Viplav Gupta
DKFZ,
Heidelberg

Activities from Cyclotron facility at German Cancer Research Center (DKFZ), Heidelberg

50 Years – Research for A Life Without Cancer


dkfz.
GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION
50 Years – Research for
A Life Without Cancer
25 YEARS OF OPERATION
The DKFZ Scanditronix MC32NI Cyclotron
Anniversary Symposium
June 30th/July 1st, 2016, DKFZ, Heidelberg

From proton to patient

The interaction of Physics, Chemistry and Medicine

Wolfgang Weber, Daniel Burkert, Oliver Neels, Viplav Gupta, Klaus Kopka

Division of Radiopharmaceutical Chemistry

Cyclotron → Target → Radiopharmacy → PET

Cyclotron

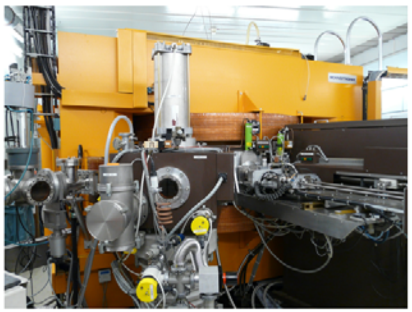


Fig. 1 *Particle accelerator*

Charged particles such as protons and deuterons are accelerated in a particle accelerator on a circular path in a magnetic field with alternating electric fields.
They fly through a so-called airless beam line and hit the target consisting of a target body with an enriched stable isotope which is transferred into the desired radionuclide after nuclear reaction.

Target

Fig. 2 *Target*

The desired radionuclide is obtained by a nuclear reaction of the charged particle and the target material.
The radionuclide needs to be processed rapidly, since it decays with a short physical half-life.

Radiopharmacy

Fig. 3 *Radiosynthesizer in clean room environment*

In a fully automated synthesis module the radionuclide is attached to a precursor (e.g., a sugar) and purified under GMP conditions.
The result is a radiolabeled pharmaceutical, which then undergoes quality control.

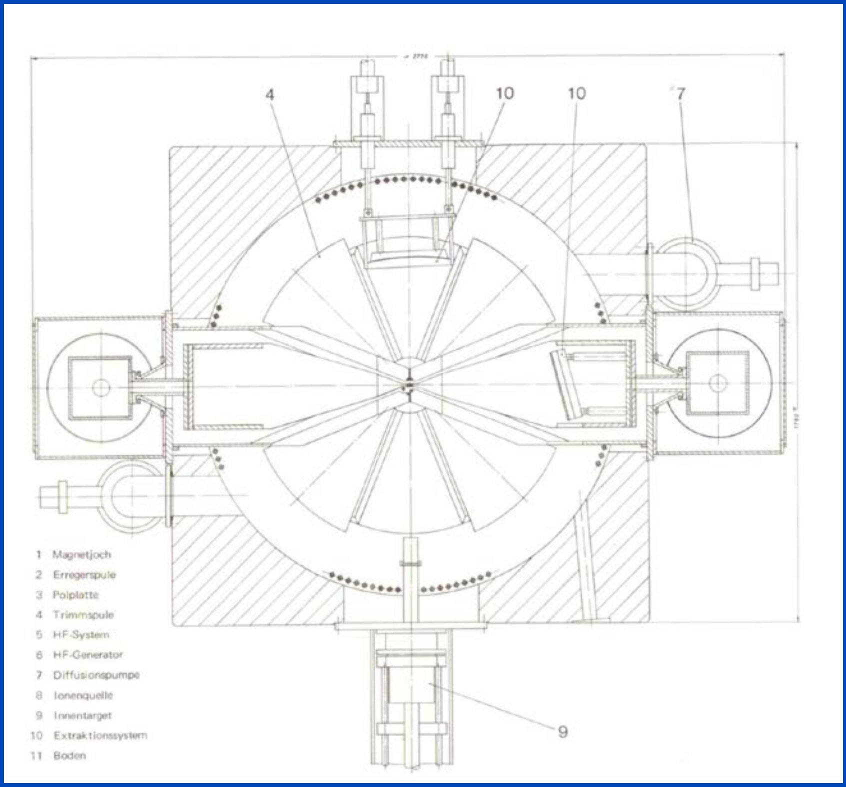
PET

Fig. 4 *Patient examination on a PET/CT scanner*

An examination of the patient takes place on a PET/CT scanner.
In modern nuclear medicine hybrid PET/CT and PET/MRI scanners are used.
The radiopharmaceutical is injected into the patient. It accumulates in the tumor. By external measuring of the radioactivity the tumor can be detected and evaluated noninvasively.

