ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

UniversitätsSpital Zürich

PAUL SCHERRER INSTITUT
PSI

Wider Horizons for Pharmacists

Radiopharmacy

Prof. Roger Schibli
Department of Chemistry and Applied Biosciences ETHZ
Center for Radiopharmaceutical Science ETH-PSI-USZ

Radiopharmacy?

Radiopharmacy!

- ***Radiopharmacy*** (= ***Nuclear pharmacy***) is a branch of pharmacy, which deals with the preparation, characterization and quality of ***radioactive materials for use in nuclear medicine procedures***
- A ***Radiopharmaceutical*** *(radiotracer, tracer)* is a radioactive compound for diagnosis and therapy of human diseases.

The Center for Radiopharmaceutical Sciences (CRS)

- Founded 1997 (PSI-USZ); 2005 (ETH); 2010 new Head
- Ca. 50 FTE (Prof., PhD, PostDocs, PhD students, staff)

Dept. Chemistry and Applied Biosciences

Department of Biology and Chemistry

Dept. for Nuclear Medicine

The Radiotracer Principle

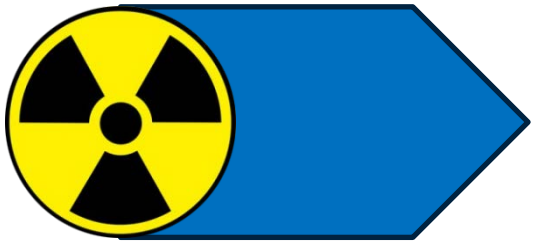
- A radioactive tracer is a chemical compound in which one or more atoms have been replaced by a radioisotope. It is applied in minimal amounts, therefore, it has no pharmacologic effect in vivo. It can also be used to explore the mechanism of bio-/chemical reactions by tracing the path that the radioisotope follows from reactant to product

George de Hevesy

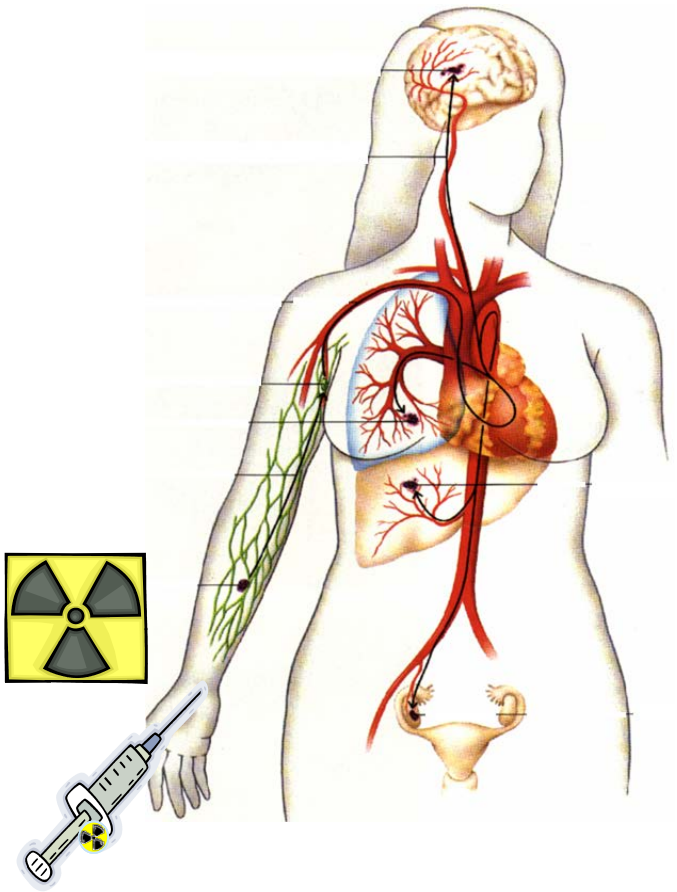
Noble Prize (1943):„…"for his work on the use of isotopes as tracers in the study of chemical processes" “

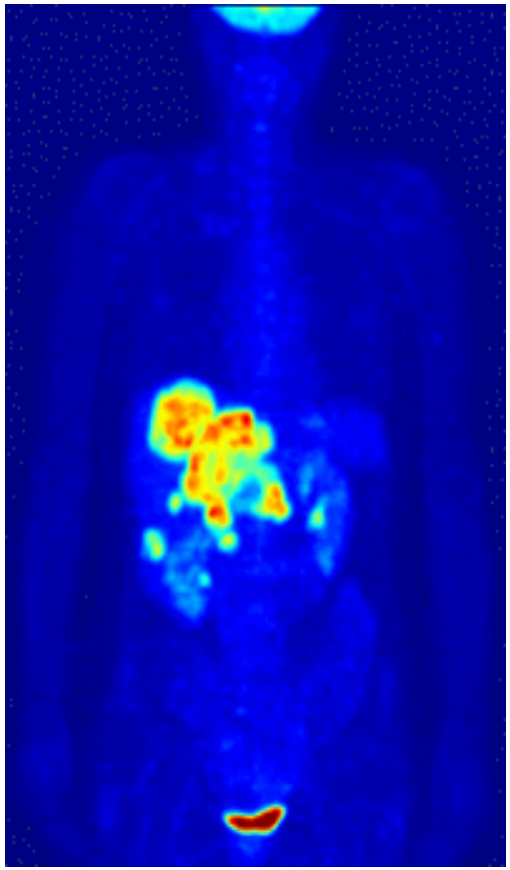
General Design of a Modern Radiopharmaceuticals

Radioactive part	Non-radioactive part
Radionuclide Defines the physical parameters such as physical half-life ($^{phy}T_{1/2}$) and type of radiation for diagnosis or therapy	**Chemical and/or biological part** Defines the biological parameters such as biological half-life ($^{biol}T_{1/2}$) and specificity



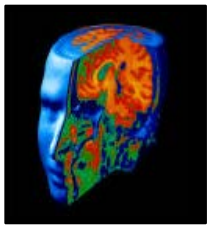
Principles of Nuclear Diagnosis





Spectrum of Imaging Techniques

Imaging Method	Spatial resolution	Sensitivity
Ultrasound	50 µm	10^{-3} Mol
CT	50 µm	10^{-3} Mol
MRI	100 µm	10^{-5} Mol
Bioluminescent	1-3 mm (depth!)	10^{-8} Mol
Nuclear*	***> 5 mm***	***10^{-9}-10^{-12} Mol***



Morphology

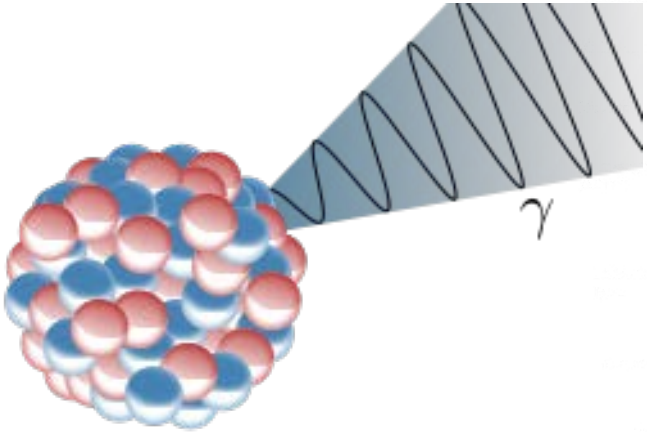
Function

E.g. 370 MBq of ^{11}C-tracer necessary for a brain scan with ^{11}CPIB corresponds to 100 picogram total mass injected.

