



Radiopharmazeutische Chemie II Anwendungen und GMP

Master – Studiengang
Medizinphysik-Experte



PET Biomarker für Patienten

– Status Tübingen –

[¹⁸ F]FDG	Tumore, Herz etc.	Zulassung
[¹¹ C]Choline	Prostata CA	Herstellungserlaubnis
[¹¹ C]Methionine	Hirntumore	Herstellungserlaubnis
[¹⁸ F]FMISO	Tumore	Herstellungserlaubnis
[¹¹ C]PIB	M. Alzheimer	Herstellungserlaubnis
[¹¹ C]Raclopride	Neurologie, Psychiatrie	Herstellungserlaubnis
[⁶⁸ Ga]DOTATATE	Neuroendokrine Tumore	AMG §13 2b
[⁶⁸ Ga]PSMA-11	Prostata CA	AMG §13 2b
[¹⁸ F]FETHyl-Tyrosine	Hirntumore	AMG §13 2b
[¹⁸ F]FETHylcholin	Prostata CA	AMG §13 2b
[¹⁸ F]Fluorid	Knochen (Tumore)	AMG §13 2b
[¹⁸ F]FLT	Tumore	AMG §13 2b
[⁶⁴ Cu]NOTA-GP6	Atherosclerotic Plaques	AMG §13 2b
[⁶⁴ Cu]DOTA-CD19-AK	CD19 positive Tumore	AMG §13 2b
[⁶⁴ Cu]NOTA-GD2-AK	GD2 positive Tumore	AMG §13 2b





PET-Messung neurobiologischer Hirnprozesse

Status von Rezeptoren und Neurotransmittern

Fehlfunktionen z.B. bei:

Morbus Parkinson

Alzheimer

Schizophrenie

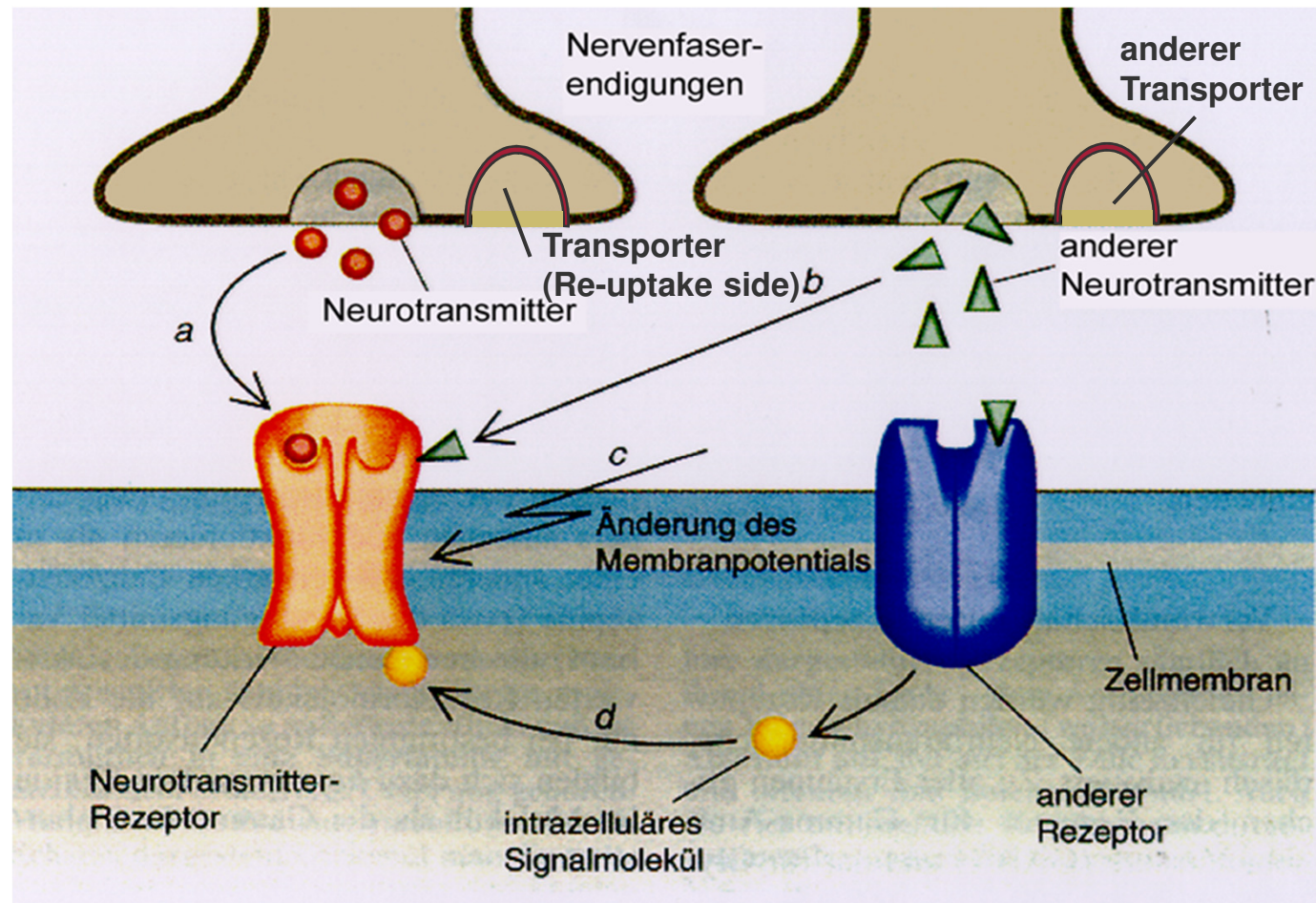
Depression

Sucht etc.



Synapsen

- Neurotransmitter, Rezeptoren und Transporter -





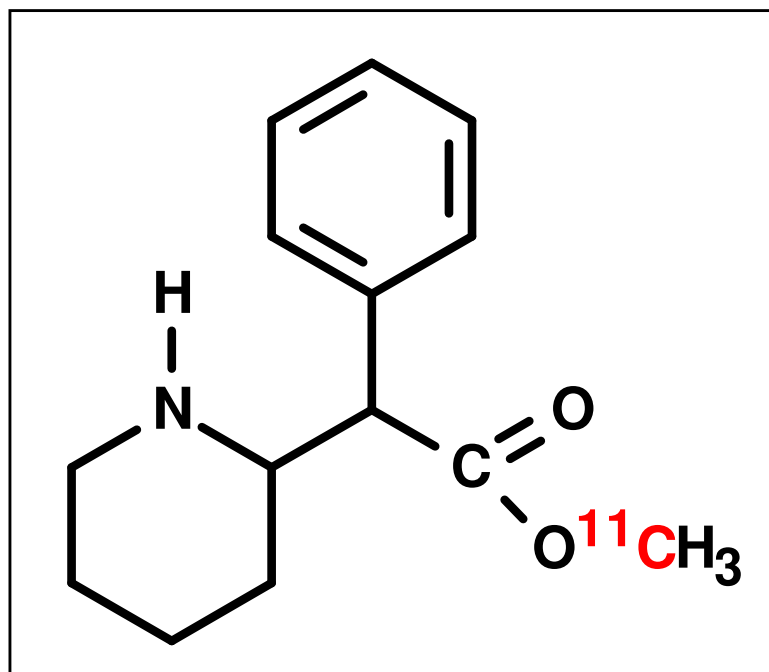
Neurobiologische PET-Projekte

Tracer	Neurotransmitter Funktion	Anwendung
[¹¹ C]Methylphenidat [¹⁸ F]FDG	Dopamintransporter Energiemetabolismus	10 Probanden Parkinson Pat. Pat. mit autosomal dominanter cerebellärer Ataxie (ADCA)
[¹¹ C]FLB [¹¹ C]Raclopride [¹¹ C]Methylspiperon	D ₂ D ₂ 5-HT _{2A}	Dosierungseffekte bei Neuroleptika
[¹¹ C]SCH 23390 [¹¹ C]Raclopride [¹¹ C]Methylspiperon	D ₁ D ₂ 5-HT _{2A}	Wirkungsprofile bei Neuroleptika
[¹¹ C]Raclopride	D ₂	Restless Legs Syndrom
[¹¹ C]Carfentanil	μ-Opiat-Rezeptor	Alkoholiker unter Entzug