A Brief Historical Overview
The first Cyclotron from AEG - 1971

1971: Bought first AEG Cyclotron (straight hill sector; proton and He – 22MeV, 3He: 28, Deutrons: 11 MeV). The acceptance test of this cyclotron was not yet finished when AEG closed their cyclotron unit due to financial problems. Thus, the cyclotron team worked for themselves for its maintenance and repairs, ran for around 18 years

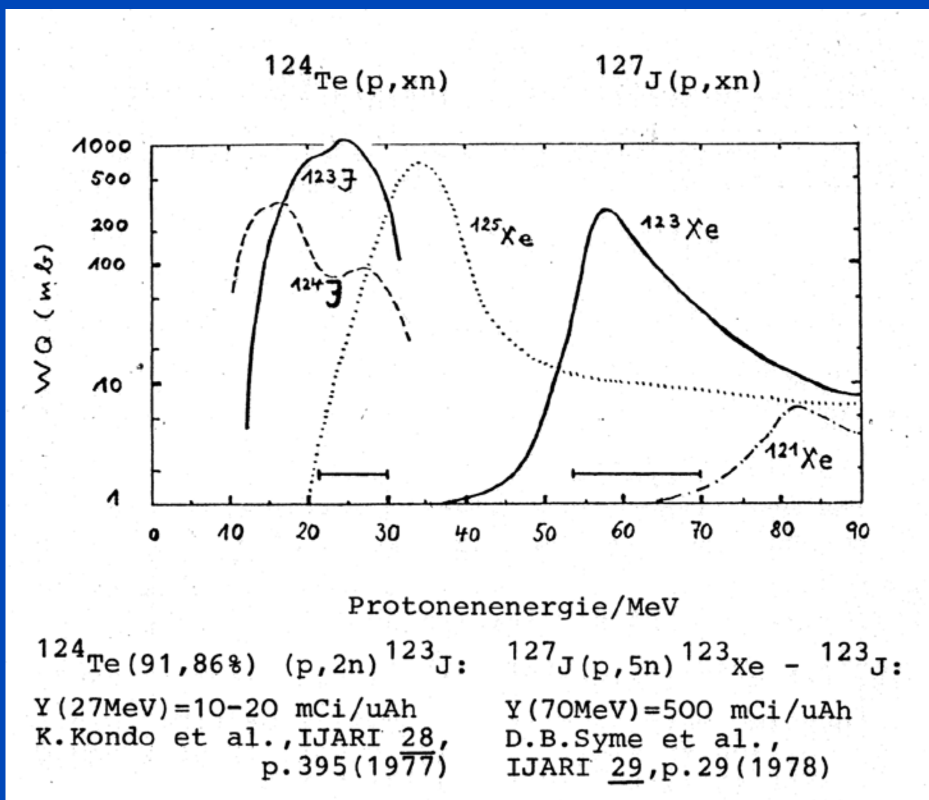


Already in 1980, it was quite obvious that AEG cyclotron, due to frequent break-downs and hard repair works, couldnt provide a long term reliability. Also, most cooperators recommended p and d with higher energies.

Overview continues 1980 - 1989

Basic considerations

a) Energy and Particles: to ease extraction and minimize radiation burden it was decided to choose a negative ion cyclotron



from the cross sections of the nuclear reactions for the relevant radionuclides ^{123}I, ^{81}Rb etc. we concluded the proton energy of the new cyclotron to be about 30 MeV