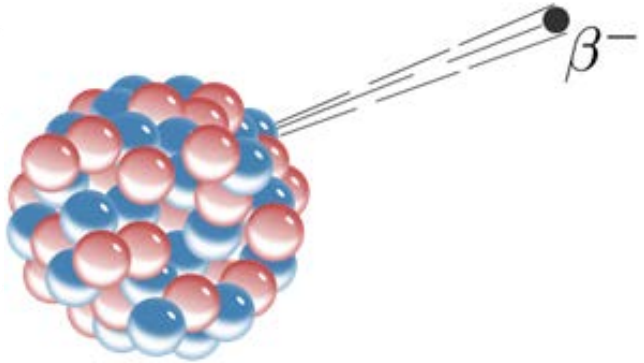
Radiopharmaceuticals are also Role Models for «Theragnostics»

Diagnosis and Therapy with one and the same method

Diagnostic isotopes



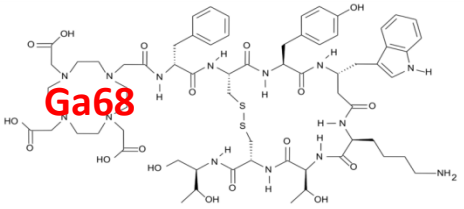
Therapeutic isotope



«Theragnosis» of Neuroendocrine Tumors

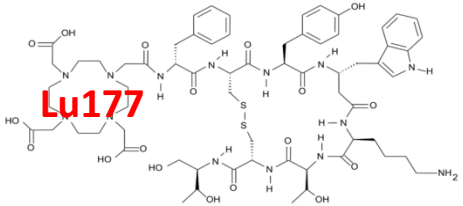
Diagnostics

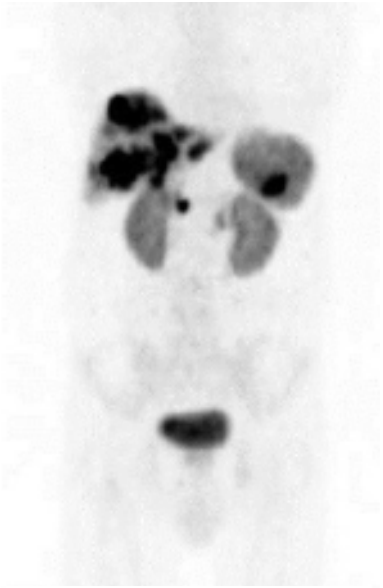
68 Gallium – DOTATATE



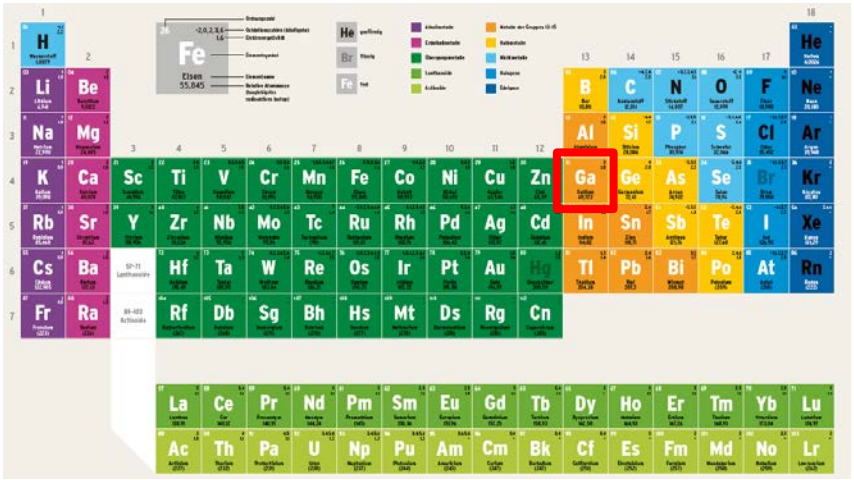
Therapy

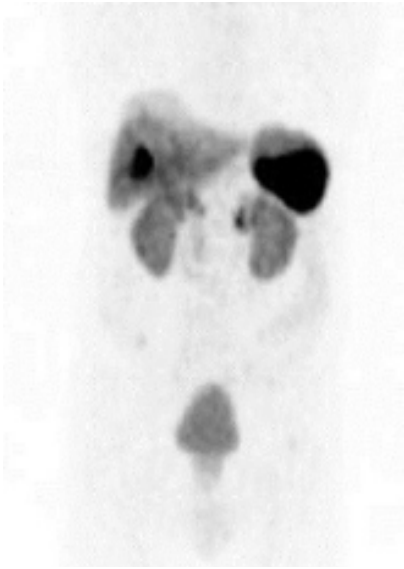
177 Lutetium – DOTATATE





PET/CT pre therapy



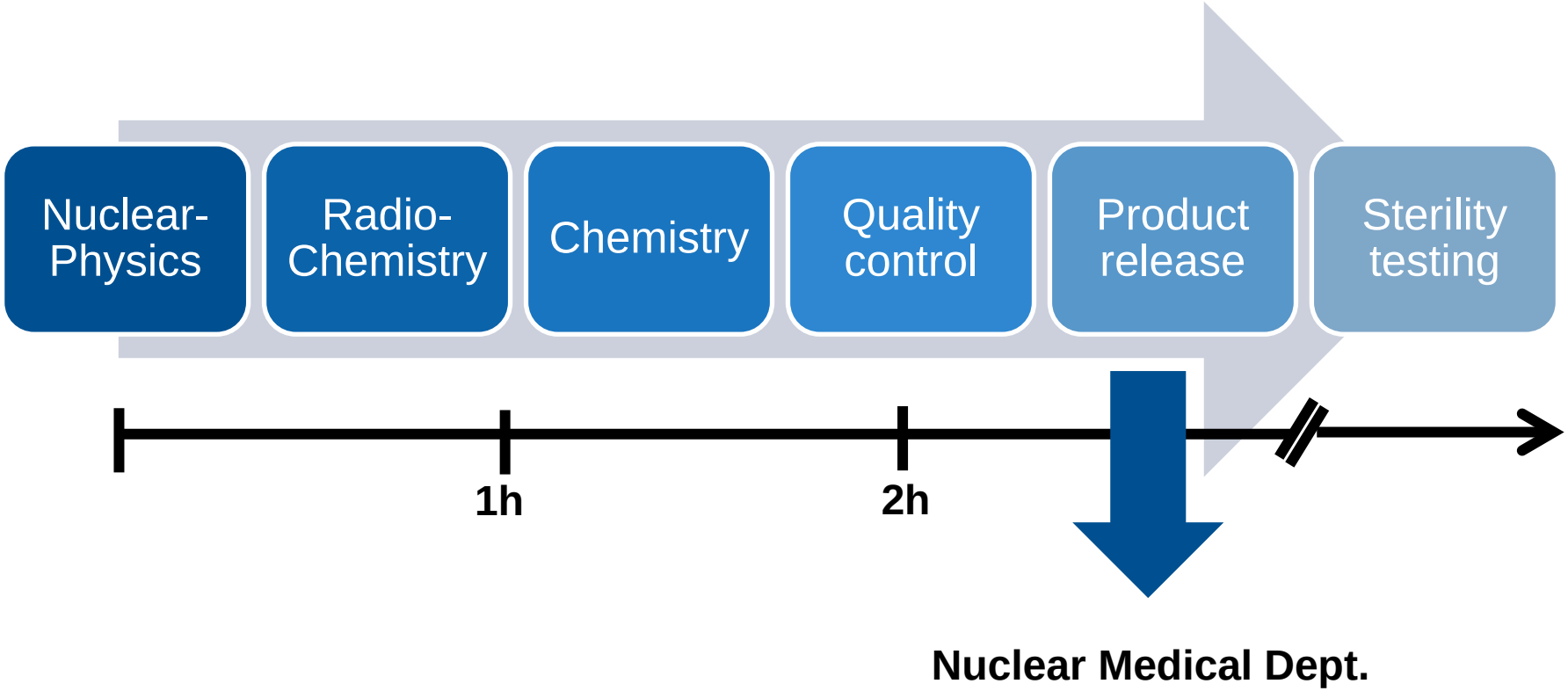


PET/CT post therapy

Baum RP et al. THERANOSTICS: From Molecular Imaging Using Ga-68 Labeled Tracers and PET/CT to Personalized Radionuclide Therapy. Theragnostics. 2012