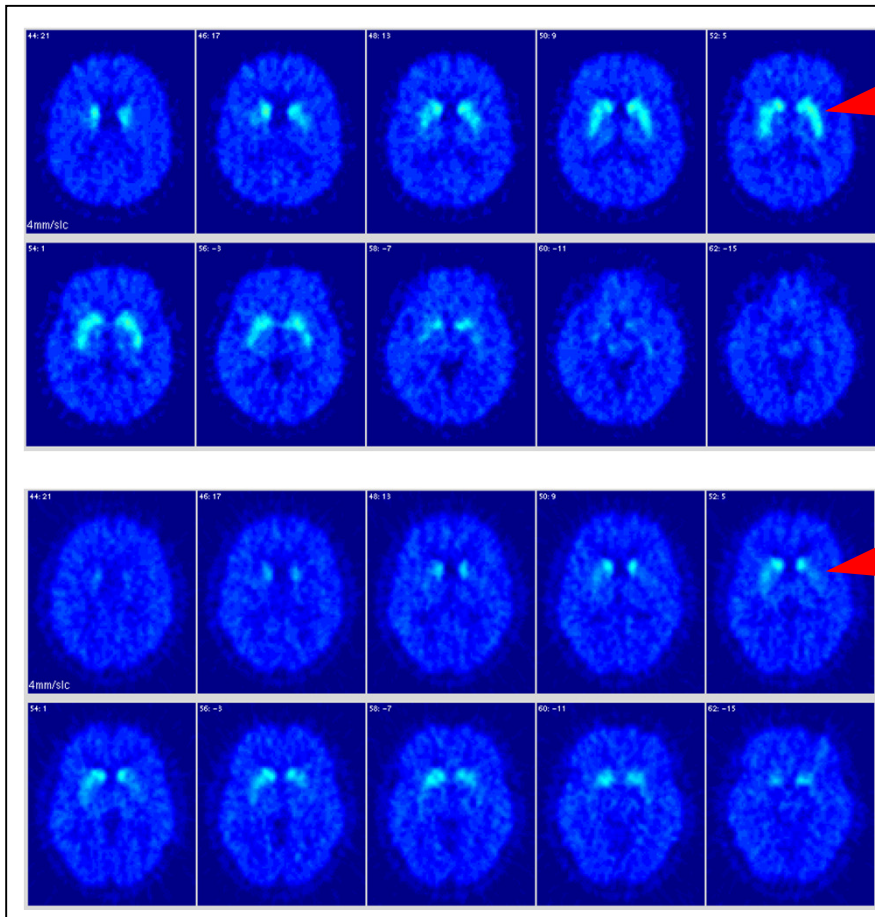


[¹¹C]Methylphenidat

- Darstellung des Dopamin-Transporters -



Dopamin-Transporter und Parkinson



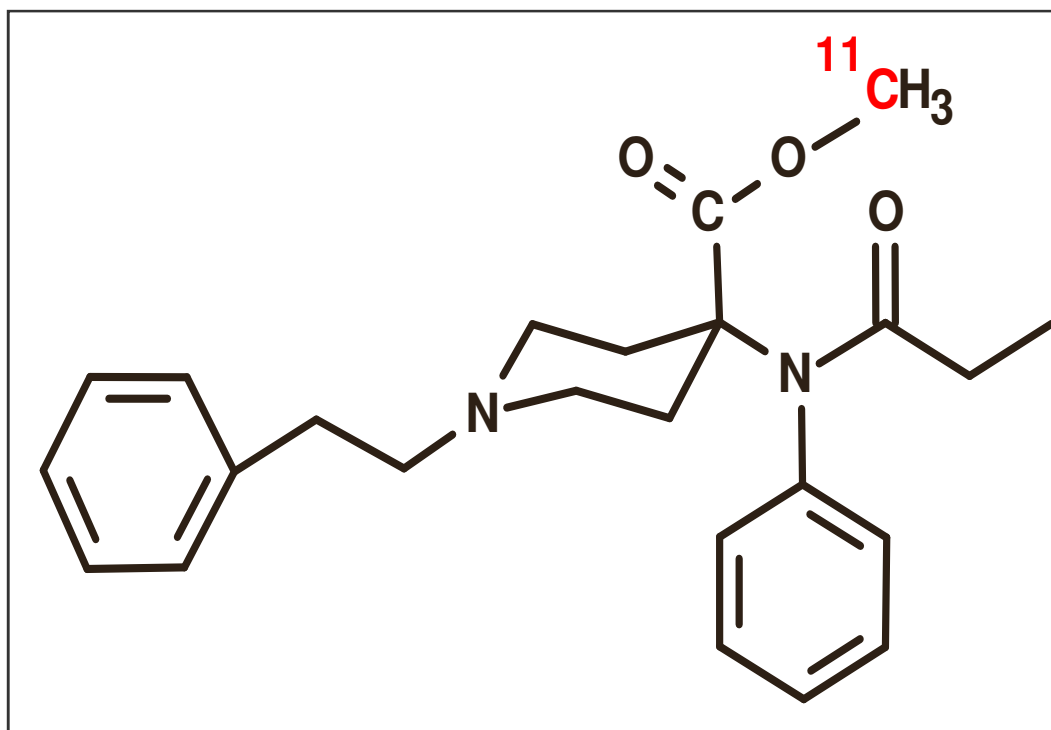
normale Bindung

**M. Parkinson:
Reduzierte Bindung
bereits im Frühstadium**



[¹¹C]Carfentanil

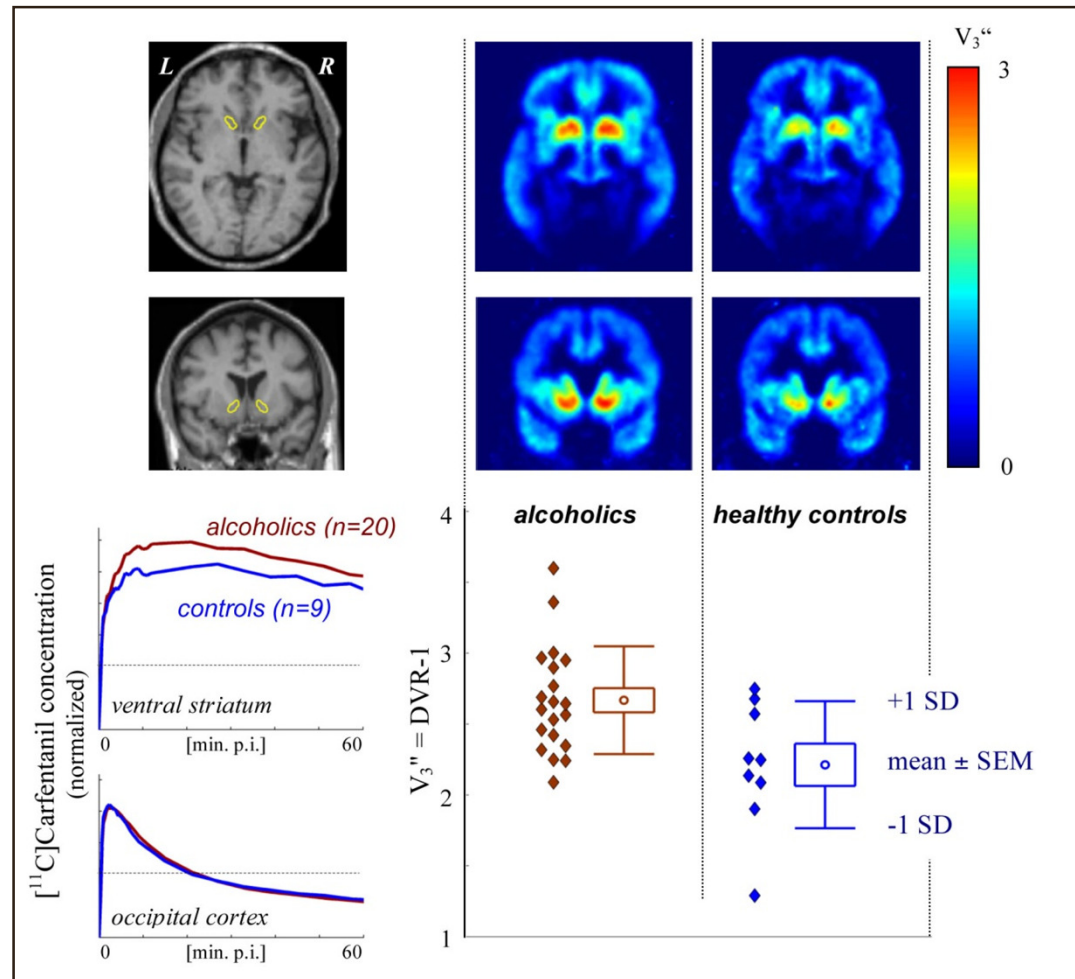
- Darstellung des μ -Opiatrezeptors -





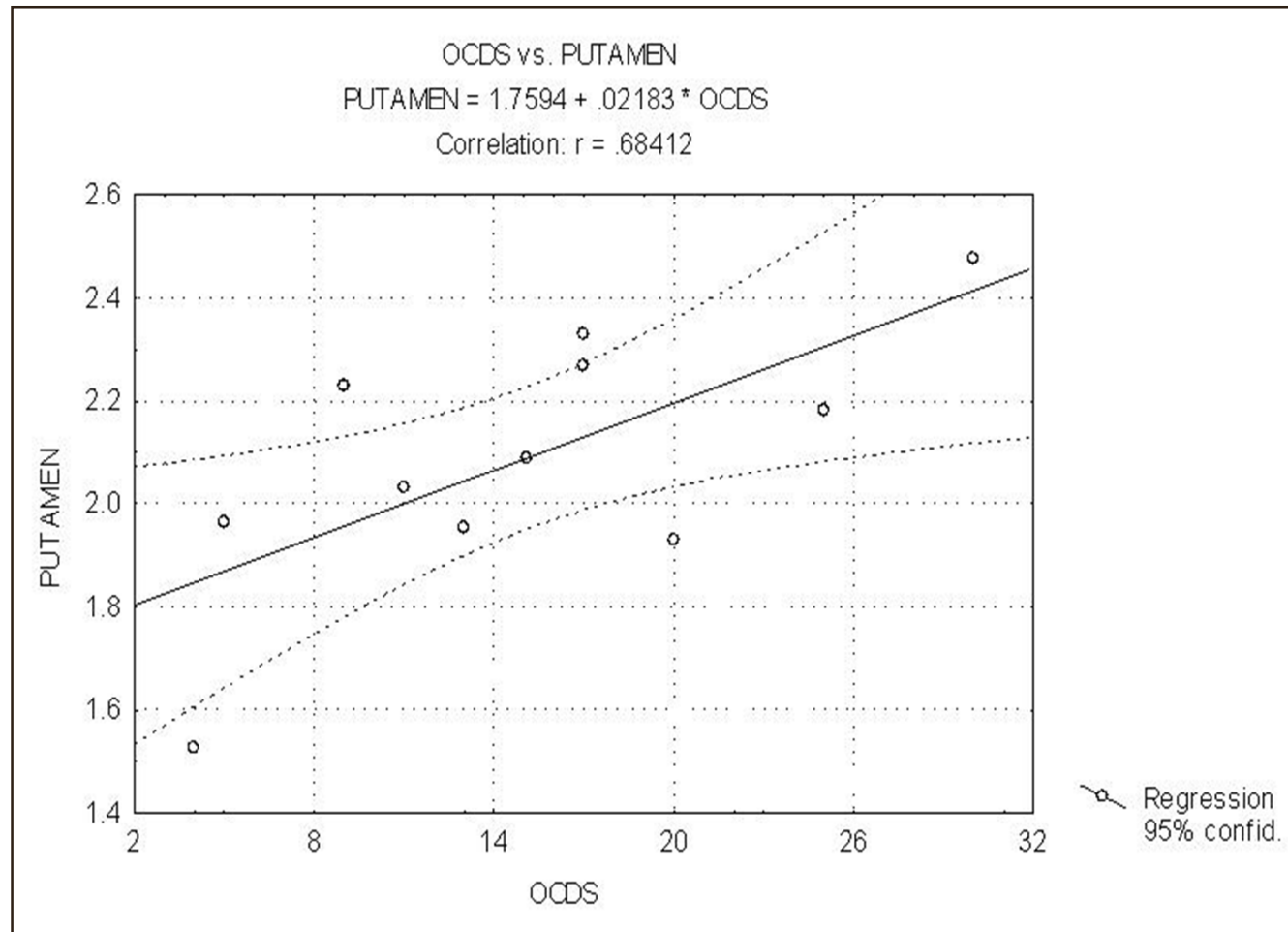
[¹¹C]Carfentanil

- Darstellung des μ -Opiatrezeptors -



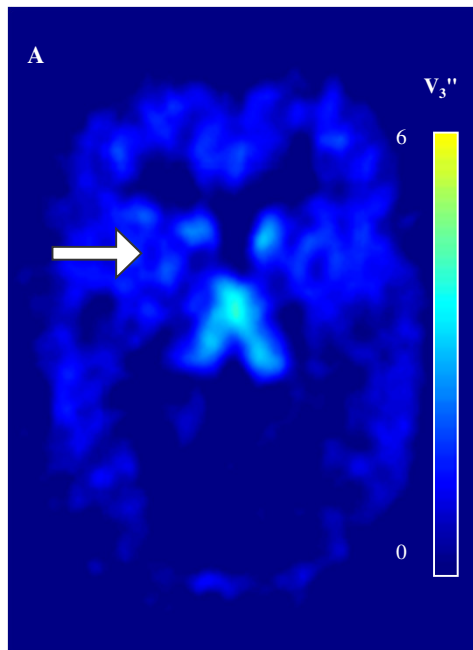


[¹¹C]Carfentanil PET - Korrelation mit Trinkverlangen (Craving) -

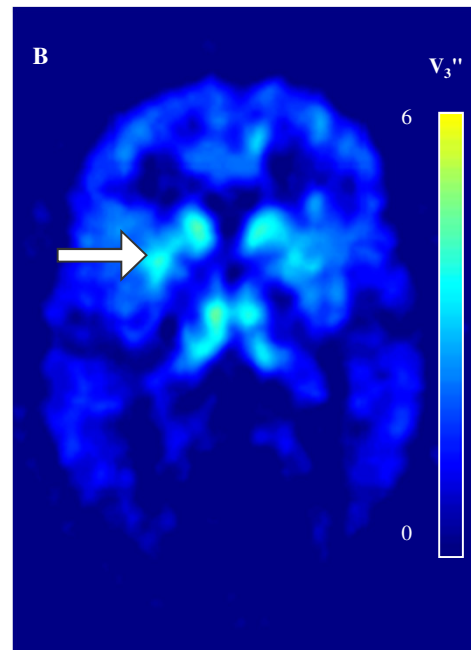


$[^{11}\text{C}]$ Carfentanil

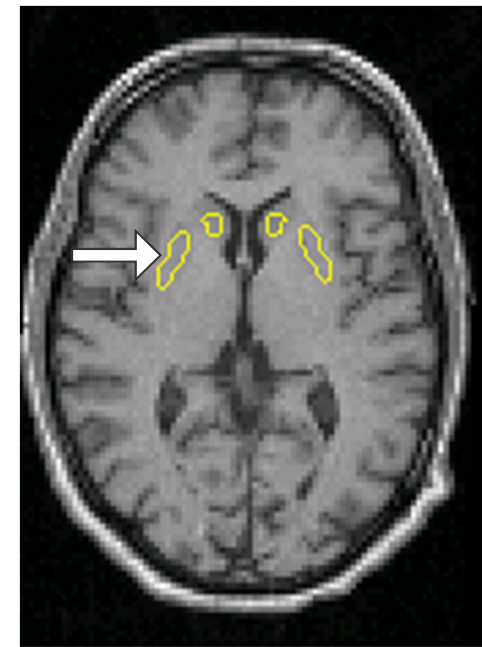
- Niedriges (A) und hohes (B) Trinkverlangen -