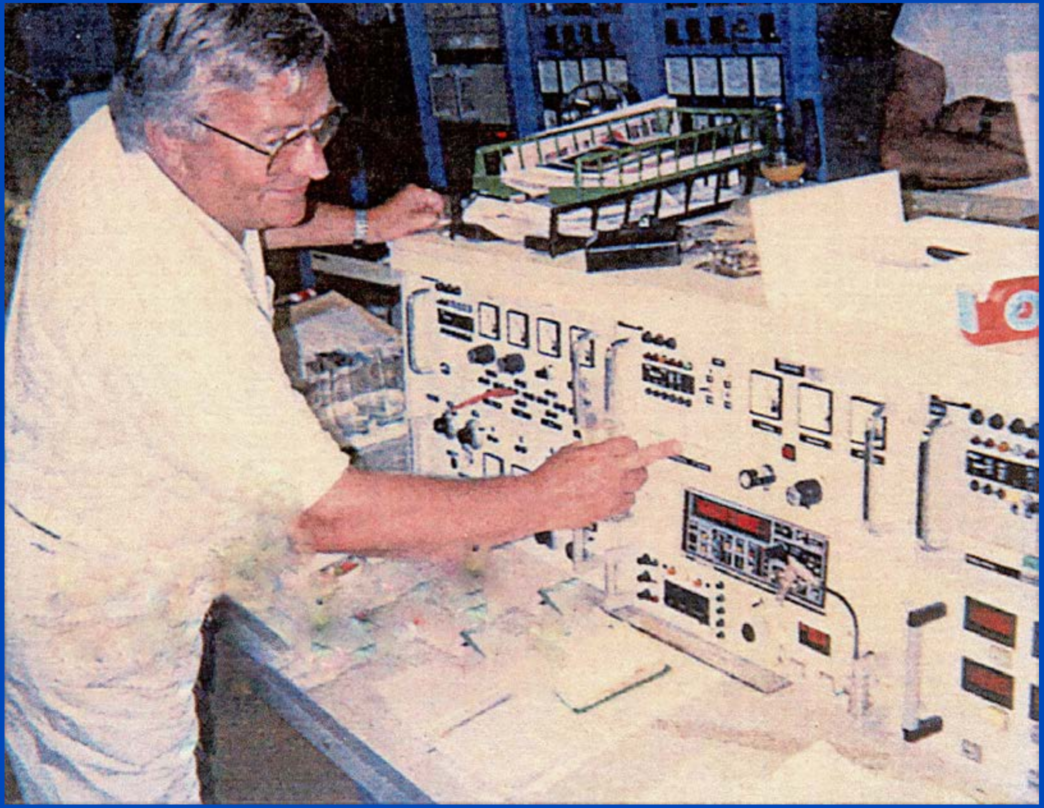
50 Years – Research for
A Life Without Cancer

b) Search for the appropriate Product

4 prominent cyclotron producers were asked:

- IBA: H^- yes, D^- no
- CGR: no negative ions
- TCC: had big problems at that time (main coils)
- Scanditronix: H^- yes, D^- we try it (Stig Lindbäck)
  - *and it worked!*

End of an Era (1971 - 1990)



- On July 15, 1990 the AEG Cyclotron was switched off by *Dr. Maier-Borst*, the then Head of the Department.
- A few weeks later, *Karl Erdmann* from Vancouver asked for the design drawings of the Magnet and took them with him.

A new Era – Scanditronix MC32NI(1991 - 2017)

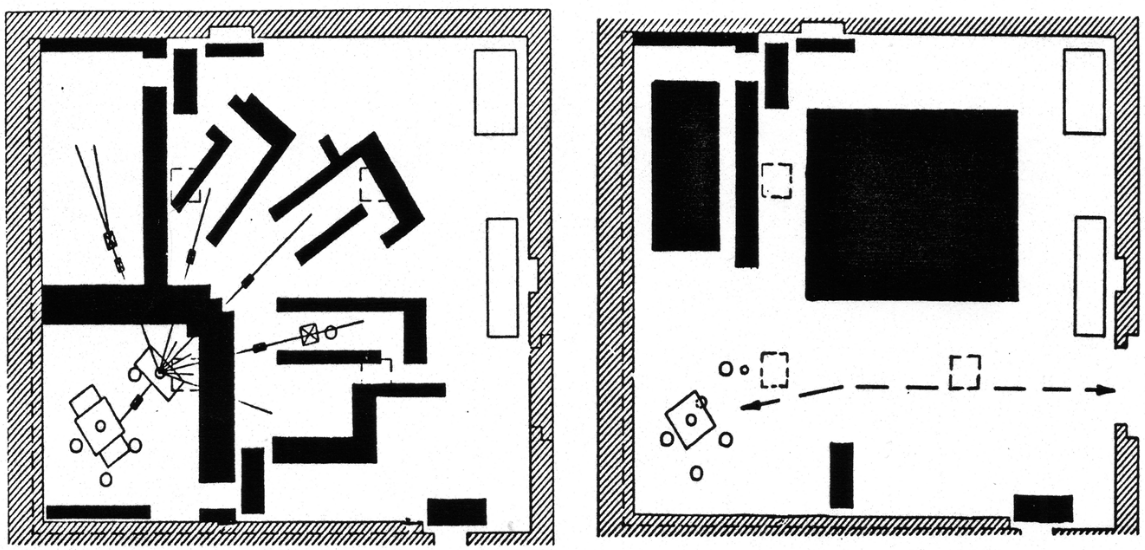
4 spiral sectors, 32 MeV H^-/p,16MeV D^-/d variable
Variable energy; 55 tons; 186 kVA

