European Commission H2020 INFRAIA call - MEDITIS-ProMed

EANM perspective

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Dept. of Nuclear Medicine, Medical University Innsbruck, Austria
Erice, April 30th 2019
an introduction
About the European Association of Nuclear Medicine (EANM)

- Medical **non-profit association** incorporated in Austria
- Aim: improving public health and promoting science and education in the field of nuclear medicine
- Core business: **Science, education, standardisation and quality control**

- Governance structure:
  - EANM Board (7 members)
  - 15 EANM Committees (approx. 150 volunteer experts)
  - Additional work groups and task forces on demand
  - EANM Executive Office in Vienna
About the EANM Community

• Approx. **3,000 members**, including
  • Nuclear medicine physicians
  • Physicists
  • Technologists
  • Scientists etc.

• Annual Congress: > 6,000 participants – **largest NM conference worldwide**
• More than 9,000 member state members
• Serving a community of more than 16,000 specialists
EANM Committees

Bone & Joint
Chair: F. Paycha (France)

Cardiovascular
Chair: H. Verberne (Netherlands)

Dosimetry
Chair: M. Kuijnenberg (Netherlands)

Drug Development
Chair: J. Verouille (France)

Ethics
Chair: W. H. Knapp (Germany)

Inflammation & Infection
Chair: A. Glaudemans (Netherlands)

Neuroimaging
Chair: I. Law (Denmark)

Oncology & Theranostics
Chair: K. Herrmann (Germany)

Paediatrics
Chair: Z. Bar-Server (Israel)

Physics
Chair: C. Hindorf (Sweden)

Radiation Protection
Chair: S. Holm (Denmark)

Radiopharmacy
Chair: M. Patt (Germany)

Technologist
Chair: A. Santos (Portugal)

Thyroid
Chair: M. Lustor (Germany)

Translational Molecular Imaging & Therapy
Chair: F. Van Leeuwen (Netherlands)
EANM Activities

• **Education, Training and Research**
  - Annual Congress (EANM’19 in Barcelona/Spain, October 12-16, 2019)
    *The World Leading Meeting in the field with more than 6,200 participants*
  - European School of Multimodality Imaging & Therapy (ESMIT)
    *3-level high quality training, focusing on multimodality*
  - EANM Research Ltd („EARL“) e.g. FDG-PET/CT Accreditation programme
    *earl.eanm.org*

• **Publications:**
  - Guidelines & Position Papers
  - EANM Paediatric Dosage Card, Dosage Calculator & PedDose App
  - EANM Technologist’s Guide Book
  - EANM Press Releases
The 3-level system

Level 1: eLearning (basic)
- no limits, full education
- eLearning.eanm.org

Level 2: School Meetings (intermediate)
- compressed learning,
  unique experience

Level 3: High End Courses (advanced)
- summit of CME
ESMIT
European School of Multimodality Imaging and Therapy

High End Courses 2019
Vienna/AT

» Brain Tumours (March 7-8)
» Bone SPECT/CT in Complications of Skeletal Metalwork (April 4-5)
» Quantification in SPECT and PET (Oncology) (June 6-7)

eanm.org/esmit
EANM Research Ltd
EARL Activities: FDG PET/CT Accreditation

EARL initiated this accreditation programme in order to support imaging sites, which perform FDG-PET/CT oncology examinations, in meeting the requirements indicated in the EANM imaging guideline.

- aims at providing a minimum standard for the acquisition and interpretation of PET and PET/CT scans with [18F]-fluorodeoxyglucose (FDG).
- goal is to enhance the quality standard of PET/CT investigations for both daily use and for multicentre studies
- PET/CT accreditation ensures similar performance of PET/CT systems within a multicentre setting by harmonising acquisition and processing of PET/CT scans.
- Accredited PET/CT centres of excellence can compare, exchange and combine FDG-PET/CT findings, including SUV values, since data are collected and processed in a standardised manner.
EANM Activities

• Networking & Public Affairs:
  • representing the community’s interests towards the EU, national and international societies, non-governmental institutions, legislative bodies etc.
  • covering topics such as: radiopharmaceutical legislation, radiation protection, harmonization of education and competencies
  • providing a platform for exchange for the EANM’s member societies
  • fostering relationships with the “sister” societies as well as partner associations in related disciplines through joint publications and other projects

• Collaboration with Springer on the EJNMMI Journal Family:
  • EJNMMI (European Journal of Nuclear Medicine & Molecular Imaging)
  • EJNMMI Physics
  • EJMMI Radiopharmacy and Chemistry
  • EJNMMI Research
  • European Journal of Hybrid Imaging – The EJNMMI Multimodality Journal (since 2017)
(Novel) Applications in Therapy / Theranostics

- Peptides (STSR)
- Small molecules
- Proteins
Somatostatin Analogues – Marketing Authorization