PET: Patient A



PET: Patient B

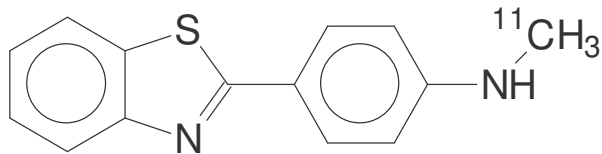


MRI: Patient B



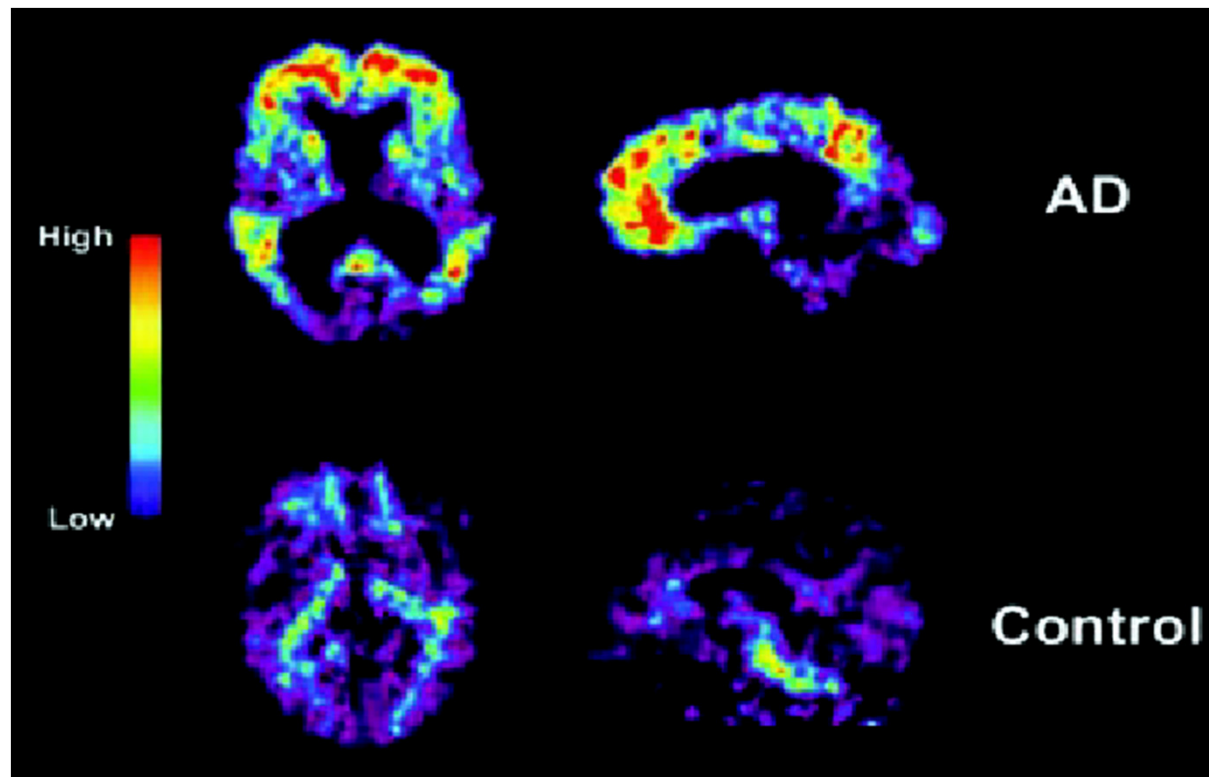
M. Alzheimer

- Darstellung der beta-Amyloid Plaques -



2-(4-[^{11}C]Methylaminophenyl)benzothiazol

[^{11}C]BTA-1



DeKosky ST et al; Science **302**:830-834 (2003)



Onkologie

Tumor-Biochemie

(Veränderungen zu gesundem Gewebe)

- Energiestoffwechsel
 - DNA-Syntheserate
 - Aminosäurestoffwechsel
 - Angiogenese
- etc.



Onkologie

- Einsatz von PET -

- Diagnostik
- Therapieplanung
- Therapiekontrolle



[¹⁸F]Fluorid

- Darstellung von Knochenmetastasen -





***In-vivo* Untersuchung von Hypoxie**

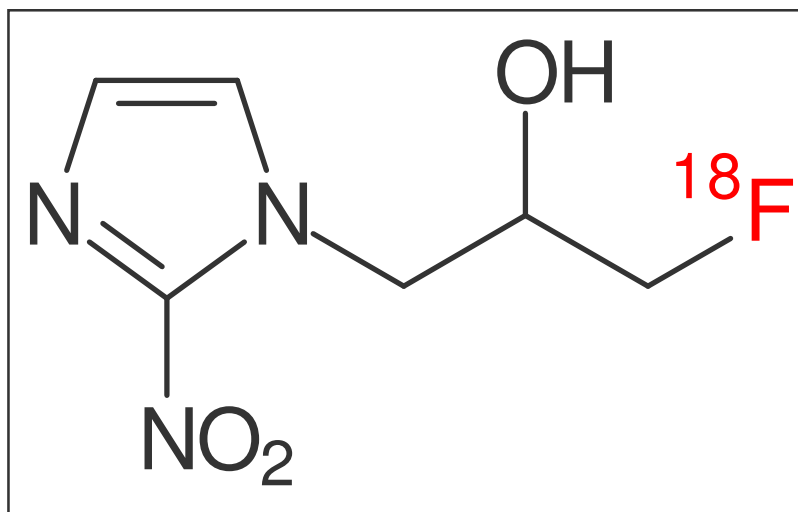
- Sauerstoffmangel -

- Gehirn (Schlaganfall)
- Herz (Infarkt)
- Transplantationen
- Tumorklassifizierung



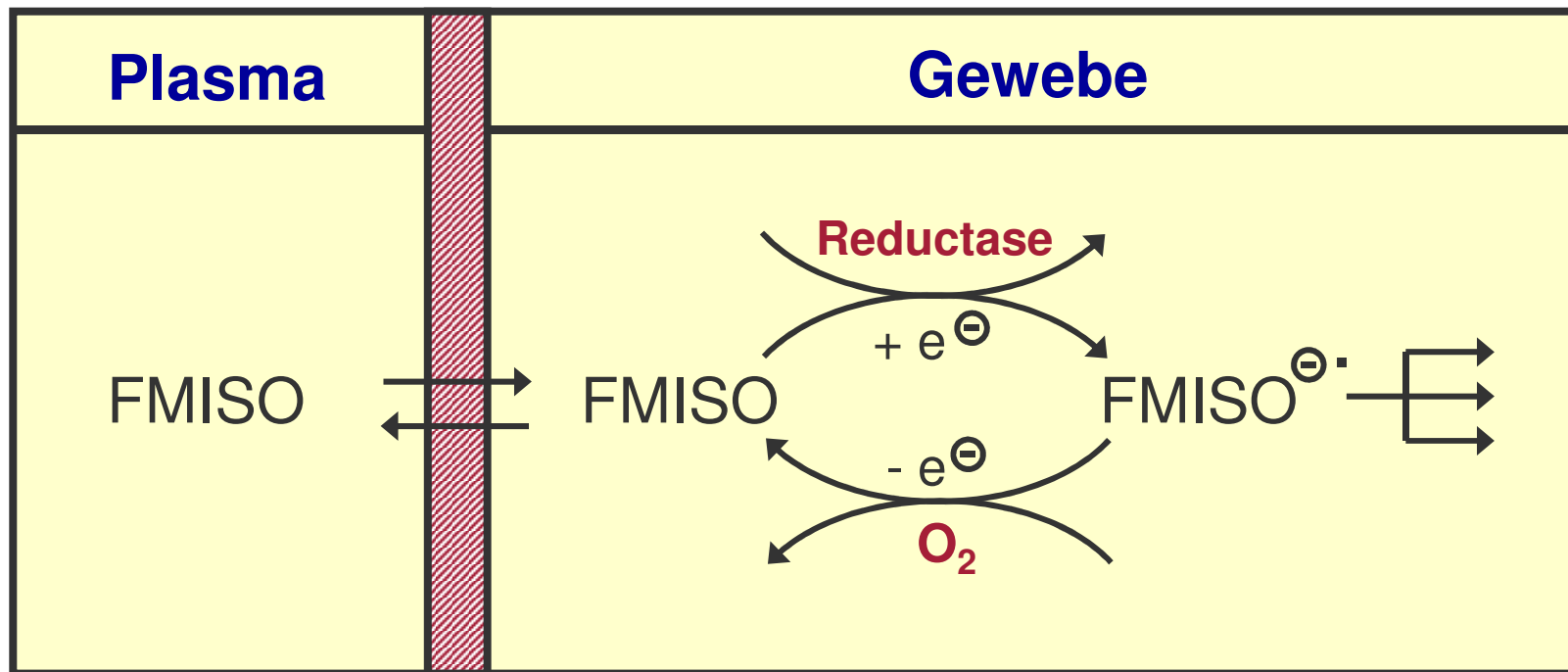
Hypoxie-PET

- 2- ^{18}F Fluormisonidazol (^{18}F FMISO) -





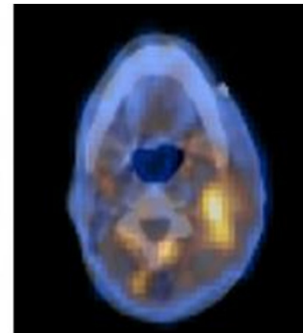
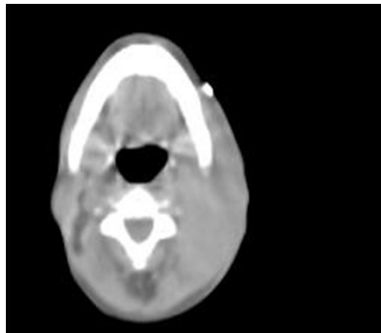
Stoffwechsel von FMISO



Biologische Planung Strahlentherapie

- hypoxiebasiert -

[¹⁸F]FMISO



konventionell

**intensitäts-
moduliert**

funktionell

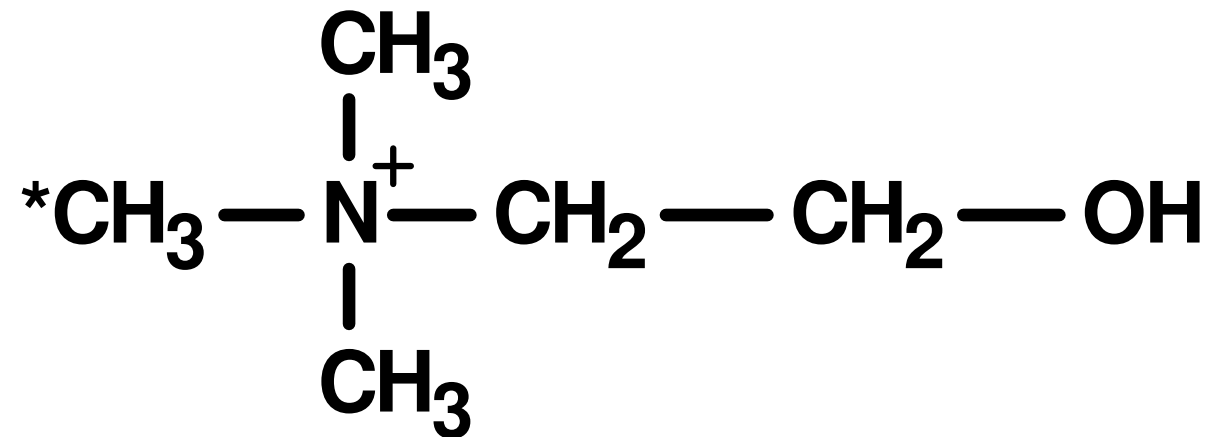
-  Risikogewebe
-  Bestrahlungsvolumen
-  Steigende Isodosen