- 1988: Approval from International Peer Review Committee
- 1989: Ordered on 31.12.89: a few weeks after reunification of Germany
- 1990: tests in Uppsala with Scanditronix
- 1991: 25.04 and 27.04 – delivery of MC32NI to Heidelberg. In July, acceptance test
- 1992: the production of RNs for PET was started on a regular basis

Viplav Gupta
DKFZ,
Heidelberg

Reconstruction of the cyclotron hall

1000 tons of heavy concrete had to be set aside to make space for the exit of the CC + 200 tons donated by the GSI / Darmstadt for shielding the new cyclotron



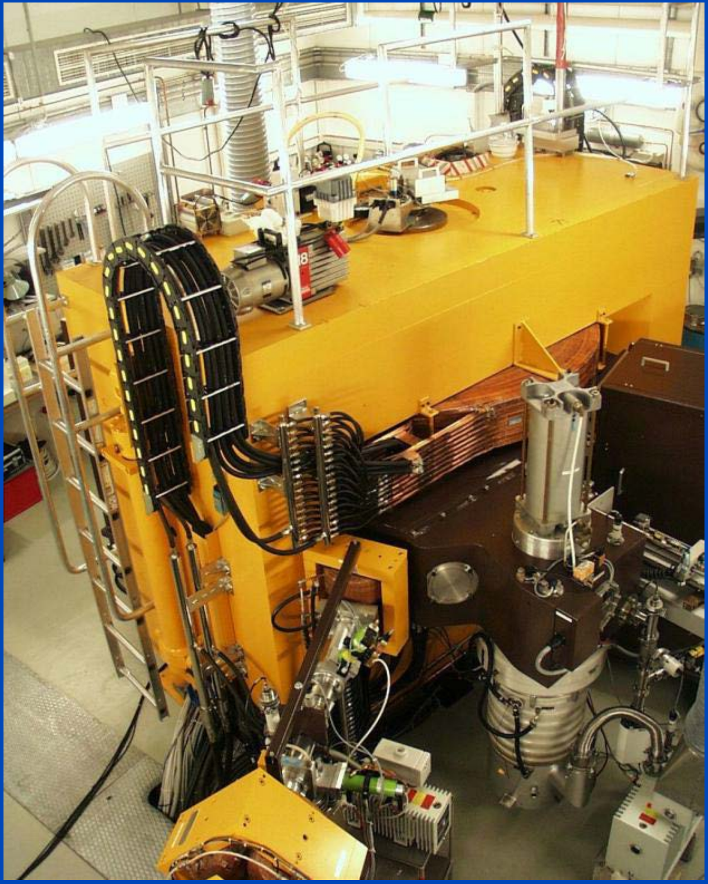
Urzustand
former structure

Weg frei für den Umzug
free way in / out