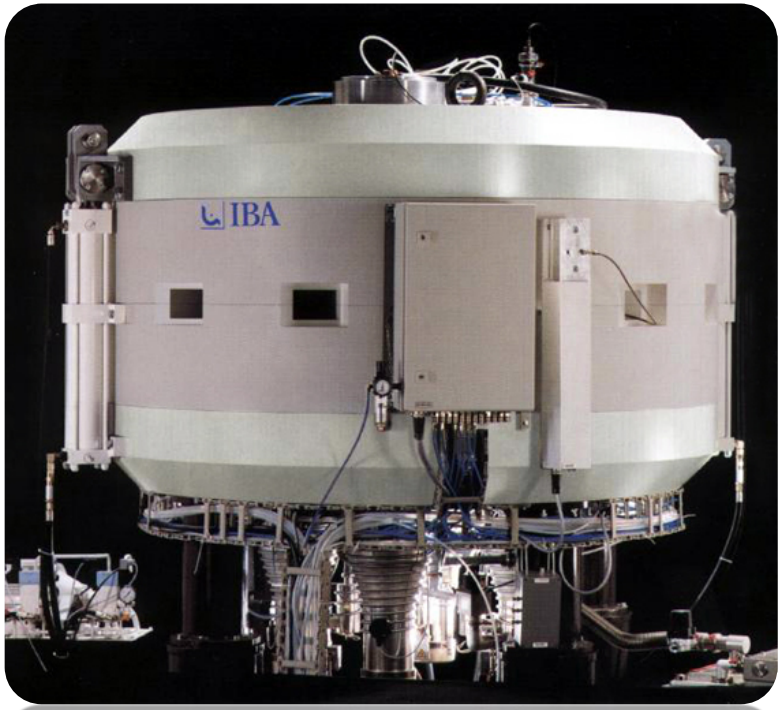
Prof. N. Schäfer wird verdankt

Preparation of Radiopharmaceuticals: *Daily* a multidisciplinary endeavor



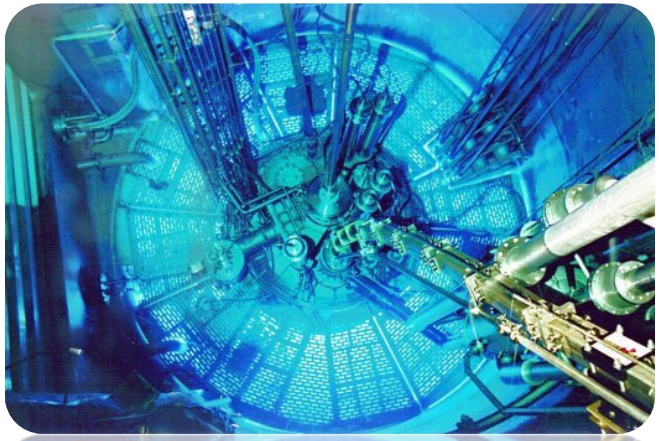
Radionuclide Production

Cyclotron



E.g.: C-11, N-13, O-15
F-18, Cu-64, In-111, I-123

Reactor: Neutron bombardment

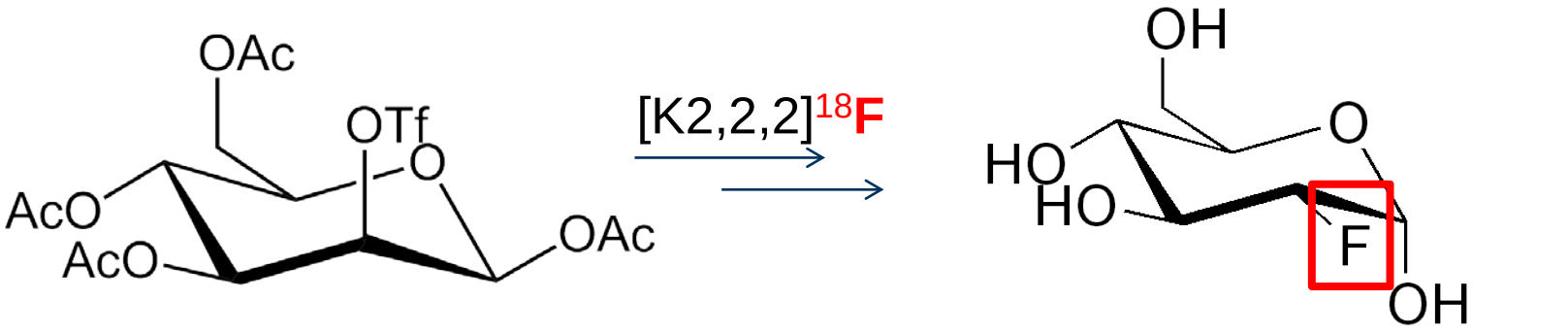


E.g.:
I-131
Sm-153
Ho-166
Lu-177
W-188

On-site generators

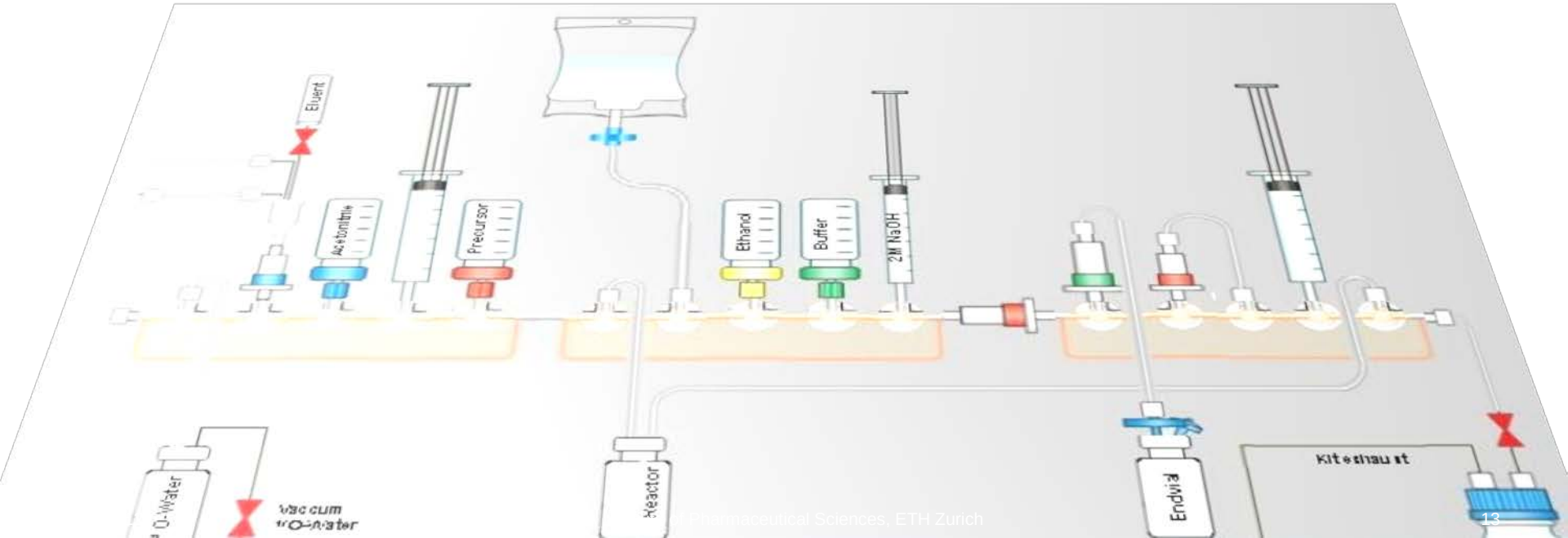
E.g.:
Ga-68
Tc-99m
Re-188

Radiosynthesis of [^{18}F]-2-Fluordesoxy-glucose (FDG)

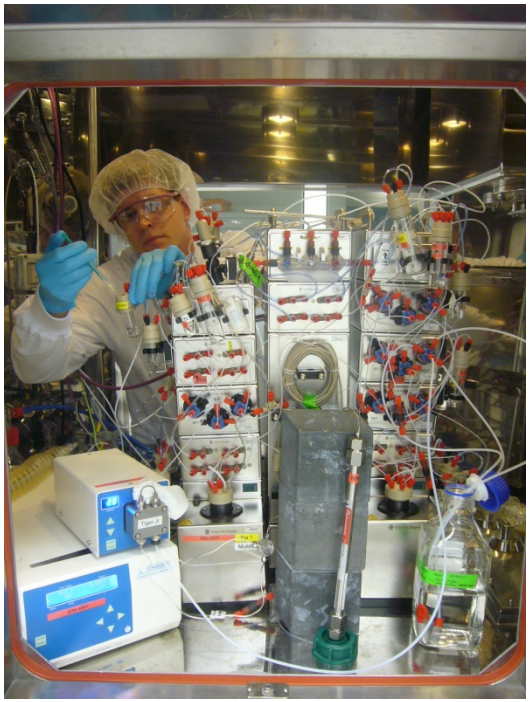


Mannose

[^{18}F]-2-Fluordesoxy-glucose (FDG)

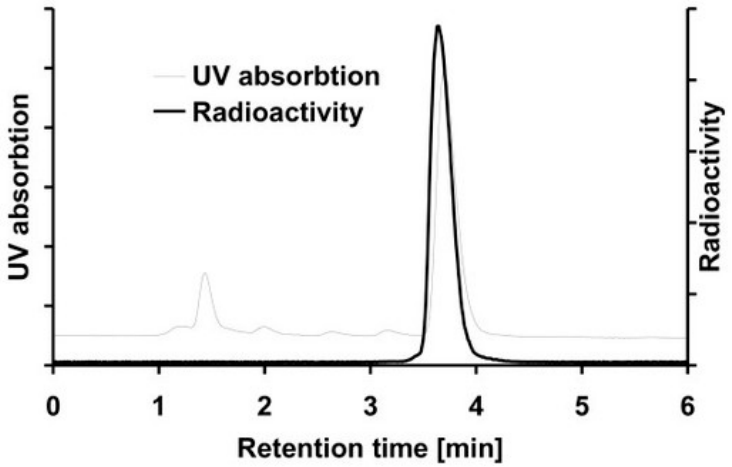


Synthesis of Radiopharmaceuticals according to GMP



Quality Control of Radiopharmaceuticals

- Isotope purity & Radionuclide identity
- Dosage of radioactivity
- Radiochemical purity
- Chemical purity
- Sterility
- Apyrogenicity
- Visible purity
- pH