[¹¹C]Cholin

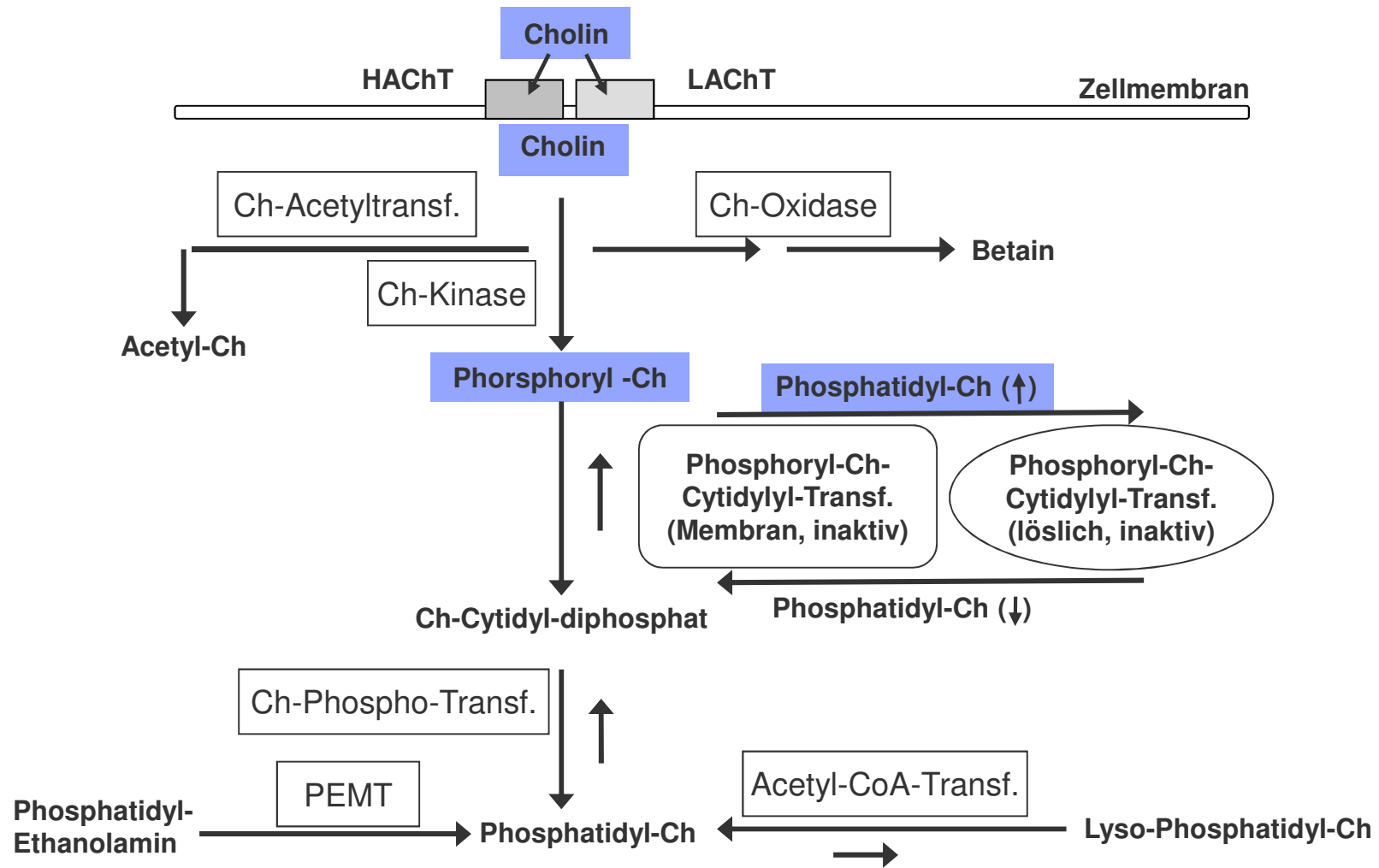
- Marker der Membranlipid-Synthese -

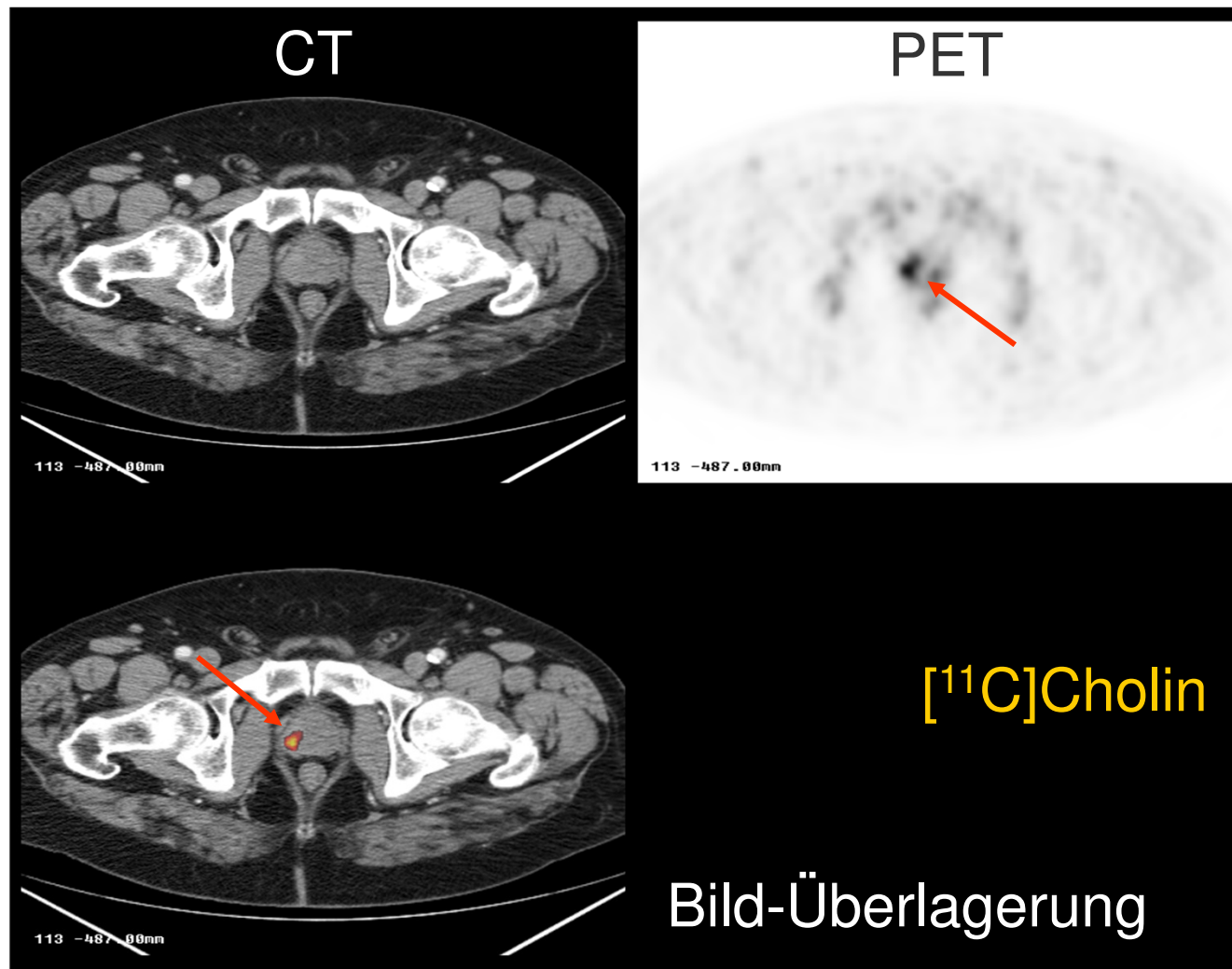
Hauptanwendung Prostata-Carcinom





Schema des Cholin-Stoffwechsels

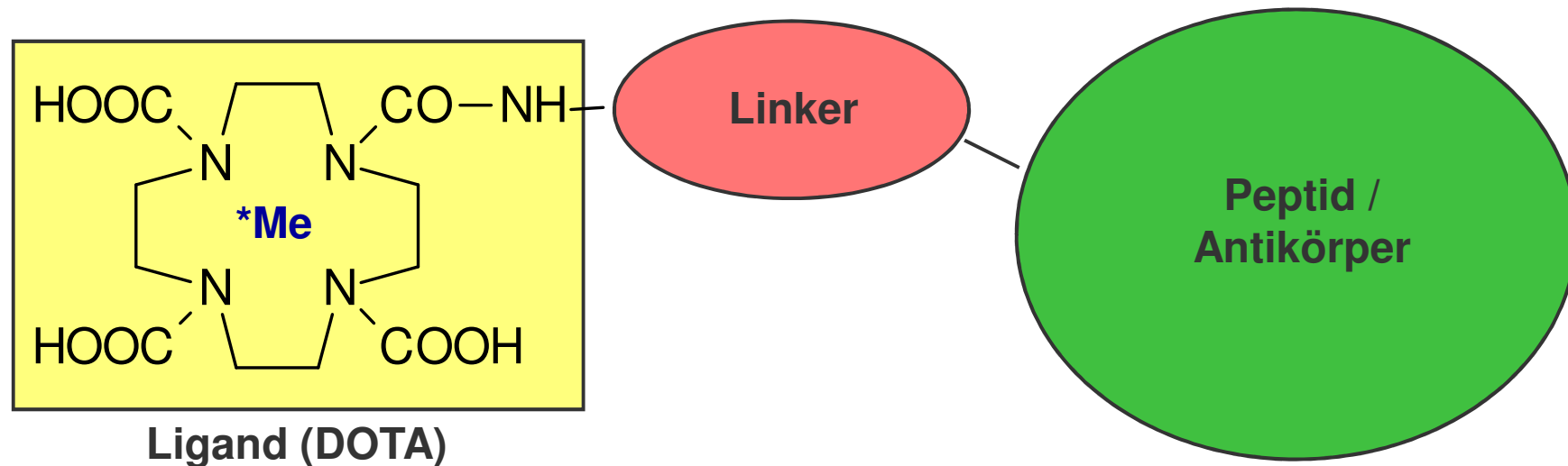






Radiomarkierte Peptide und Antikörper für die Bildgebung

Peptid- / Antikörpermarkierung mit Radiometallen



Vorteil: Stabile Bindung des *Me

*Me: PET oder SPECT oder Therapie-Isotope

Auch paramagnetische Isotope für MRT

Auch Liganden für die Optische Bildgebung

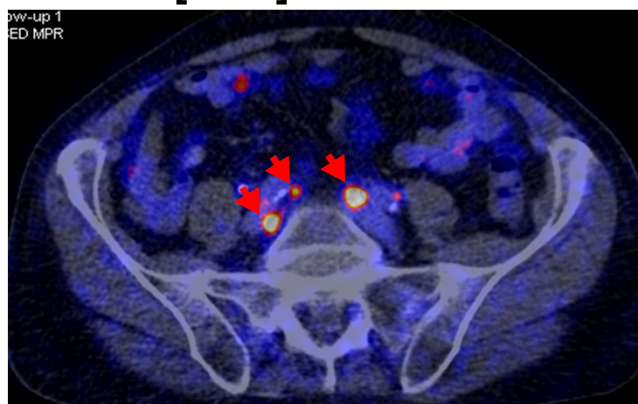
➔ Breites Spektrum an Peptiden/Aks für Imaging