2 of its kind in the world

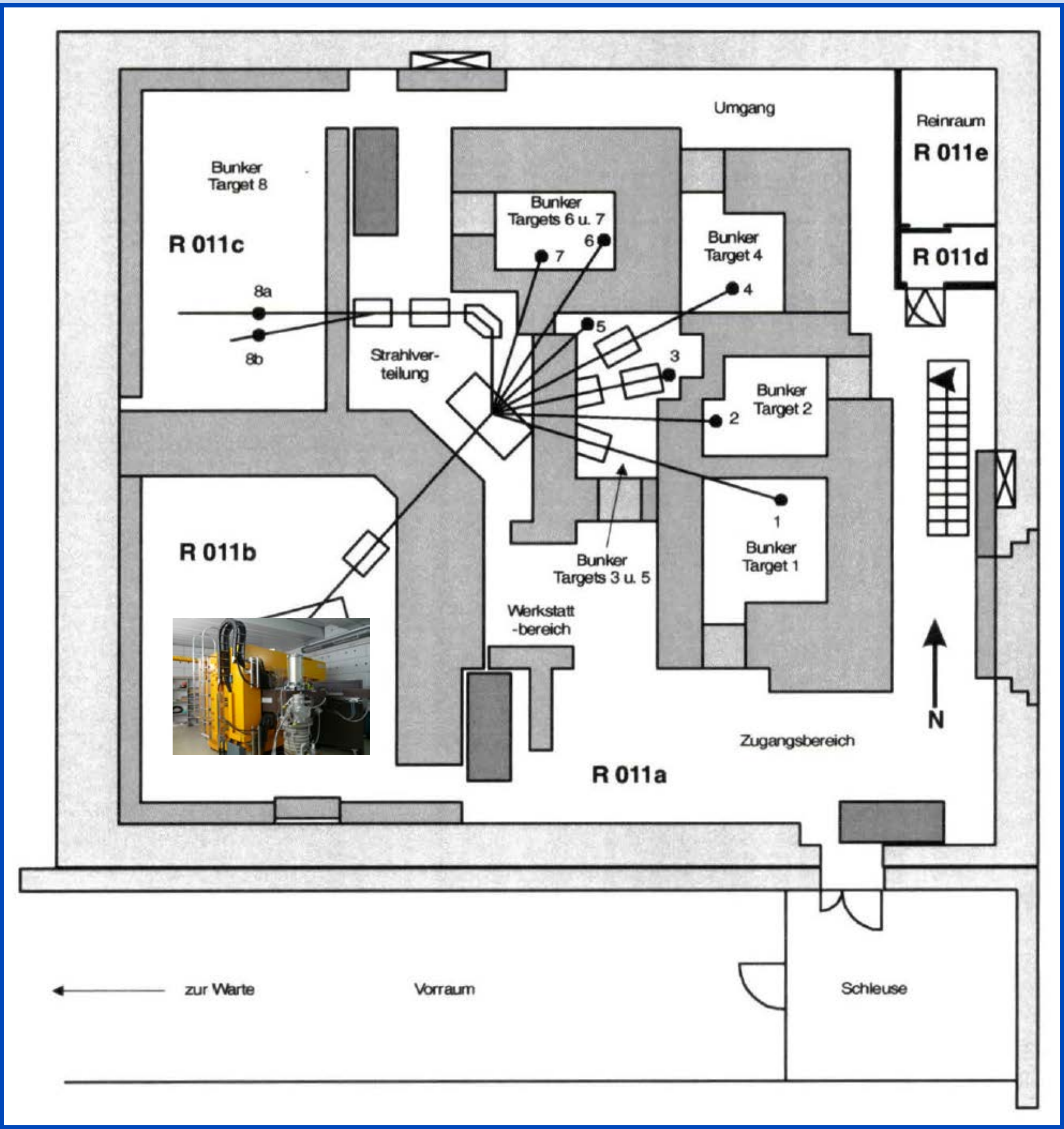
MC32NI @ DKFZ
Heidelberg, Germany

MC32NI @ Rigshospital
Copenhagen, Denmark
Pic: Dr. Holger Jensen, Copenhagen



Viplav Gupta
DKFZ,
Heidelberg

Layout of Heidelberg Cyclotron Hall



Currently radioisotopes production from our cyclotron

The cyclotron is employed for daily production of **$^{18}F^-$** which is further used for labelling of precursors of ;

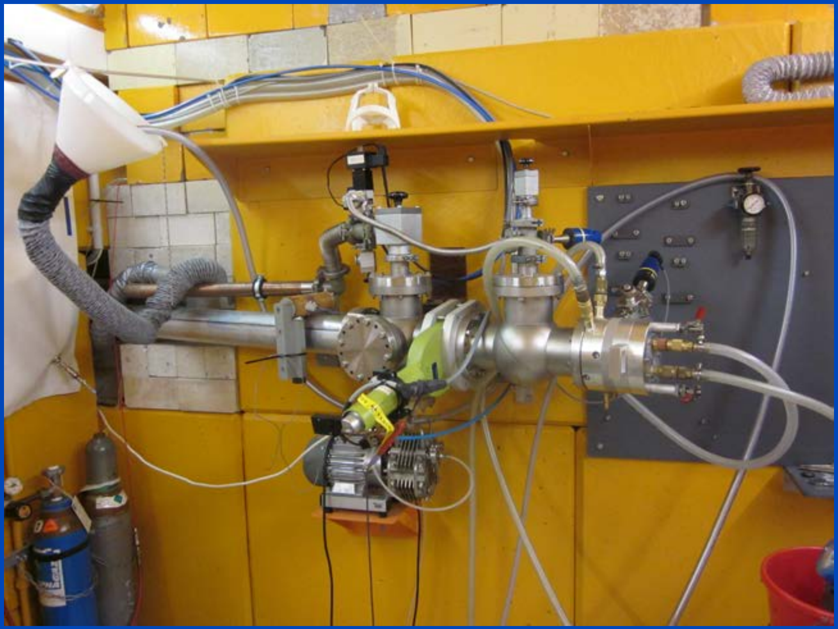
[^{18}F]Fluorodeoxyglucose (FDG),
[^{18}F]Fluorethyltyrosine (FET),
[^{18}F]Natrium Fluoride (NaF),
[^{18}F]Fluorothymidine (FLT),
[^{18}F]Fluoroazomycin Arabinoside (FAZA)
[^{18}F] PSMA-1007