Important β+ Emitters in Radiopharmacy

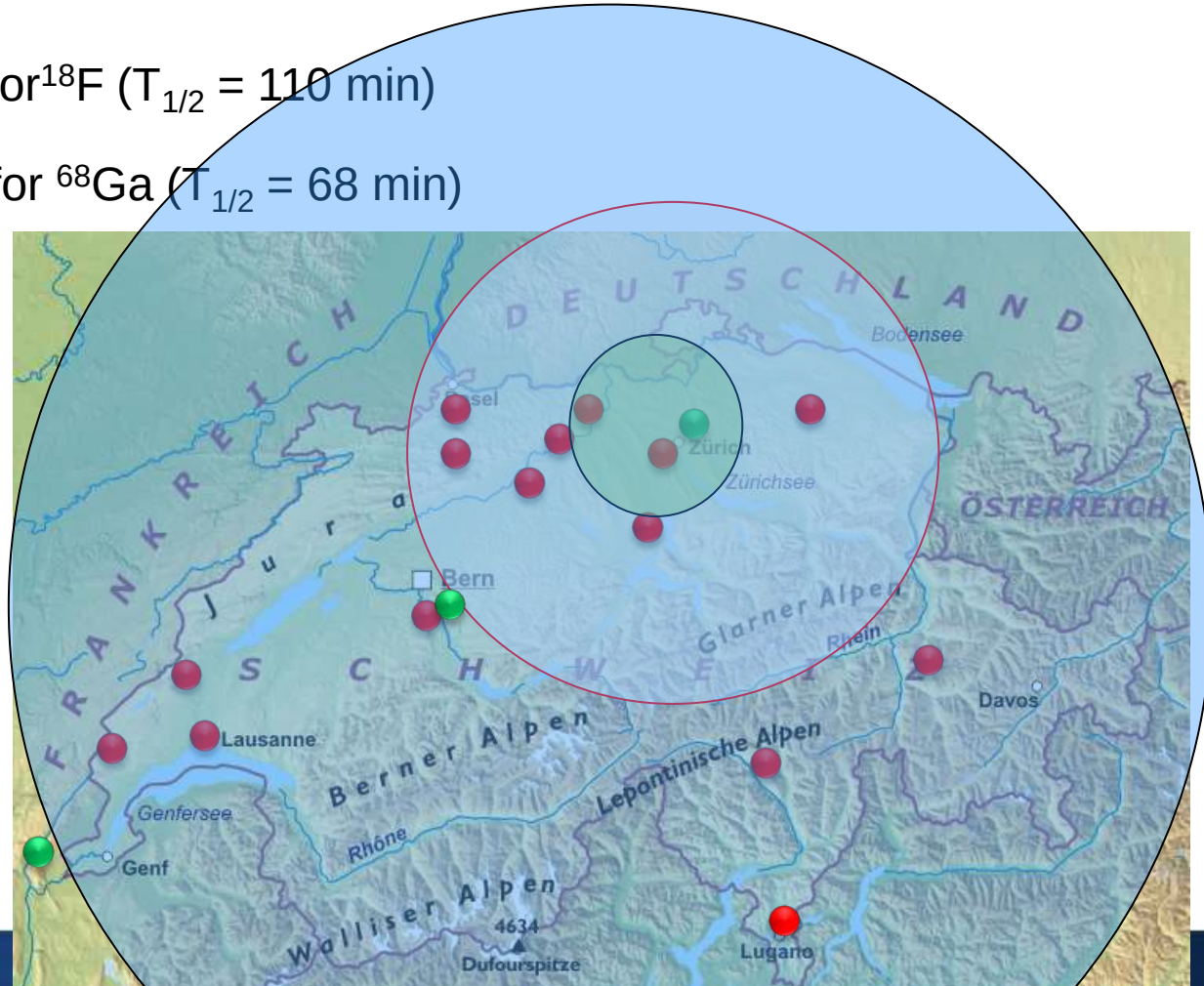
Radionuclide	$T_{1/2}$	Mean β^+ energy (keV)	Resolution (mm)
^{11}C	20 min	386	1.1
^{15}O	2 min	735	1.5
^{18}F	110 min	250	0.7
^{64}Cu	12.7 h	278	0.7
^{68}Ga	1.1 h	830	2.4
^{76}Br	16.3 h	1180	3.2
^{124}I	4.17 d	820	2.3
^{89}Zr	3.27 d	396	1.1

From *decentralized* to *centralized* production: Logistic & Commercial Challenges for Radiopharmacies

= optimal radius for ^{44}Sc ($T_{1/2}$ = 3.9 h)

= optimal radius for ^{18}F ($T_{1/2}$ = 110 min)

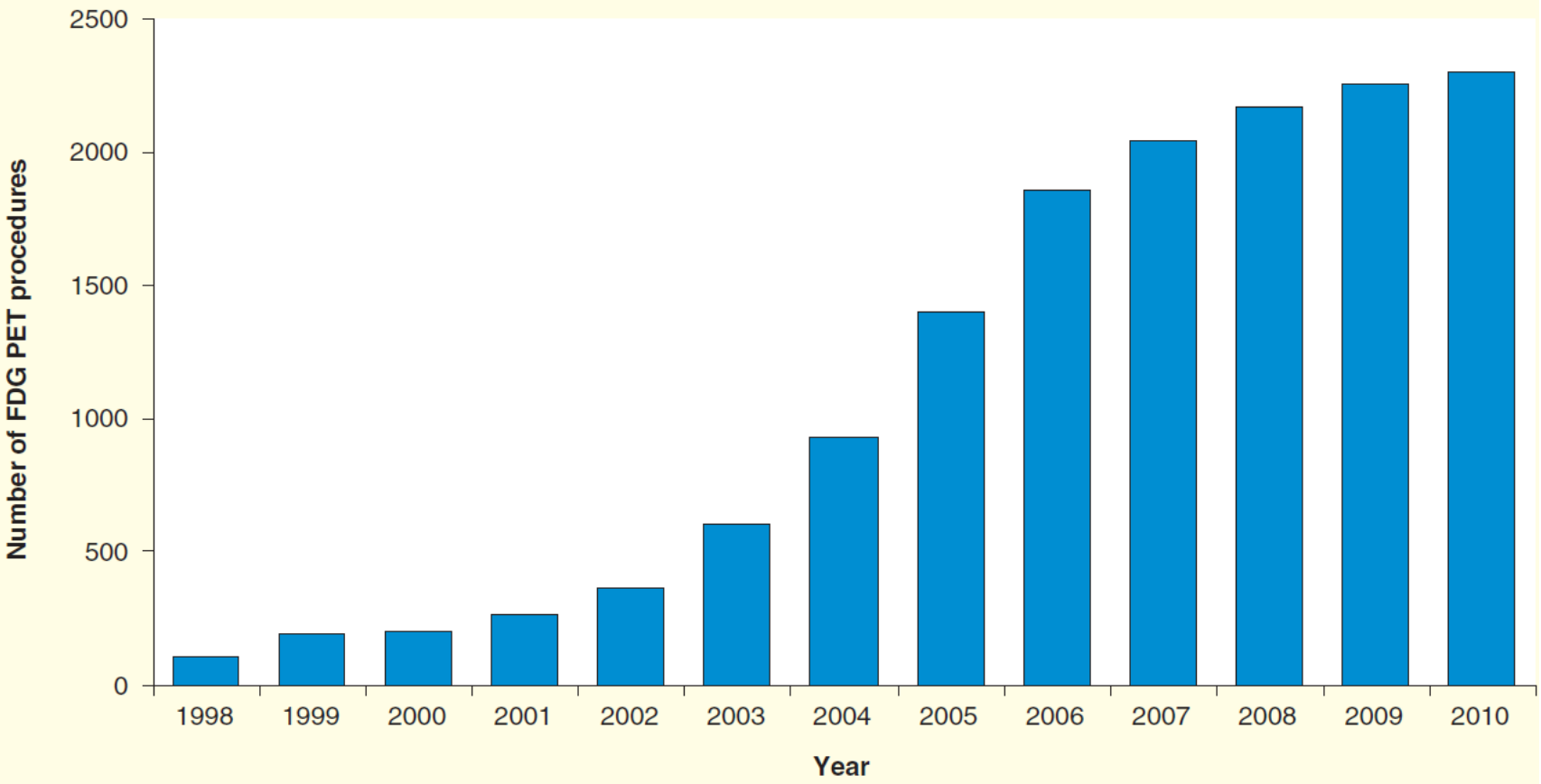
= optimal radius for ^{68}Ga ($T_{1/2}$ = 68 min)