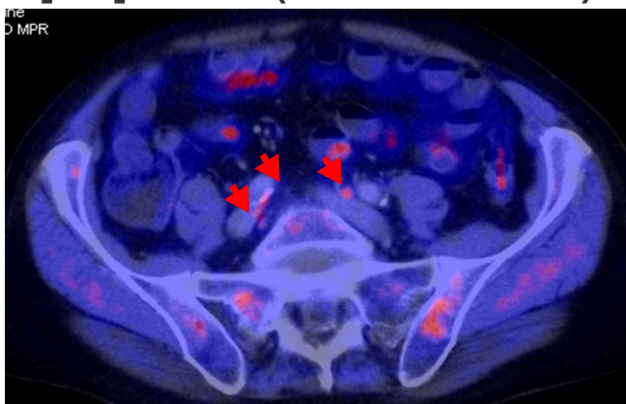
[⁶⁸Ga]PSMA-11

– Prostata Tumor –

[⁶⁸Ga]PSMA-11



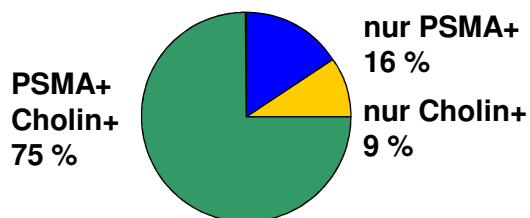
[¹¹C]Cholin (Gold Standard)



Lymphknoten Befall

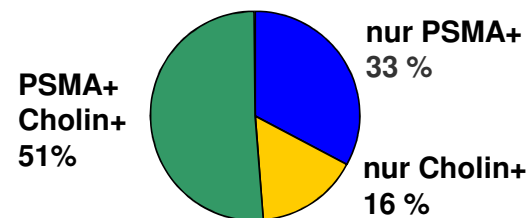
Vergleich im gleichen Patienten (n = 68)

Primär Tumor (n = 13)



PSMA positiv 90.8%
Cholin positiv 84.2%

Biochem. Rezidiv (n = 55)



PSMA positiv 84.0%
Cholin positiv 68.0%

Schwenck J. et al., EANM 2014





[⁶⁸Ga]PSMA-11

– Prostata Tumor –

- Insgesamt **123 Patienten** untersucht – Daten bestätigt
- **Höherer** Uptake mit **PSMA**-Ligand
(Primärtumor, Lymphknoten, Knochenmetastasen)
- **Höhere** Detektionsrate für **PSMA**-Ligand
- PSMA-Ligand zeigt **Vorteile gegenüber [¹¹C]Cholin**,
insbesondere beim Nachweis kleiner Lymphknoten und
bei niedrigen PSA-Werten
- **ABER:** geringer Anteil [¹¹C]Cholin positive, PSMA negative
Lymphknoten und Knochenmetastasen

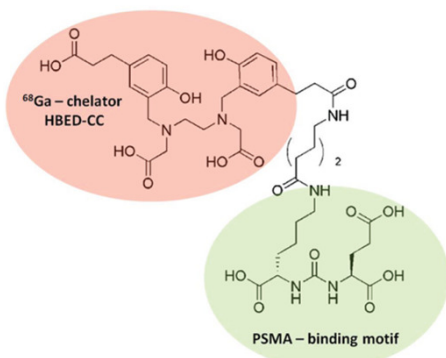
Limitation der Studie: Keine histologische Verifizierung

Aktuell: Laufende prospektive Registerstudie (PET/CT)

→ **THERANOSTICS: [¹⁷⁷Lu]PSMA-617**

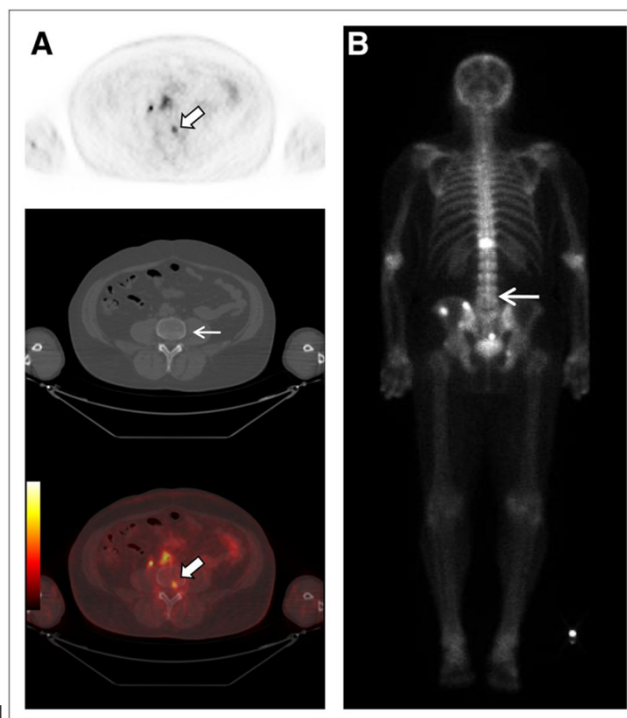
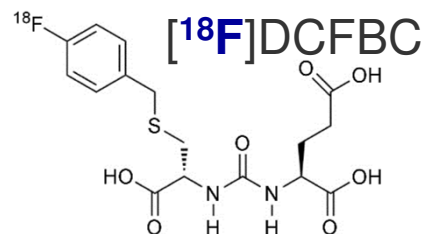
PSMA Bildgebung

– Andere Isotope –



[⁶⁸Ga]PSMA-11

Eder et al. Bioconjug. Chem.
2012;23:688-97



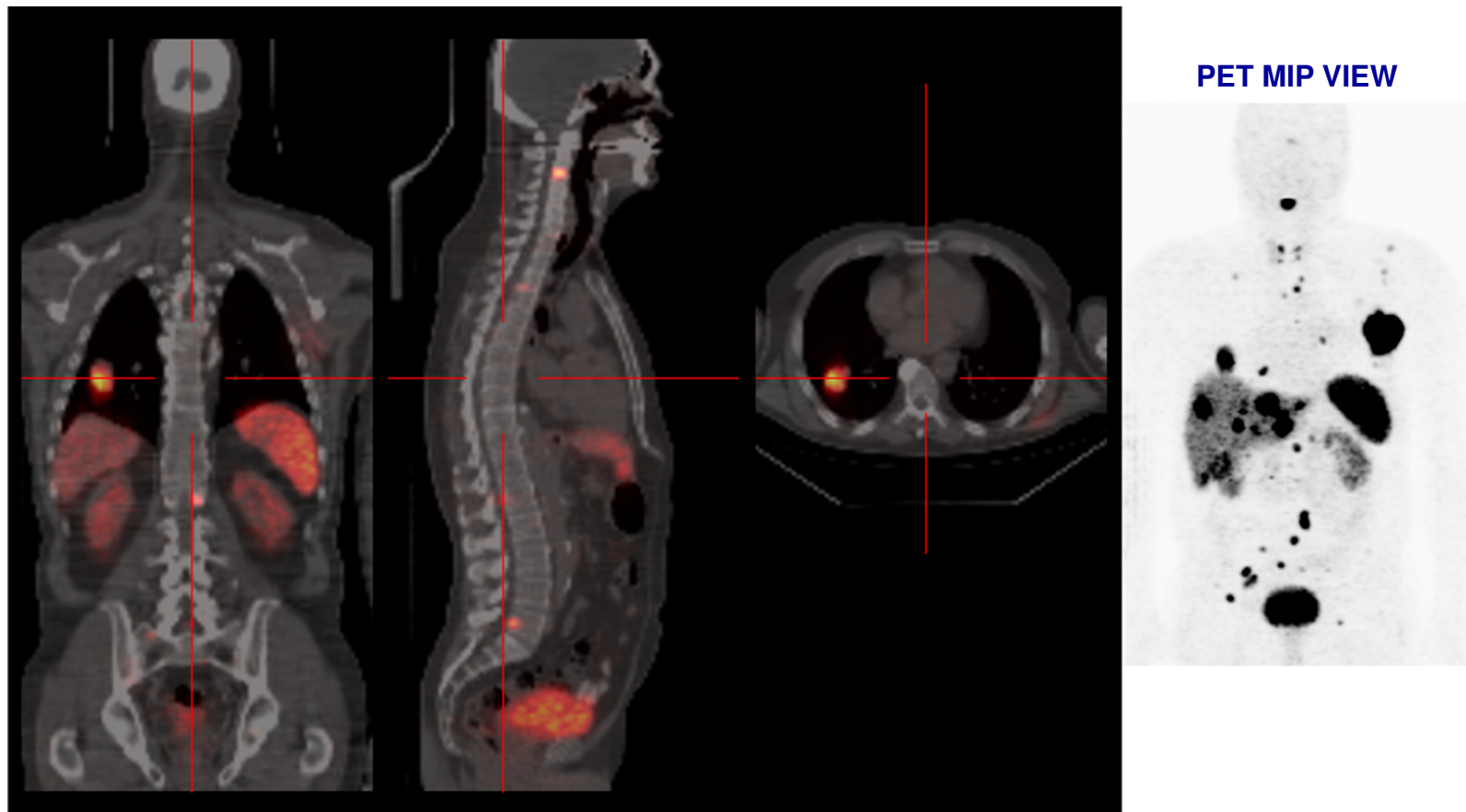
Pomper et al.
JNM 2012;53:1883-1891

... [⁶⁴Cu]PSMA-xx

[⁶⁸Ga]DOTATOC



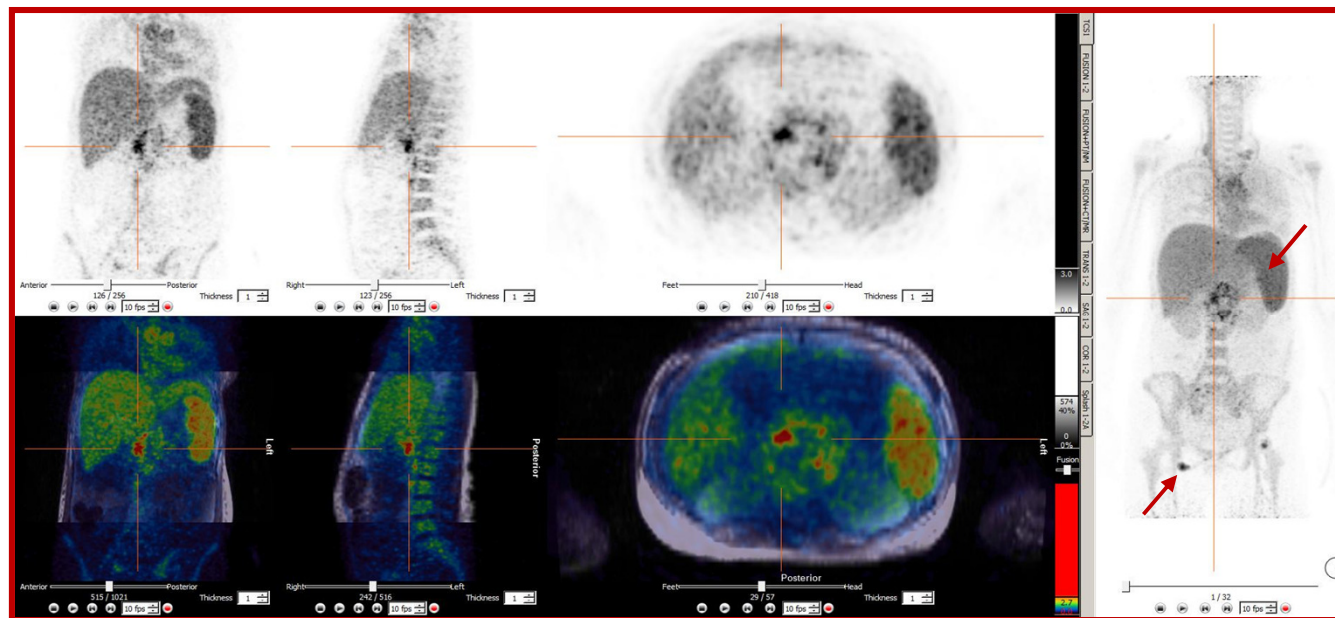
[⁶⁸Ga]DOTATOC (PET/CT)