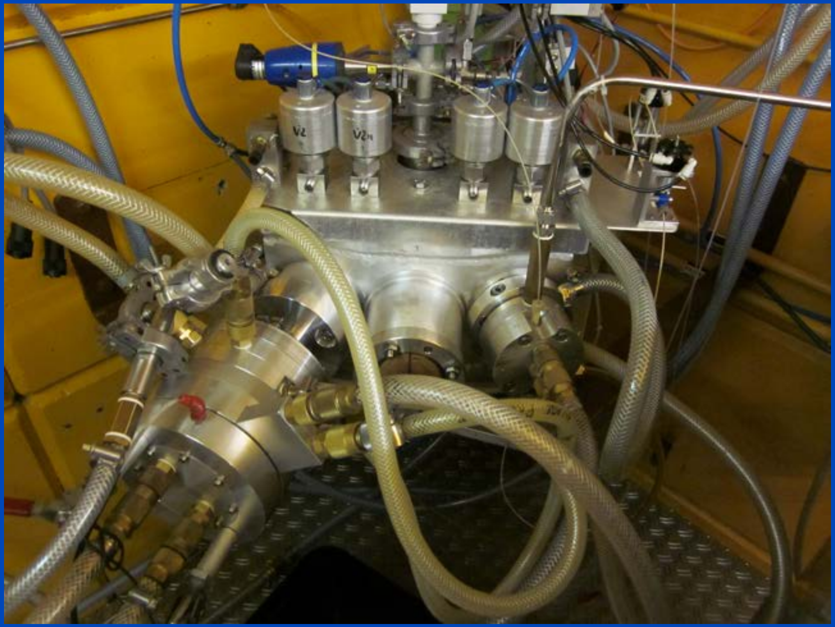
Nuklides	Nuclear Reactions Production in Cyclotron)	$T_{½}$ [min]
^{11}C	$^{11}B(p,n)^{11}C$	20,3
^{13}N	$^{16}O(p,\alpha)^{13}N$	9,97
^{15}O	$^{15}N(p,n)^{15}O$	2,03
^{18}F	$^{18}O(p,n)^{18}F$	109,8
^{64}Cu	$^{64}Ni(p,n)^{64}Cu$	12,7 h