177Lu-DOTATATE (Oxodotretotide)
20 heavily pretreated pts: 8 completed 2 cycles, 12 had 1 cycle
After only 1 cycle, evaluable pts had (RECIST 1.1):
  - PR in 7/19 (37%), SD in 9/19 (47%), PD in 3/19 (16%)
Prolonged but reversible G3/4 toxicity in 4/8 (50%) treated with 2 cycles
Favorable response justifies continuation
# Peptides for Molecular Imaging in Oncology

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Target</th>
<th>Application</th>
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<tbody>
<tr>
<td><strong>Somatostatin</strong></td>
<td>sst1-sst5, sst2</td>
<td>Neuroendocrine Tumors</td>
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<tr>
<td><strong>Gastrin, CCK</strong></td>
<td>CCK2</td>
<td>Medullary Thyroid Carcinoma</td>
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<td></td>
<td>Small Cell Lung Cancer, GEP-NET *</td>
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<tr>
<td><strong>Neurotensin</strong></td>
<td>NTS1, nts2, nts3</td>
<td>Ewing Sarcoma</td>
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<tr>
<td><strong>Substance P</strong></td>
<td>NK-1, Neurokinin-1</td>
<td>Exocrine Pancreatic Tumors</td>
</tr>
<tr>
<td><strong>Bombesin (BB1-3)</strong></td>
<td>NMB, Neuromedin-B, GRP, Gastrin rel. Peptide R BB3</td>
<td>Ileal Carcinoids</td>
</tr>
<tr>
<td><strong>MCR (MC1R)</strong></td>
<td>melanocortin receptor</td>
<td>Prostate Cancer, Breast Cancer</td>
</tr>
<tr>
<td><strong>Neuropeptide Y</strong></td>
<td>Y1-Y6</td>
<td>Bronchial Carcinoids, Glucagonomas</td>
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<tr>
<td><strong>GLP-1</strong></td>
<td>glucagon like peptide R</td>
<td>Melanoma</td>
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<tr>
<td><strong>RGD</strong></td>
<td>αvβ3 Integrin</td>
<td>Breast Cancer, Brain</td>
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<td>Insulinoma</td>
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<td>Angiogenesis</td>
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</table>

*G-protein coupled receptors*
PSMA-Targeting

N-acetyl-L-aspartyl-L-glutamate (NAAG)
Folate-Polyglutamate

N-acetyl-L-aspartate + L-glutamate
Poly-glutamate + Folate

Mesters JR et al. EMBO J 2006; 25: 1375-1384.

Glu-ureido–based PSMA inhibitor
exemplifying rational design of urea-based glutamate carboxypeptidase II inhibitors. Klaus Kopka et al. J Nucl Med 2017;58:17S-26S
**RADIOPHARMACEUTICAL OF THE YEAR**

**225** Actinium-PSMA-617

CRPC

DIFFUSE BONE DISEASE

ALREADY TREATED WITH EVERYTHING

PSA > 400

CRPC

AFTER 1 CYCLE

PSA = 3
Development of quinoline based theranostic ligands for the targeting of fibroblast activation protein (FAP)

- Targeting non-malignant tumour stroma (up to 90% of tumour volume)
- Cancer associated fibroblasts express fibroblast activating protein (glycoprotein, peptidase) in epithelial tumours

**FIGURE 7.** A. Maximum intensity projection (MIP) 1 h after intravenous administration of 270 MBq ⁶⁸Ga-FAPI-04 to one patient with metastasized breast cancer. B. Imaging of Bremsstrahlung 3 h and 1 day after therapeutic treatment with ⁹⁰Y-FAPI-04 of the same patient.
High grade bladder cancer (pT1 GIII, CIS)
- flat, high-grade (GIII), noninvasive urothelial carcinoma
- high risk for extravesical “recurrence” (20%) → therapy by cystectomy
- associated with >50% rate of progression (no watchful waiting)

Targeting w intravesical Bi-213-anti-EGFR immunoconjugates
Local instillation of 350 to 820 MBq (40 ml) Bi-213-anti-EGFR(Cetuximab)
- 12 patients treated: CIS refractory to BCG instillation, histol. proven tu

Results
- Excellent local tolerance w/o any side effects
- 4 / 12 CR (long lasting, up to > 44 months) → avoiding cystectomy
- 4 / 12 SD → postponing surgery/cystectomy

Promising new therapy option
**Arm 1**
- **rituximab**
- **lilotomab 40 mg**
- **177Lu-lilotomab satetraxetan**

**Arm 4**
- **rituximab**
- **lilotomab 100 mg/m²**
- **177Lu-lilotomab satetraxetan**

**lilotomab- (Arm 2+3)**
- **rituximab**
- **177Lu-lilotomab satetraxetan**

†Different regimens of rituximab
Path of a „new“ Radioisotope to the patient

Radionuclide Production

“Cold“ Chemistry

Radiochemistry

Biological characterization in vitro

Biological characterization in vivo

Pharmaceutical formulation

Clinical Trial

Medicinal Product
What are (therapeutic) Radiopharmaceuticals?