[⁶⁴Cu]DOTA-CD19-AK

Imaging CD19 positiver Tumore

F 25 y, follikuläres Lymphom, Grad IIIb, div. Therapien
PET/MRT: 294 MBq [⁶⁴Cu]DOTA-CD19-AK



Theranostics: **Radioimmuntherapie** mit 1200 MBq [⁹⁰Y]DOTA-CD19-AK



Radiopharmaceutical Production

Good Manufacturing Practice (GMP)



US: FD&C Act; 501(a)(2)(B)

“...to assure that such drug meets the requirements of this Act as to *safety* and has the *identity* and *strength*, and meets the *quality* and *purity* characteristics, which it *purports* or is *represented to possess*.”



GMP Principles

- ... a way of thinking
- It is all about quality !
- currentGMP = cGMP = *dynamic*, never perfect
- Ensure uniform *quality* and *effectiveness* of product
- Encompassment of everything that has a bearing on quality of the pharmaceutical product

 Installation of a quality assurance system



Quality Assurance System

Premises

- Laboratory planning
- Quality of air (classes A-B-C-D)
- Flow of personnel & materials

Personnel

- Sufficient staff
- Responsibilities
- Qualification
- Training & retraining

Equipment

- In-process controls
- Qualification and Validation (DQ,IQ,OQ,PQ) of Equipment, Processes and QC

Raw materials

- Traceability
- Release for use

Sanitation, Hygiene and Monitoring

Quality control (QC)

- Specifications

Documentation

- Standard Operating Procedures (General, Equipment, Material & Products)
- Records
- Reports

Distribution, Complaints, Recalls

Self inspection



GMP Regulations

World Health Organization
Quality Guidance TRS 908

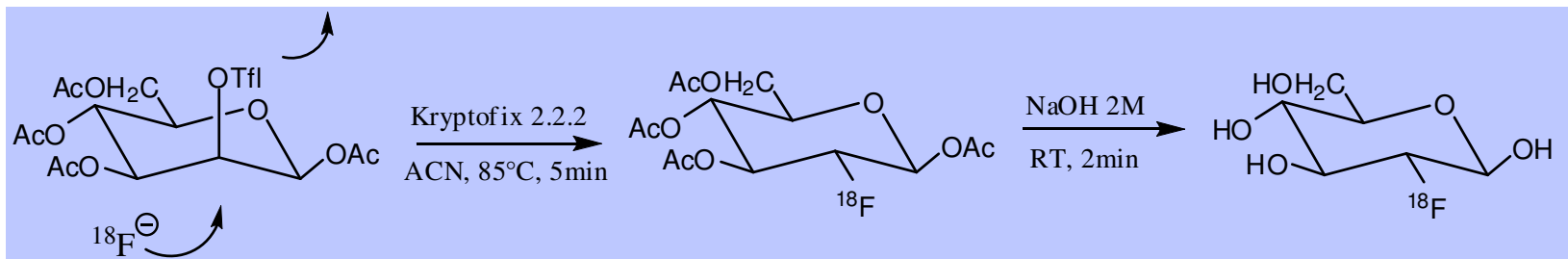
European Union
Guidelines

US FDA
Part 210 - Part 211
Part 212 – PET Radiopharmaceuticals



FDG Synthesis

- Reaction scheme -





PET Radiopharmacy Lab

- Radiation Protection -

- Classification „SK2“ or „SK3“
- Controlled area ($> 6 \text{ mSv/a}$)
(e.g. $>18 \text{ y}$; lab coat; dosimeter)
- Cyclotron vault Prohibited area ($> 3 \text{ mSv/h}$)
- Min. 10-fold air exchange (100 % fresh air)
- Pressure lower than surrounding
- „UGG“ (TÜ):

C-11	700 GBq	
F-18	300 GBq	
O-15	300 GBq	etc.



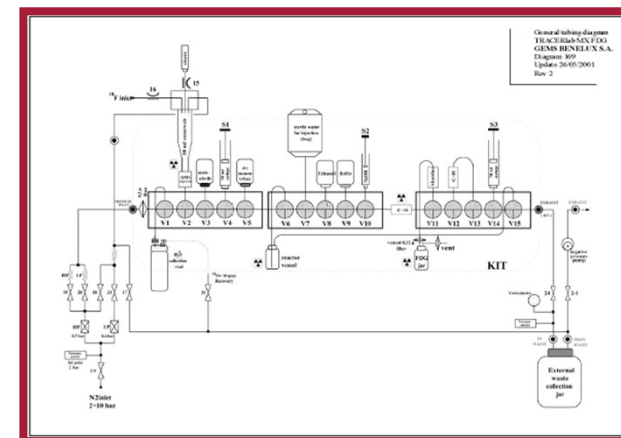
PET-Radiopharmaceutical

- GMP Synthesis -



FDG Automated Synthesis

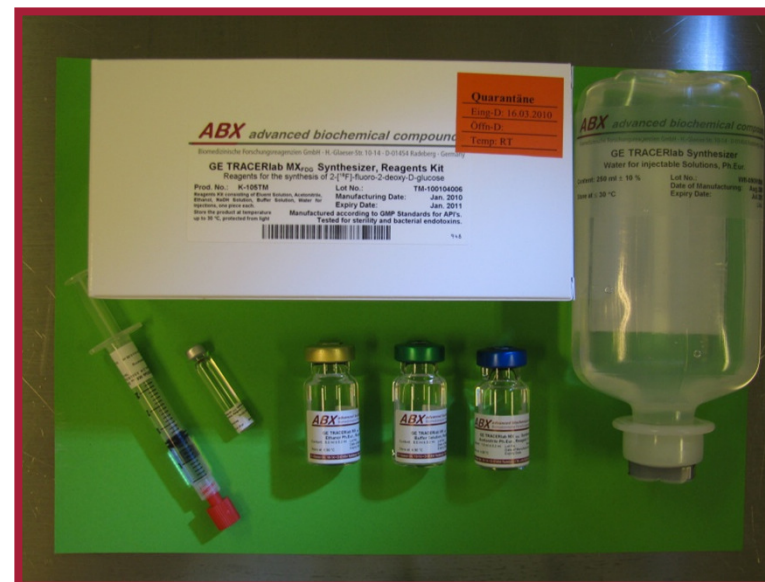
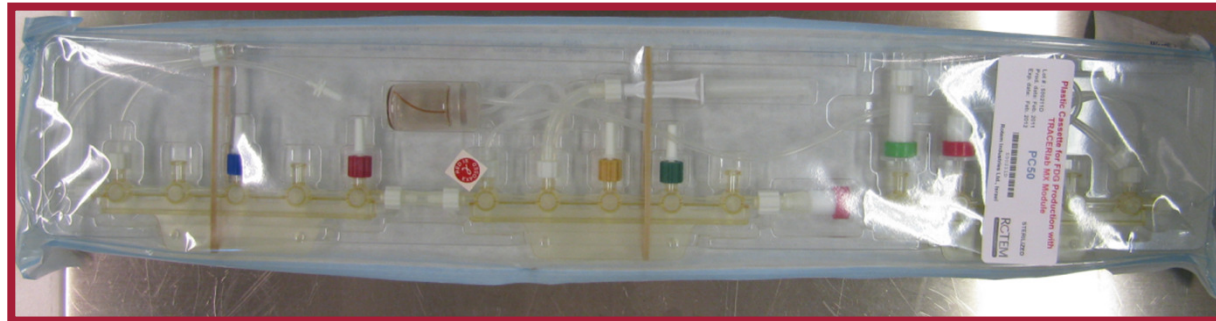
- GE TracerLAB MX -





FDG Automated Synthesis

- Materials -





GMP Requirements

Synthesis in hot cell in clean room class C (10,000)
(lower pressure than room)

Room: class C (10,000)

Higher pressure than surrounding rooms
(↔ Radiation protection)

Dispensing in clean room class A (100)
Isolator (no surrounding class B needed)

Isolator can be in class C



PET-Radiopharmaceutical

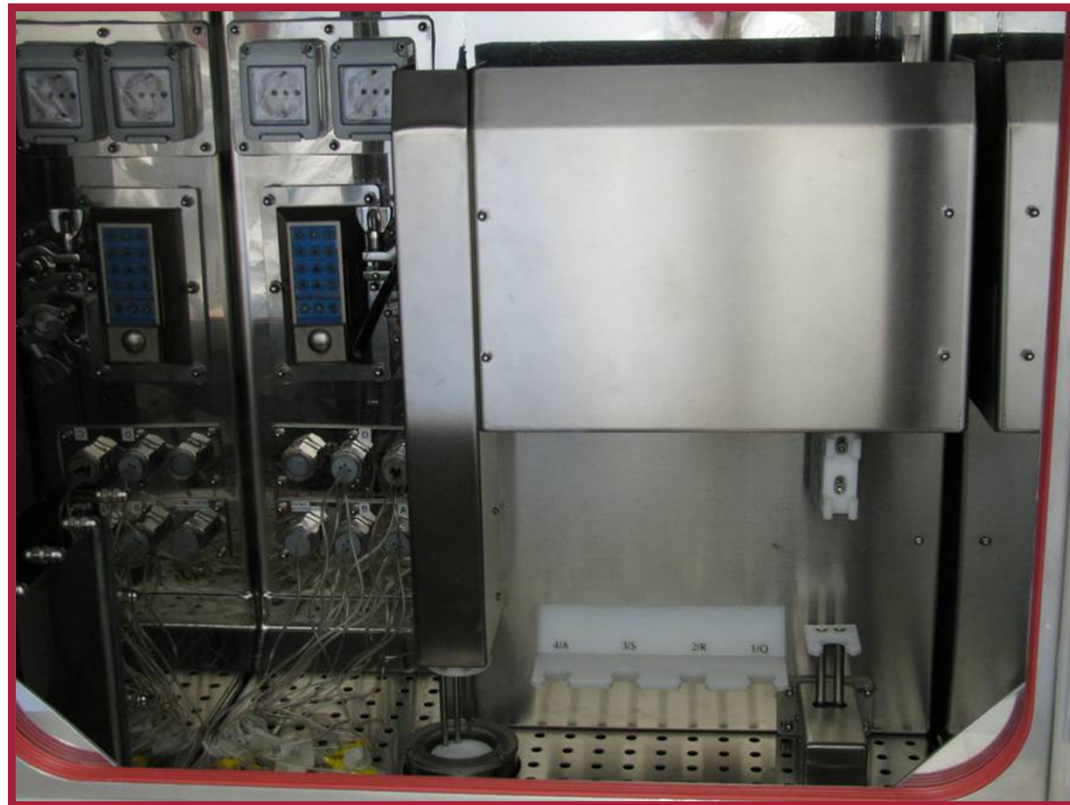
- GMP Dispensing -





PET-Radiopharmaceutical

- Dispensing System -





Dispensing

- Preparation -





Dispensing





Quality Control [^{18}F]FDG-Tü

- acc. Ph.Eur. -

Properties:

Volume (Batch)	20 ± 2 mL
Volume (Customer)	1– 20 mL
Activity at EOB (Batch)	6,000 – 60,000 MBq
Activity at calibration (Customer)	350 – 54,600 MBq
Activity concentration	350 – 2730 MBq/mL
Appearance	clear, colorless, no particles

Identity:

HPLC ^{18}F FDG vs. ^{19}F FDG	0.5 ± 0.5 min before
Half life	105 – 115 min
Gamma spectrometry	main at 511 ± 1 keV



Quality Control [^{18}F]FDG-Tü

- acc. Ph.Eur. -

Purity:

pH

5.0 – 8.0

Sterility

sterile

Endotoxins (LAL; turbidometric)

< 3 I.U./mL

Bubble-Point-Test (2 filters poss.)