And bimonthly/monthly production of **^{64}Cu** for PET studies

Viplav Gupta
DKFZ,
Heidelberg

Solid Target Design





Nuclear Reaction and Radiochemical Yield - ^{64}Cu

$^{64}Ni\ (p,n)^{64}Cu$

Energy at the target =11,7MeV

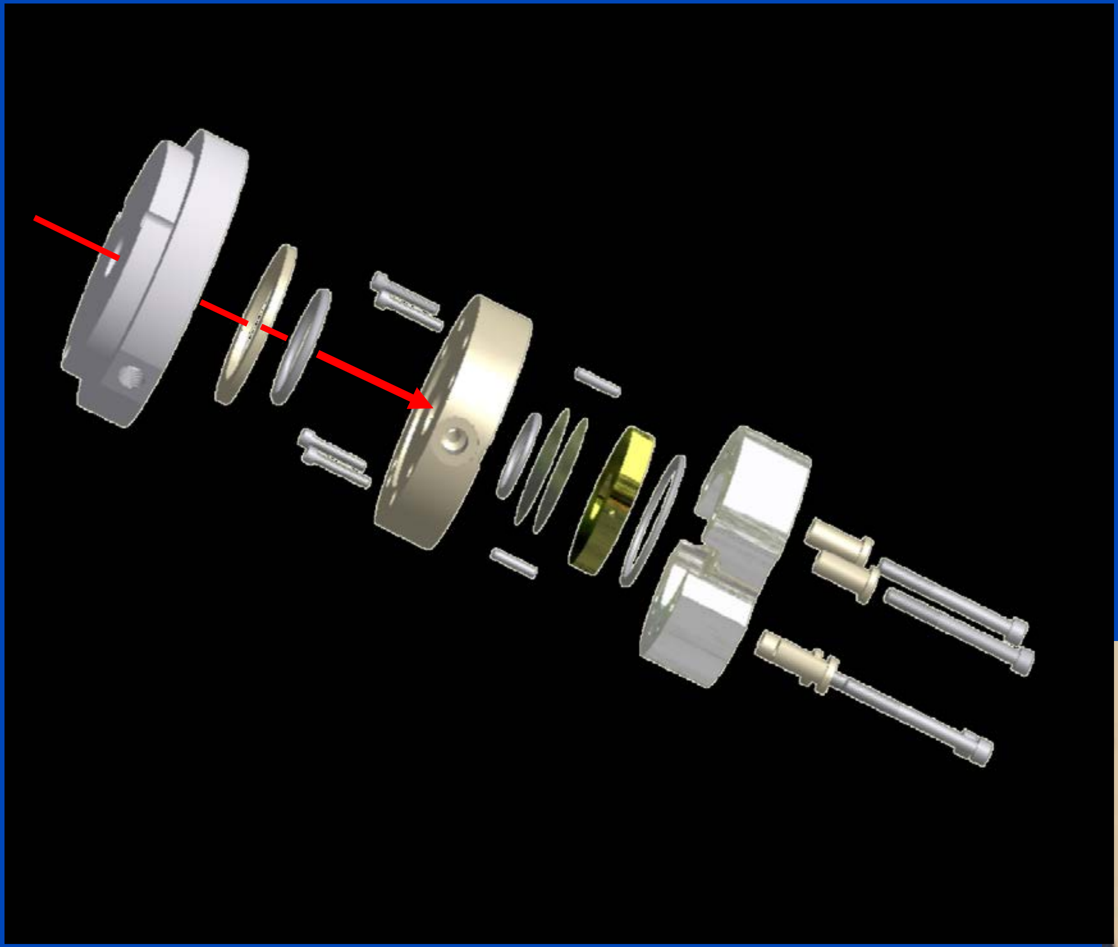
Beam Current = 25 µA

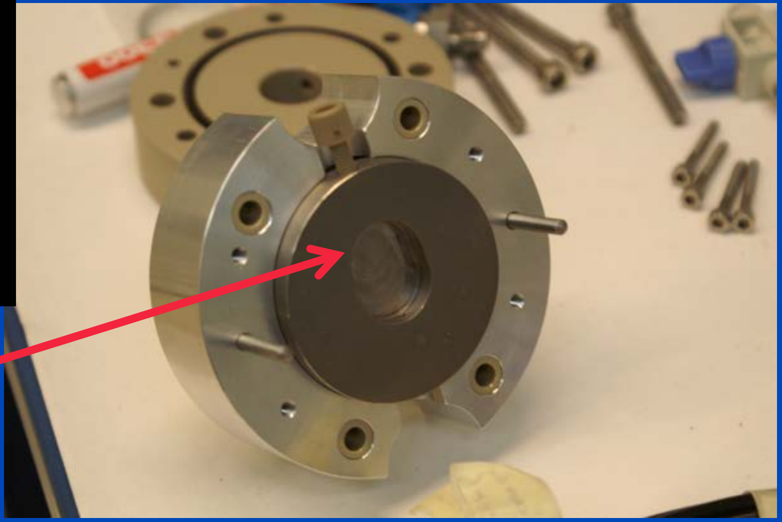
Power = 292,2 Watt

Start Energy (MeV)	Energy at the target (MeV)	Coulomb (µAh)	Amt. of Ni (mg)	Target disc	Yield (mCi)	mCi/µAh	Thickness of the target (µm)	
25	11,7	30	89,6	Gold	68,7	2,29	356,4	