- Nucl. Med. Dept.
- Rad. Pharm. with cyclotron

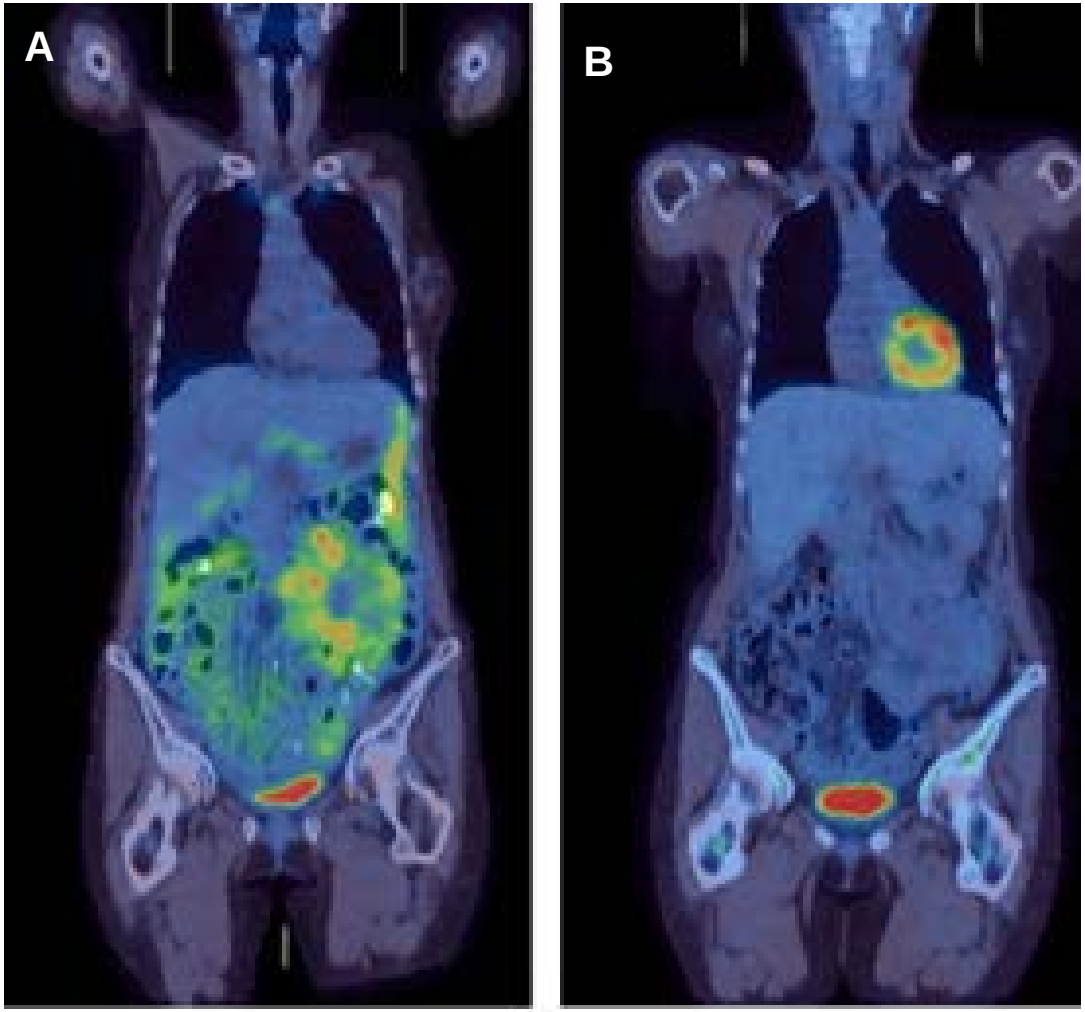
[^{18}F]-FDG: The Working Horse in Nuclear Medicine

- Number of [^{18}F]-FDG scans in the USA(x1000)



Expert Rev. Mol. Diagn.

Combination of Functional and Morphological Imaging (PET/CT) Changed the Patient Care in Medicine



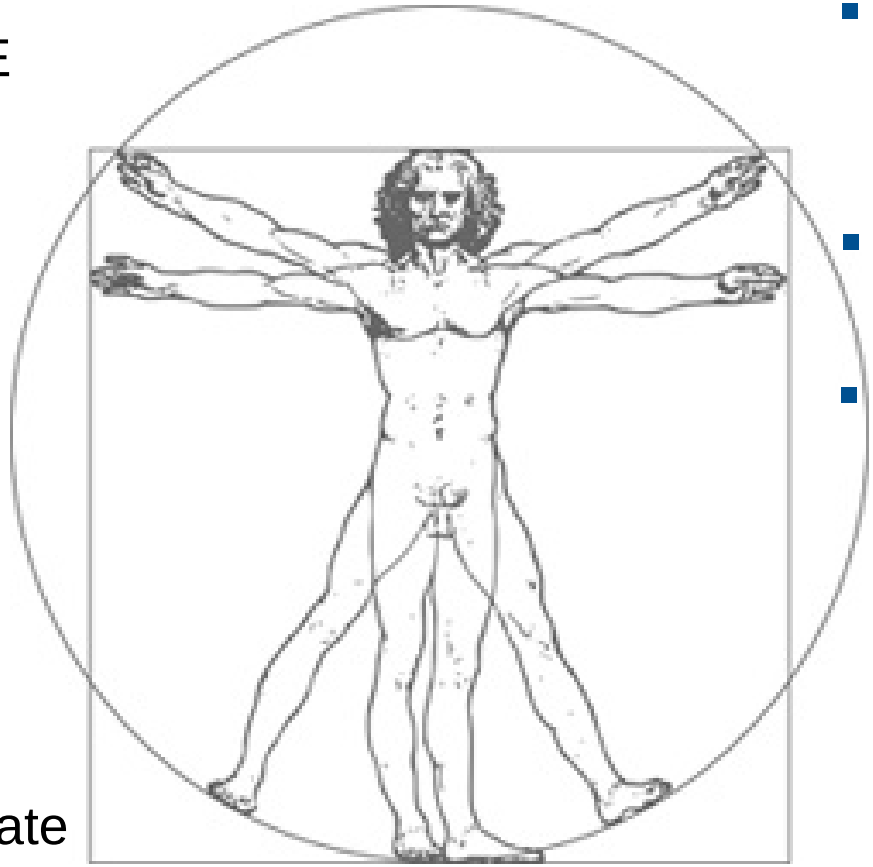
[^{18}F]-FDG/CT:

(A) At staging, patient with diffuse large B-cell lymphoma

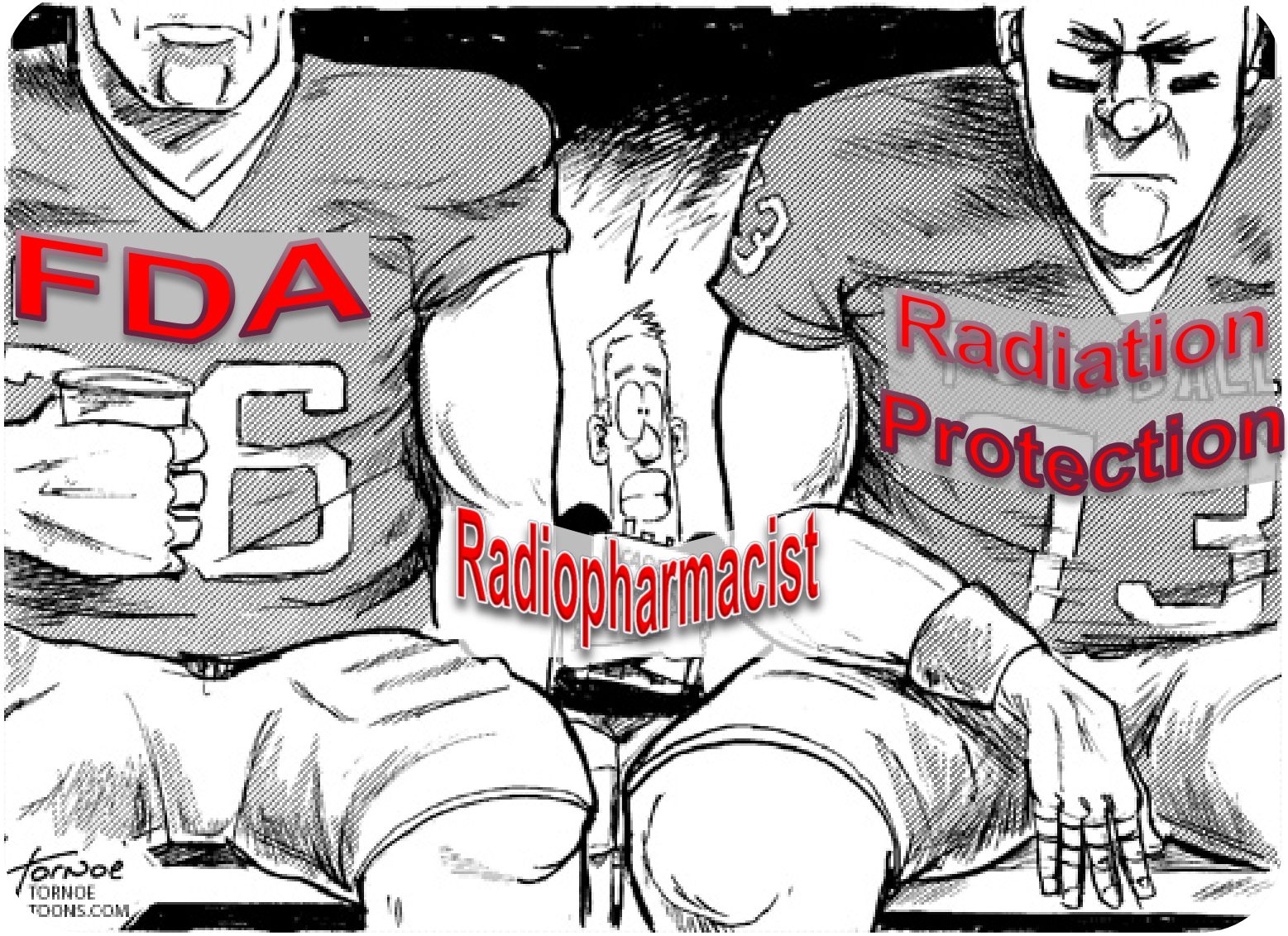
(B) Interim scanning after 2 cycles of chemotherapy showed complete response.

Clinically Approved Radiotracer Daily Produced

- ^{68}Ga-DOTATATE
- ^{177}Lu-DOTATATE
- ^{90}Y-Zevalin
- Na^{18}F
- ^{18}F-FDG
- ^{18}F-Choline
- ^{18}F-DOPA
- ^{18}F-FET
- ^{11}F-Flutametamol
- ^{15}O-H_2O
- ^{13}N-NH_3
- ^{99m}Tc-Pertechnetate
- ^{99m}Tc-MDP



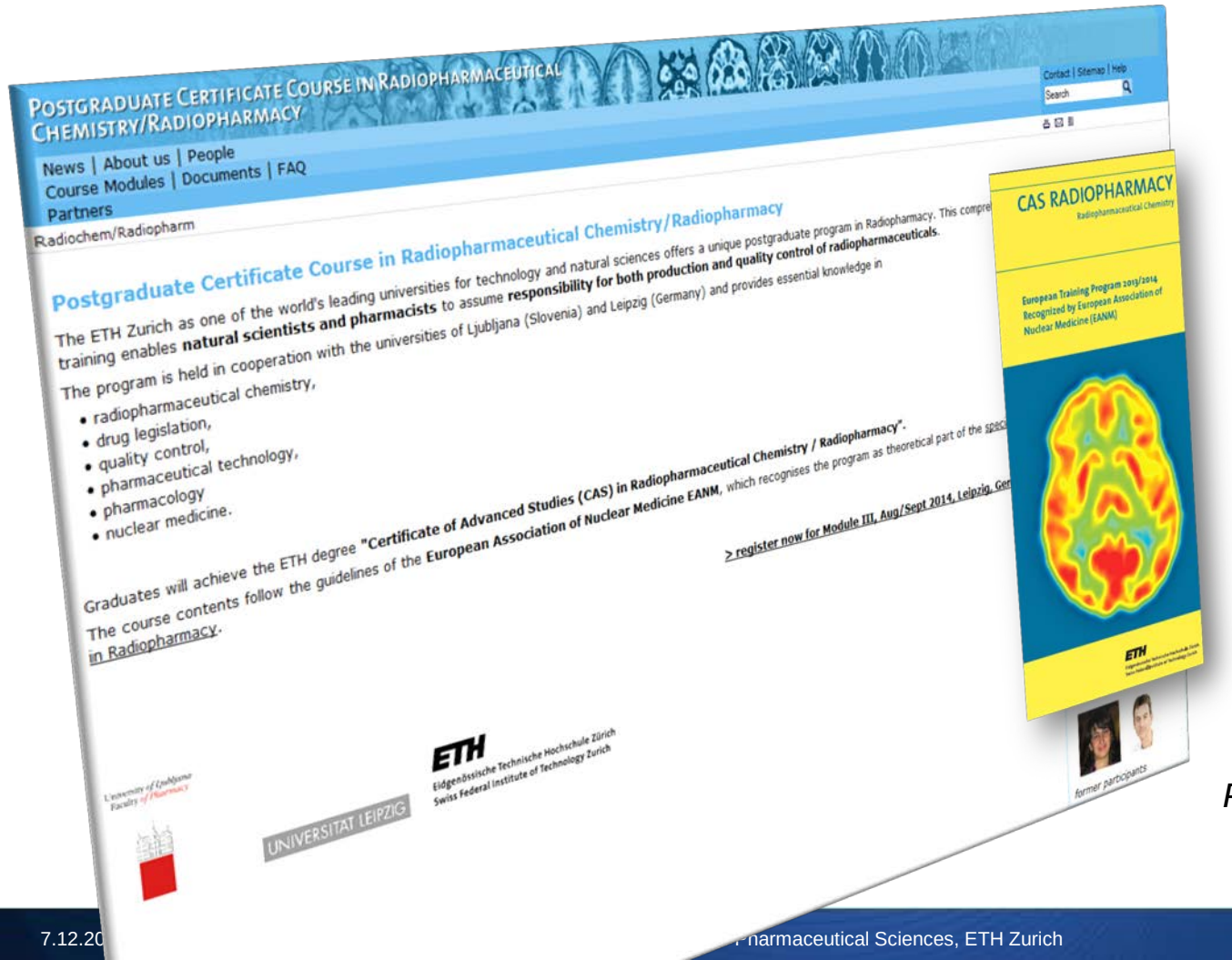
- ^{99m}Tc-Nanocol
- ^{99m}Tc-MAG3
- $^{223}RaCl_2$
- ^{99m}Tc-HMPAO
- ^{99m}Tc-EDC
- ^{153}Sm-EDTMP
- Na^{131}I
- ^{131}I-MIBG
- ^{131}I-Bexxar
- ^{18}F-MISO
- ...


FDA
Radiation Protection
Radiopharmacist
TORNOE
TOONS.COM

There are Master and Post Graduate Courses in Radiopharmacy

«Radiopharmaceutical Chemistry» is a mandatory part of the ETH Bachelor Pharmacy curriculum (2 ECT)

Accreditation of Courses by the European Soc. Nuclear Medicine



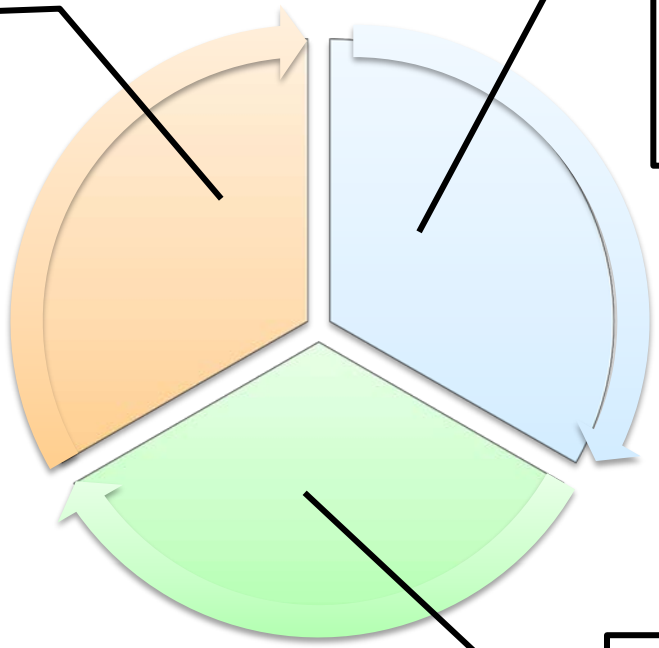
Prof. T. Gmeiner Stopar

Prof. M. Schulz-Siegmund

Post-Graduate Course in Radiopharmacy in Europe

Completed a nationally acceptable course on radiation safety.