≥ 3.0 bar or ≥ 3.5 bar

HPLC FDG (comp. Ref. a)

≤ 25 mg/L (0.5 mg/20 mL)

HPLC CIDG (once p. month)

≤ 25 mg/L (0.5 mg/20 mL)

HPLC unknown impurities

$A(\text{unkn.}) \leq A(\text{FDG})$ Ref. a

Kryptofix 2.2.2

< 100 mg/L

GC ethanol

2000 - 5000 mg/L

GC isopropanol

≤ 1000 mg/L

GC acetonitrile

≤ 200 mg/L

GC unknown

$A(\text{unkn.}) \leq 1\%$ comp. to
 $A(\text{acetonitrile})$ GC-Std. 2



Quality Control [^{18}F]FDG-Tü

- acc. Ph.Eur. -

Radionuclidic purity:

Gamma spec. short lived

none but $511 \pm 1 \text{ keV}$

Gamma spec. long lived

F-18 $\geq 99,9 \%$

Radiochemical purity:

HPLC [^{18}F]FDG

$\geq 95 \%$

HPLC [^{18}F]FDM

$\leq 2 \%$

HPLC unknown impurities

$\leq 5 \%$

DC [^{18}F]FDG + [^{18}F]FDM

$\geq 95 \%$

DC [^{18}F]Fluoride

$\leq 3 \%$

DC partial hydrolysates

$\leq 3 \%$

DC unknown impurities

$\leq 4 \%$



The situation

Production of Radiopharmaceuticals under GMP in

Europe (> 25 countries)

Germany (federal republic)

The state of Baden-Württemberg

Tübingen

???



Aide Memoire (AiM 07120802)

- published July 2011 -

- Guide (23 pages) for inspectors for radiopharmaceutical production sites (PET only)
- Only guide (no must)
- For harmonization
- Production, Dispensing and QC
- Including GMP rules (personell, rooms, equipment)
- Considering: short half life, single dose batches, one-day batches)



Four possibilities in Germany

- human application -

1. Marketing licence (AMG; §21 ff)
2. Clinical Trial (AMG; §40 ff)
3. §2 Abs.1 of „Verordnung über radioaktive oder mit ionisierenden Strahlen behandelte Arzneimittel“ (AMRadV)
4. Use §13 Abs. 2b AMG (shortly: Production under direct responsibility of physician, who will use the radiopharmaceutical)



Four possibilities in Germany

- human application -

Marketing licence:

- Pharmaceutical can only be distributed with **permission from federal authority** (Bundesinstitut für Arzneimittel und Medizinprodukte; BfArM): Licence (AMG §21 Abs. 1). Exemptions, see below.
- Application: **Dossier** (5 moduls) to prove pharm./chem. quality, efficacy and no-risk. Inspections to check for GMP compliance. Requirement: **Permission for production** (§13 AMG) from state authority (GMP).
- **Holders of licences** are commercial companies, universities and hospitals.

Clinical trials:

- (§40 AMG ff). Products **without licence** can be used (preparations under investigation).
- **Production permission** ok.
- Investigational Medicinal Product Dossier (**IMPD**), to prove pharm./chem. quality.



Four possibilities in Germany

- human application -

§2 Abs. 1 AmRadV:

- In general: „Verkehrsverbot“ (§7 Abs. 1; AMG)
- AmRadV **allows exemptions**, described in §2 Abs. 1 Satz 3
- No licence, no clinical trial !
- ONLY **diagnostics** (e. g. PET radiopharmaceuticals)
- **Required:**
 1. Within **one institution**
 2. permission for production (**GMP**)
 3. **20 cases** per week, only lit.-known products
 4. For defined patients (**prescription**)

§13 Abs. 2b AMG:

- **NO** permission for production (BUT GMP ???)
- Pharmaceutical is produced under direct responsibility of **physician**, who will personally apply to „his“ patient.
- Physician needs at least **training** in production and QC
- **NOT** in clinical trials
- Local authority has to **be informed**



PET Radiopharmaka in Ph.Eur.

- 2015 -

Monographien:

Radiopharmaceutical preparations

[¹¹C]Methionine

[¹¹C]Acetate

[¹¹C]Raclopride

[¹¹C]Flumazenil

[¹³N]NH₃

[¹⁵O]H₂O

[¹⁵O]O₂

[¹⁵O]CO

[¹⁸F]FDG

[¹⁸F]Fluoride

[¹⁸F]Fluoride for labeling

[¹⁸F]FDOPA (elektrophil)

[¹⁸F]FLT

[¹⁸F]FMISO

[¹⁸F]FET

[⁶⁸Ga]DOTATOC

[⁶⁸Ga]Ga for labeling

Entwürfe:

[¹⁸F]FDOPA (nukleophile Herstellung)



Precursors for PET products

- Monographs -

Mannose triflate

More to follow (Task force)



Actual situation and future perspective

- D and EU -

- Marketing **licence expensive** to achieve and to keep up to date
- Which **products beyond FDG** (for the market) ?
- **GMP** necessary for any human application !!!
>>> Cost



Actual situation and future perspective

- D and EU -

Germany:

Many small academic radiopharmacies, limited resources,
large investments necessary to follow GMP

Change of situation in Germany in future:

Will all institutes survive?

Cooperations with companies (**PPP**):

Company distributes licenced products, university pushes research
into new products (in a unit with one cyclotron)

Actual:

Hannover Medical University MHH and Siemens **PETNET**
(1. PETNET site in Germany; Siemens wants to expand)

Munich University LMU and **IBA**
(3 more IBA sites in Germany)



And the industry ?

Available tracers from Radiopharmaceutical companies in Germany:

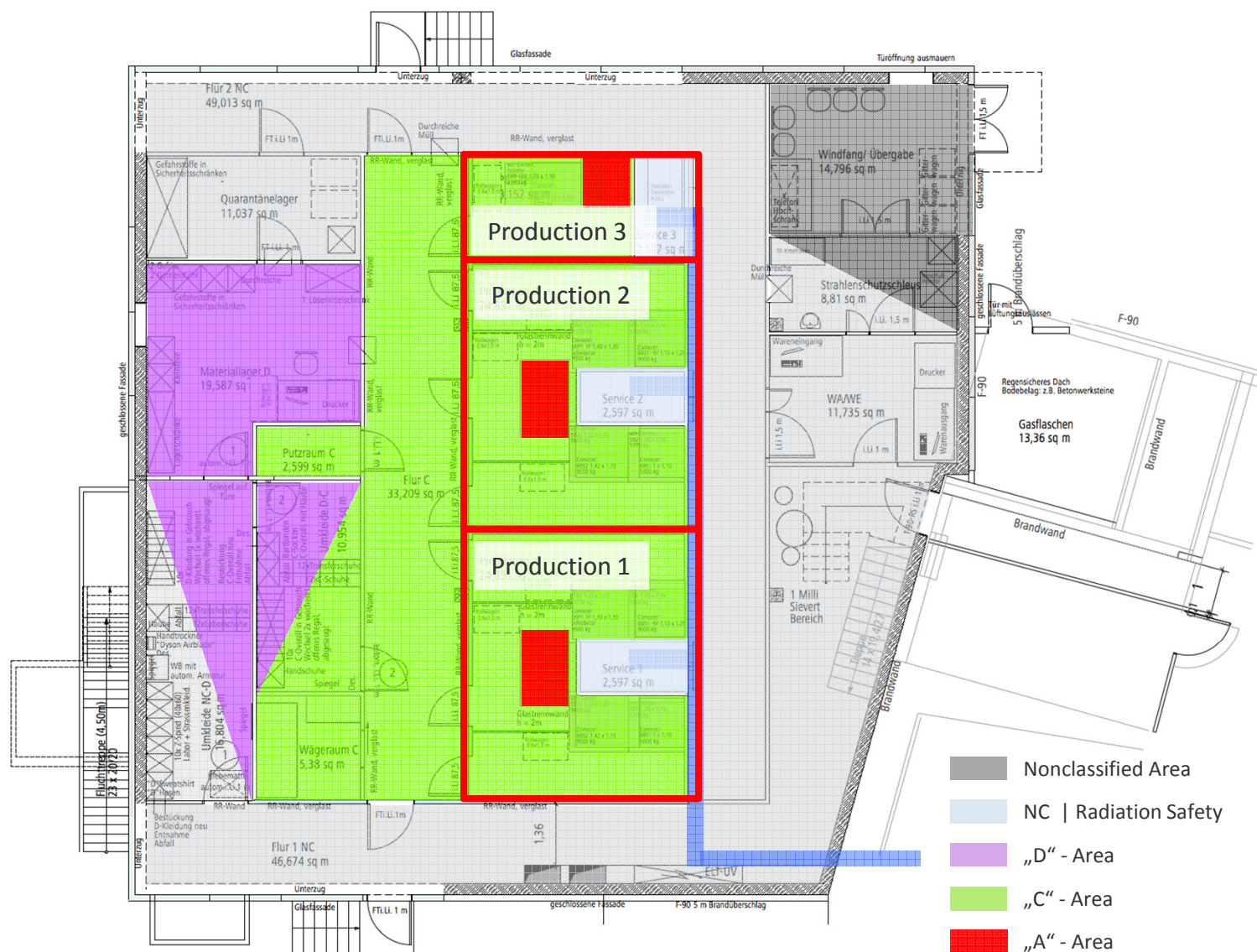
[¹⁸F]FDG
[¹⁸F]Fluoride
[¹⁸F]Fluorocholine
[¹⁸F]FDOPA
[¹⁸F]FET