Medical Devices vs. Medicinal Products

- **Sealed sources** *(SIRTEX®, TheraSphere®)*: Medical Device
- Other therapeutic radiopharmaceuticals: Medicinal Products
  → new (therapeutic) radiopharmaceuticals are usually
  **Investigational Medicinal Products (IMPs)**

**EANM support for**

→ Development within **controlled, prospective Clinical Trials according to current regulations**
Are all clinical translations of radiopharmaceuticals in Europe „Clinical Trials“?

National regulations allow(ed) the use of (new) radiopharmaceuticals **outside the strict EU definition** of a clinical trial

- „Compassionate Use“
- „Experimental Radiopharmaceuticals“
- „Compounding“ Practice
- Other specific National Procedures

May require authorisation by an ethical board, local or national authority
Authorisation of a „trial“, Authorisation of the „drug“

→ $^{68}$Ga/$^{177}$Lu-DOTA-Somatostatin analogues
→ $^{68}$Ga-PSMA-11, CXCR4, Bombesins…

Not supported by EANM
A radiopharmaceutical (and Medicinal Product) is?

Directive 2001/83/EC, Article 1

6. **Radiopharmaceutical:**
Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

7. **Radionuclide generator:**
Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.

8. **Kit**
Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.

9. **Radionuclide precursor:**
Any other radionuclide produced for the radiolabelling of another substance prior to administration

**Legal Implications:** Directive applies to these products including requirement for authorisation of the institution, licensing (marketing authorization), responsibilities, distribution, labelling……..
Radiopharmaceuticals, radionuclide generators, kits and radionuclide precursors are Medicinal (Drug) Products.

In radionuclide generators both mother and daughter radionuclide are considered as Drug Substance (Active Substance, Active pharmaceutical ingredient API).

A new radionuclide legally has to be considered either as Medicinal Product or API.
<table>
<thead>
<tr>
<th>Type of manufacture</th>
<th>Non-GMP*</th>
<th>GMP Part I &amp; II (increasing) including relevant annexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPs, PET RPs, radioactive precursors</td>
<td>Reactor/cyclotron production</td>
<td>Chemical synthesis</td>
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<tr>
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<td>Purification steps</td>
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<tr>
<td></td>
<td></td>
<td>Processing, formulation and dispensing</td>
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<tr>
<td></td>
<td></td>
<td>Processing, final sterilization</td>
</tr>
<tr>
<td>Radionuclide generators</td>
<td>Reactor/cyclotron production</td>
<td>Processing</td>
</tr>
</tbody>
</table>

*target and transfer systems from cyclotron to synthesis rig may be considered as the first step of active substance manufacture*
GMP – Good Manufacturing Practices

Directive 2003/94/EG → GMP Annex 13 (IMP’s)

GMP is mandatory for IMP Production

A new radiopharmaceutical is an IMP

Valid for:

Radiopharmaceutical in clinical Trial

Active Pharm.Ingredient (API, “drug substance”)

“API starting materials” (chemical precursors)?

Radionuclide Precursors?
Path of a „new“ Radioisotope to the patient
Be ware of G`s

„Cold“ chemistry
Radionuclide Production
Radiochemistry
Biological characterization in vitro
Biological characterization in vivo
Pharmaceutical formulation
Clinical Trial
Medicinal Product

„Cold“ chemistry
Radionuclide Production
Radiochemistry
Biological characterization in vitro
Biological characterization in vivo
Pharmaceutical formulation
Clinical Trial
Medicinal Product

GMP
GLP
GCP

1E-4 1E-3 0,01 0,1 1 10 100 1000
0,0
0,5
1,0
1,5
2,0
2,5
3,0

bound [% of total]
peptide conjugate [nM]
peptide conjugate        IC50 [nM]
 DOTA-MG11             1,07
 HYNIC-MG11            1,74
 Minigastrin I human   1,15

N N
HOOC
HOOC COOH
O
O
NH
NH
NH
O
O
O
NH
NH
O
NH
NH
O
O
OH
H2N
S
S
HN
OHOH
OH
NH
EANM & „novel“ Radionuclides

- EANM understands itself as representing the whole NM community, and has not defined a particular research area of interest.
- EANM cannot serve as official partner in research projects, but is glad to provide support (suggesting experts, providing dissemination channels, networking, regulatory activities,...)
- **Therapeutic radiopharmaceuticals** are seen as a **very important** segment for NM in the years to come.
- EANM is supporting the translation of novel (theranostic) radiopharmaceuticals within **controlled prospective clinical trials**.
- The **regulatory** environment is seen as a **major hurdle** and in particular initiatives for easy and reliable provision of (novel) radionuclides are in the focus of the EANM.
Thank you for your attention