University postgraduate diploma courses (three modules à 2 weeks)



Open for pharmacists, chemists, biochemists and biologists (min. Master level)

Completed a two-year period of experience in a radiopharmacy

Content of the Post Graduate Course

Block 1: Pharmacy (Uni. Ljubljana)

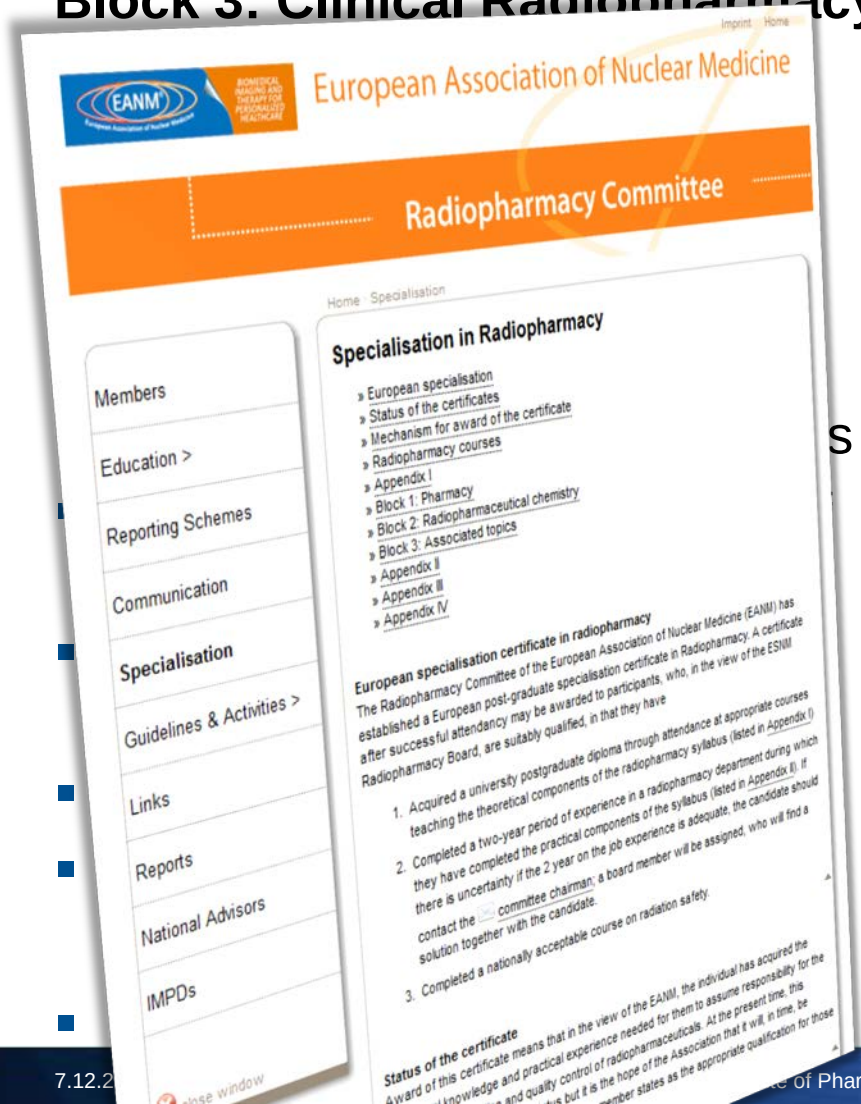
- Pharmaceutical Technology
- Implications of GMP
- Sterile Manufacture
- Pharmaceutical microbiology
- Parenteral Products
- Formulation and Packaging
- Pharmaceutical Analysis
- Pharmacopoeia monographs
- Quality Control Procedures Stability and Shelf Life
- Biopharmacy (Pharmacokinetics, membrane transport, biodistribution, metabolism)
- ….

Radiopharmaceutical chemistry

- Physics of radioactivity
- Production of radionuclides in nuclear reactor and cyclotron
- Targetry, nuclear chemistry, generators
- PET - radiopharmaceuticals (^{18}F, ^{11}C, ^{13}N, ^{15}O)
  Synthesis of labelled compounds
- Bioconjugation chemistry
- Radionuclides in analytics, autoradiography
- ^{99m}Tc-radiopharmaceuticals
- Animal models
- …

Content of the Post Graduate Course & Conditions for EANM Certificate

Block 3: Clinical Radiopharmacy



Practical Components (2 years)

- Working in a sterile environment
- Design and application of a quality assurance program
- Use of safe radiation practices,
- Use, maintenance and calibration of equipment used in radiopharmacies
- Procurement of Radiopharmaceuticals
- Radiopharmaceutical preparation
- Quality control of radiopharmaceuticals
- Supply of radiopharmaceuticals
- …

Radiopharmacists are national and international organized in Societies

Summary & Conclusion

- Radiopharmacy and radiopharmaceutical preparation is multi-disciplinary endeavor
- There is a clear trend from decentralized to centralized radiopharmaceutical production with qualified personnel in qualified environment due to increasing regulations
- Pharmaceutical, (radio)chemical and radiophysical/ radiation protection know-how is essential
- Education of radiopharmacists is necessary at the University level (master or higher) to cope with complexity
- International standards have to be achieved to shape the future of radiopharmacy

Acknowledgment

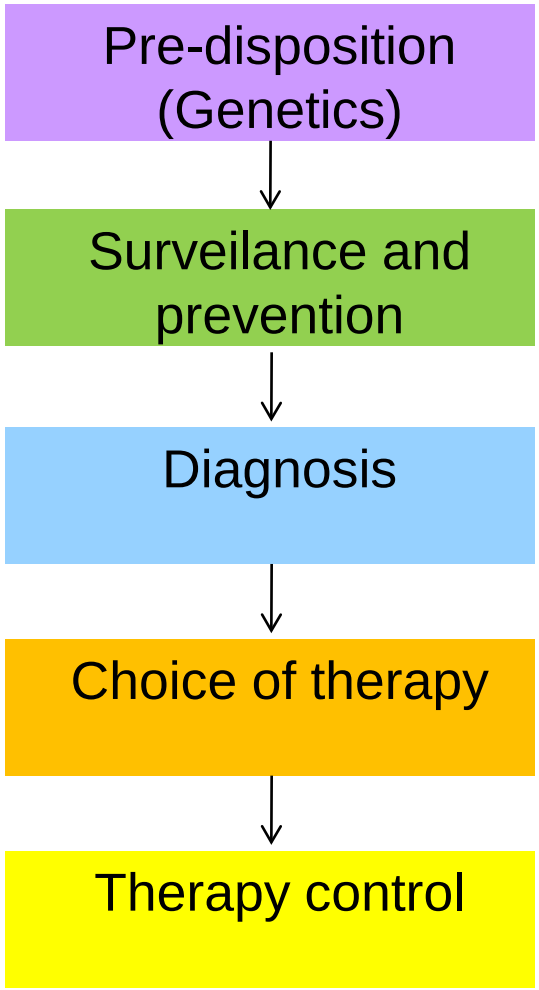
- President of Scientific Committee (Prof. Dr. Borut Božič)
- Prof. Irena Mlinarič-Raščan
- Prof. Prof. T. Gmeiner Stopar

- Dr. Angela Küng & Regular Furegati (ETH)

University of Ljubljana
Faculty of Pharmacy

EAFP EUROPEAN ASSOCIATION OF FACULTIES OF PHARMACY

Radiotracer and radiopharmaceuticals play an important role in personalized medicine

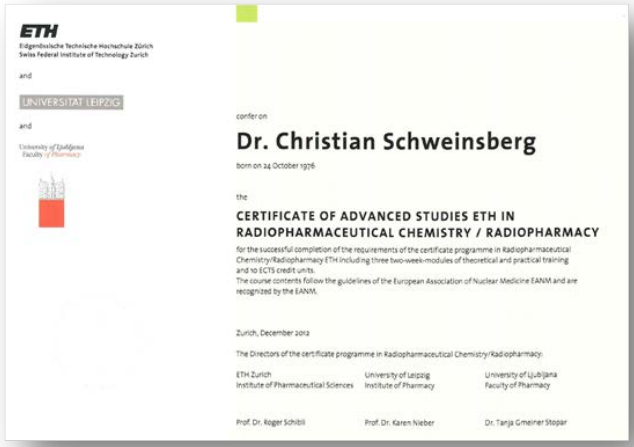


- Diagnosis & Therapy control
  - Protein expression (receptors, enzymes)
  - Protein function(transport, metabolism)
  - Assessment of biological function (e.g. blood flow)
- Drug development
  - Efficiency
  - Pharmacokinetics
- Therapy
  - Optimize therapy of specific cancer

