18F]fluoro-2-deoxy-D-glucose fraction not exceeding 10 per cent of the total radioactivity. Not less than 90.0 per cent of the radioactivity corresponds to fluorine-18. The content of 2-fluoro-2-deoxy-D-glucose is not more than 10 μg per maximum recommended dose of injection.
Application in medicine and science

Oncology

Tumor diagnostics:

• Evaluation of the nature of the change
• Diagnosis and staging of cancer
• Monitoring during and after treatment
• Radiotherapy planning

Application in medicine

Oncology

Evaluation of the change

CT

PET
Application in medicine

Oncology

Diagnosis and staging of cancer

Application in medicine

Oncology

Monitoring during and after treatment

Before

After
Application in medicine

Oncology

Radiotherapy planning:

CT
PET + CT
Therapy

Principles:

• increased glycolysis in tumor cells — Warburg phenomenon — 20-30-times higher glucose metabolism

• increased permeability of biological membranes of tumor cells

• increased protein synthesis

• specific reactions
Application in medicine

Oncology

Principle:

• increased glycolysis in tumor cells — *Warburg phenomenon* — 20-30-times higher glucose metabolism

\[ \text{\textsuperscript{18}F-FDG (2-Deoxy-2-fluoro-D-glucose)} \]

Standard radiopharmaceutical in clinical practice: diagnosis of most cancers

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Application in medicine

Oncology

Principle:

• increased permeability of biological membranes of tumor cells

\[ \text{\textsuperscript{11}C-choline,} \quad \text{\textsuperscript{18}F-choline} \]

Diagnosis of prostate cancer
Application in medicine

Oncology

Principle:

- Increased protein synthesis

\[ ^{18}F \text{-thymidine} \quad ^{11}C \text{-metionine} \quad ^{18}F \text{-methylotyrosine} \]

Brain cancer, others as supplementary tracers

Application in medicine

Oncology

Principle:

- Specific reactions

\[ ^{18}F \text{-MISO} \]

Diagnosis of hypoxia
Application in medicine

Neurology

• Brain cancer diagnostics
• Diagnosis and staging of dementia (AD) and movement disorders (PD)
• Neuroactivation

Cardiology

Diagnosis and evaluation of heart: $^{13}$NH$_3$, $^{18}$F-FDG, $^{11}$C-palmitate

Application in science and R&D

AnimalPET

• Drug discovery
• Clinical studies
Application in science nad R&D

All-in-one systems with generators

Transport
Costs
Simplicity

Available generators

- $^{68}$Ga - halflife 67.8 min.
- $^{82}$Rb - halflife 1.26 min.
- $^{94}$Tc - halflife 53 min.
- $^{122}$I - halflife 3.6 min.
- $^{124}$Tc - halflife 4.15 dni
ImmunoPET

$^{124}\text{I}, ^{89}\text{Zr} -$ PET radiotracers ($t/2 \approx 80-100\text{h}$), labelling MAB (monoclonal antibodies)

$^{211}\text{At} -$ alpha emitter for treatment
Summary

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Concluding remark
Radiopharmaceuticals for Position Emission Tomography (PET)

Krzysztof Kilian
University of Warsaw, Heavy Ion Laboratory