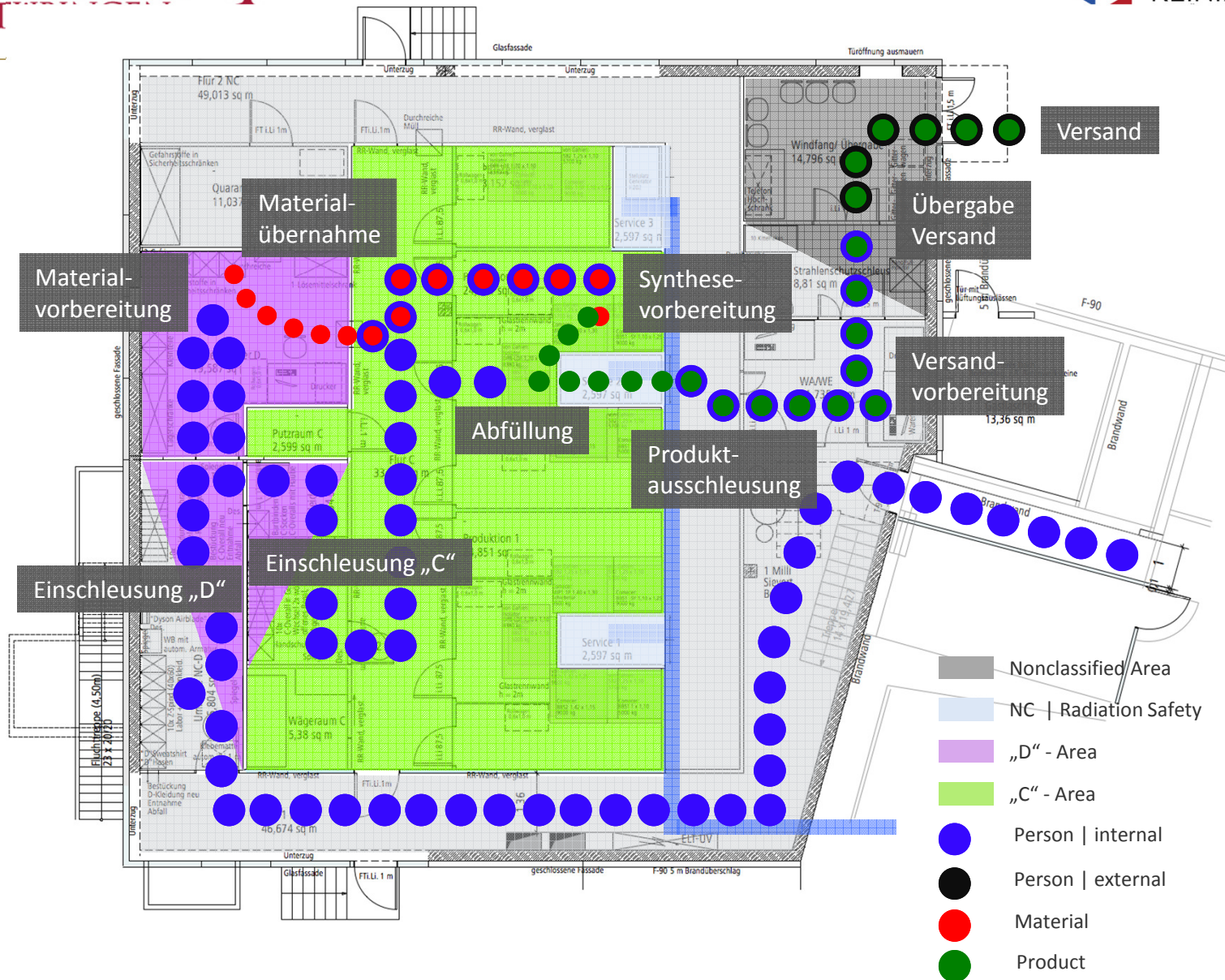
Companies with *proprietary* new products
(future licence in progress):

Siemens:	F-18 Alzheimer tracer F-18 Tau protein tracer
GE:	F-18 Alzheimer tracer, more in pipeline
Piramal:	F-18 Alzheimer tracer



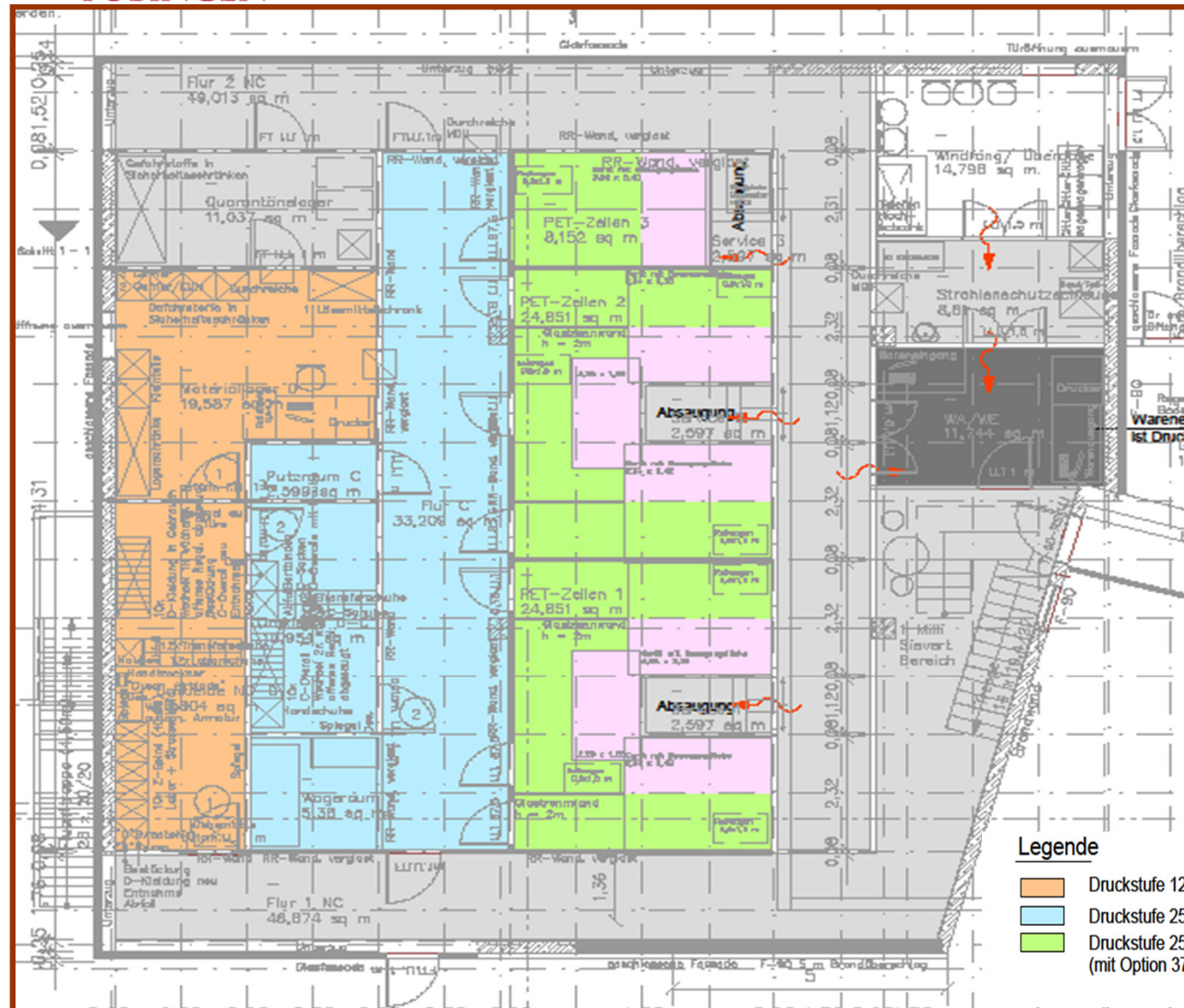


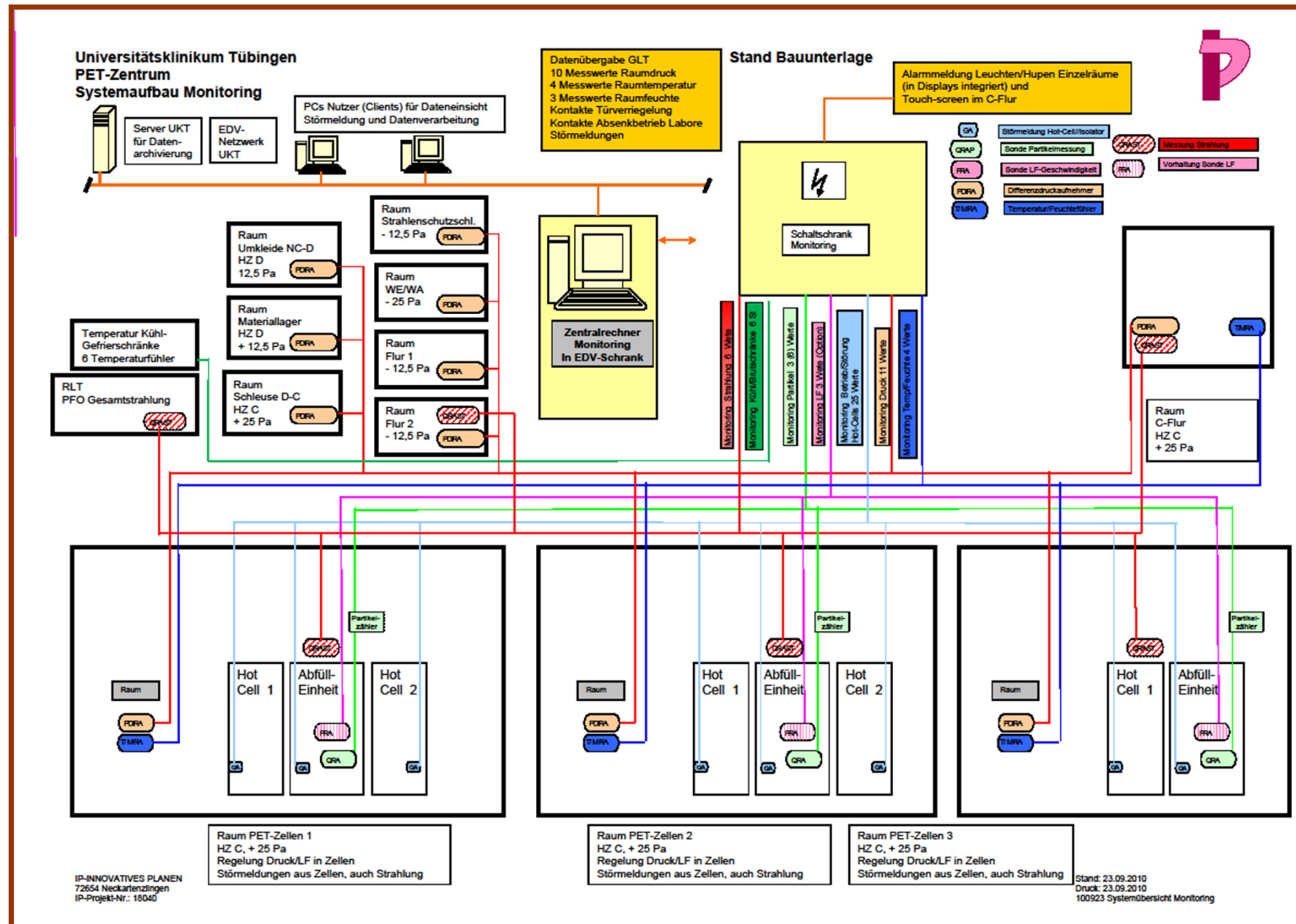






Pressure cascades













Summary

- General aspects -

Visualization of function (*in vivo* biochemistry)

Spezific, selective PET markers for
diagnostic valuable information: **PET is more than FDG**

Mandatory: Knowledge of the biochemical mechanism

Reliable availability for clinical application

Evaluation of new tracers *in vitro*, *in vivo*, *ex vivo*
in radiopharmaceutical development

Small animal PET (or PET/CT, PET/MRT) for
preclinical development of new tracers and drugs

Multi-disciplinary cooperation of biochemists, biologists,
chemists, engineers, pharmacists, physicians, physicists, etc.
(alphabetical order)



Summary

- Production -

Radiopharmaceutical Production

- Isotope production
- Labeling
- Purification
- Formulation
- Dispensing
- Delivery
- QC + release

Quality Assurance

- GMP (international standards)
- Regulation and inspection
- Control of all that influences product quality
- QC is not enough
- Qualification, re-qualification, monitoring
- Documentation
- Constant evolutionary process



Perspective

- New **isotopes** available (broader range of half life)
- Identification of new biochemical **targets**
- Development of new **tracers**
- **Evaluation** of new tracers preclinically, in clinical trials
- More tracers **available on the market** for a broader spectrum of clinical application