Examinations and certificates 2011/12

	Module	Module II	Module III
participants	28	26	21
examinees	26	22	20
examination centers	7	6	10
success rate	100 %	100 %	100 %
graduates of CAS	6	2	9

17 graduates at present cycle


ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich
and
UNIVERSITÄT LEIPZIG
and
confer on
Dr. Christian Schweinsberg
born on 24 October 1976
the
CERTIFICATE OF ADVANCED STUDIES ETH IN RADIOPHARMACEUTICAL CHEMISTRY / RADIOPHARMACY
for the successful completion of the requirements of the certificate programme in Radiopharmaceutical Chemistry/Radiopharmacy ETH including three two-week-modules of theoretical and practical training and 10 ECTS credit units.
The course contents follow the guidelines of the European Association of Nuclear Medicine EANM and are recognized by the EANM.
Zurich, December 2012
The Directors of the certificate programme in Radiopharmaceutical Chemistry/Radiopharmacy:
ETH Zurich
Institute of Pharmaceutical Sciences
University of Leipzig
Institute of Pharmacy
University of Ljubljana
Faculty of Pharmacy
Prof. Dr. Roger Schibli
Prof. Dr. Karen Nieber
Dr. Tanja Gmeiner Stopar

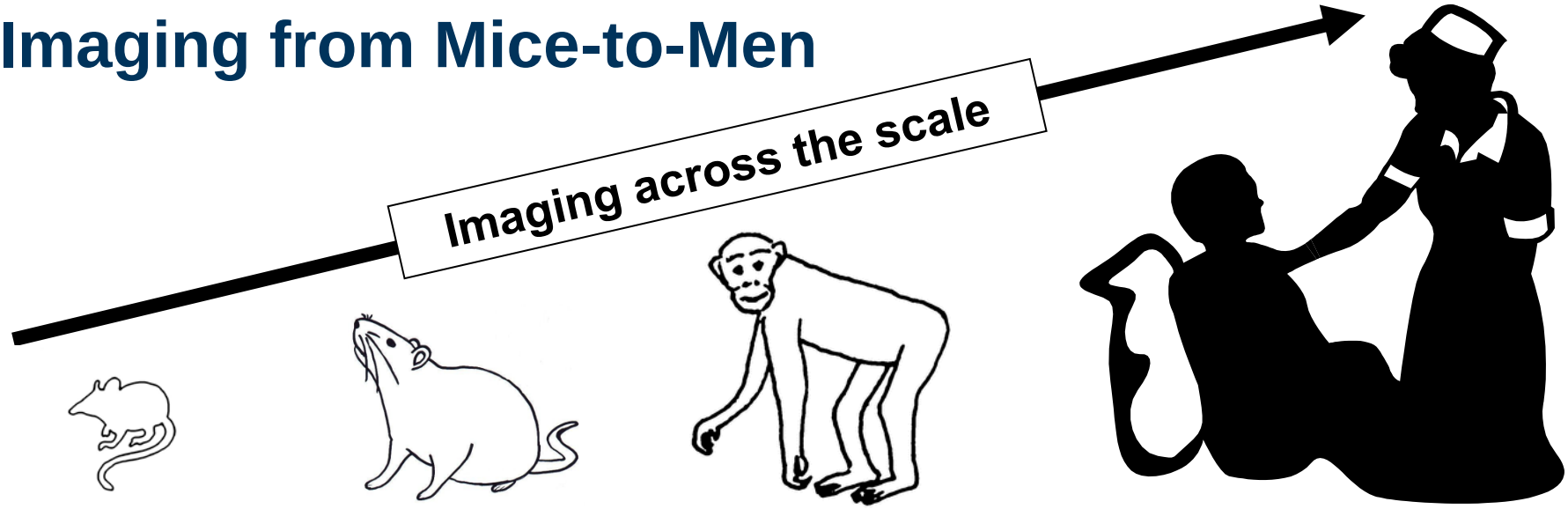
Financial aspects

Costs for entire CAS program

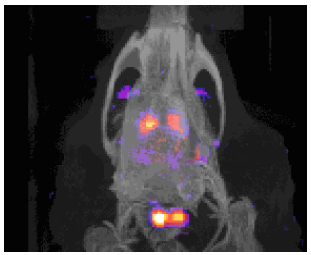
Study fees payable to ETH “Schulgeld”	CHF 17’400.-
Advisory board meeting	CHF 3’500.-
Promotion (Advertisement, Flyers, Mailing, Website)	CHF 6’000.-
ETH visit of partner university during course	CHF 2’000.-
total	**CHF 28’900.-**

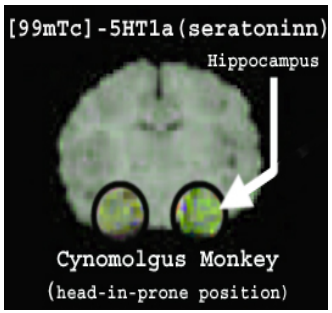
(occuring biannually, based on 30 participants)

Imaging from Mice-to-Men

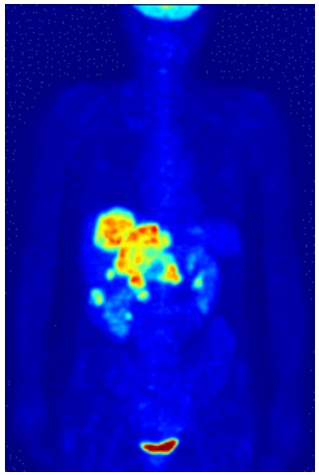


Pre-clinical



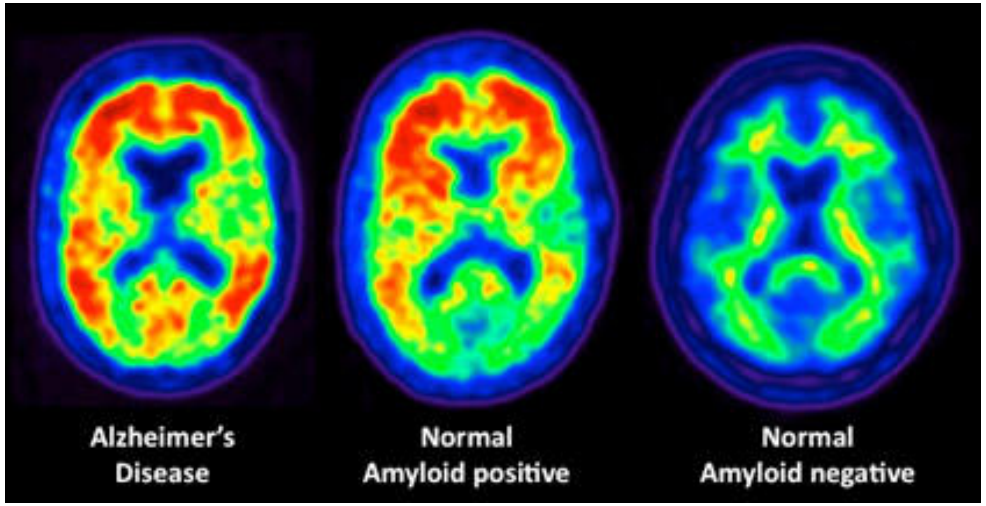


Clinical

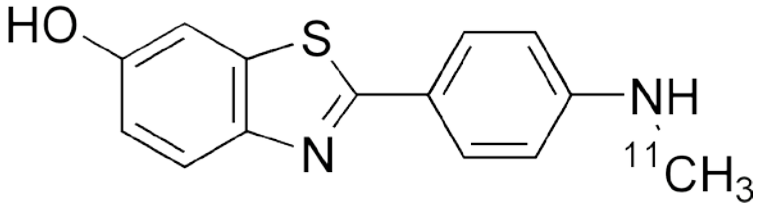


Radiopharmaceuticals are ideal for non-invasive imaging

Hieronymus Bosch Entfernung des Wahnsinnssteines



Detection of beta-amyloid plaques, the pathologic hallmarks of Alzheimer's disease in brain tissue via ^{11}C-PIB



(Pittsburgh compound B)