Viplav Gupta
DKFZ,
Heidelberg

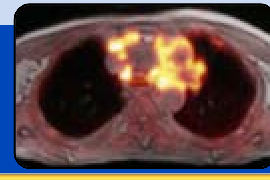
Liquid Target Design





Target filling
Volume: 3.06 ml

Goal & Challenge ➔ Translation into the Clinics



Imaging:

Detection tumor multifocality and biologic heterogeneity on a whole-body level

Radiopharmacy

Developing novel radiopharmaceuticals for diagnosis and therapy

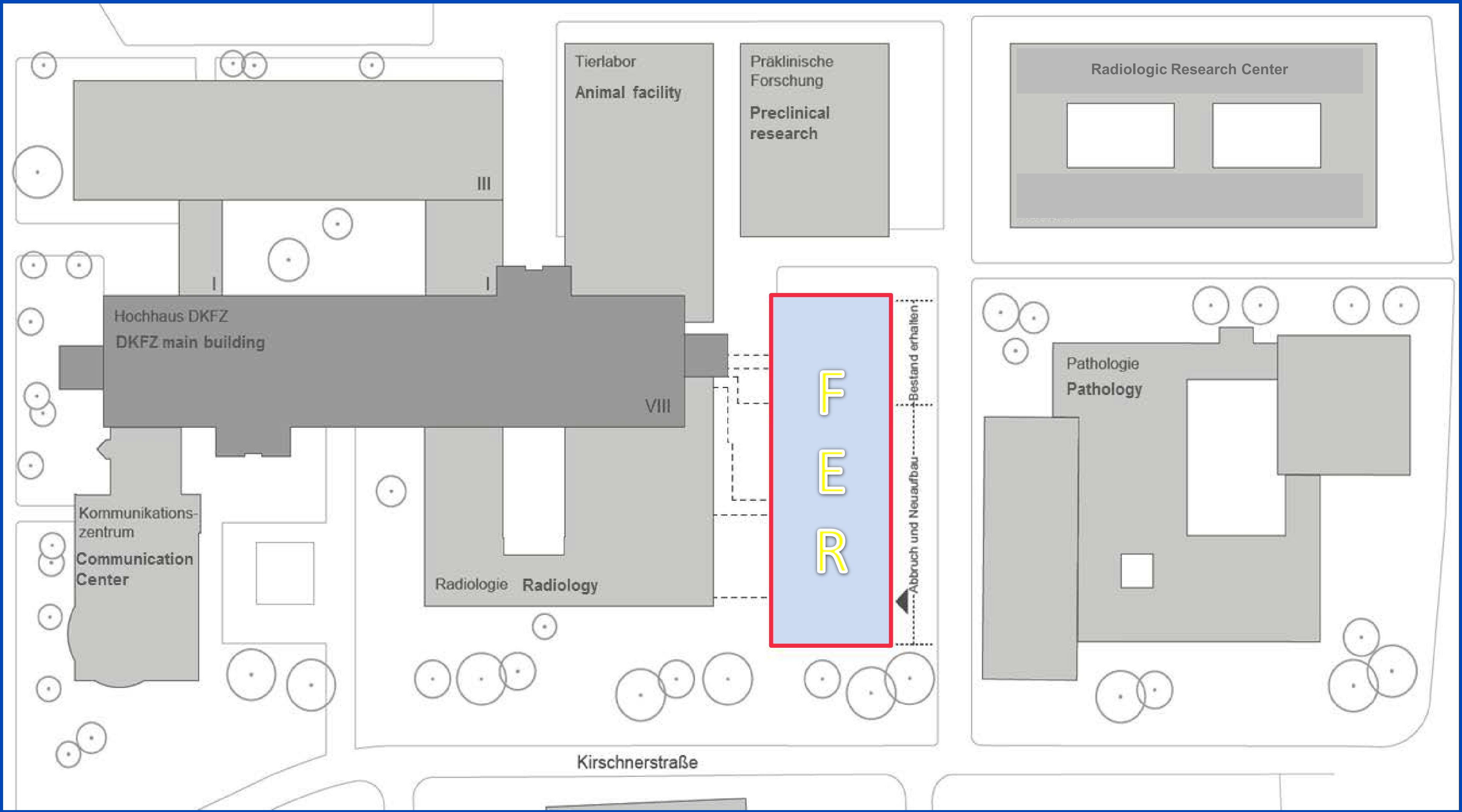
Radiooncology & Radiobiology

Developing biologically personalized, image-guided high-precision radiotherapy

New Faciltity ?????

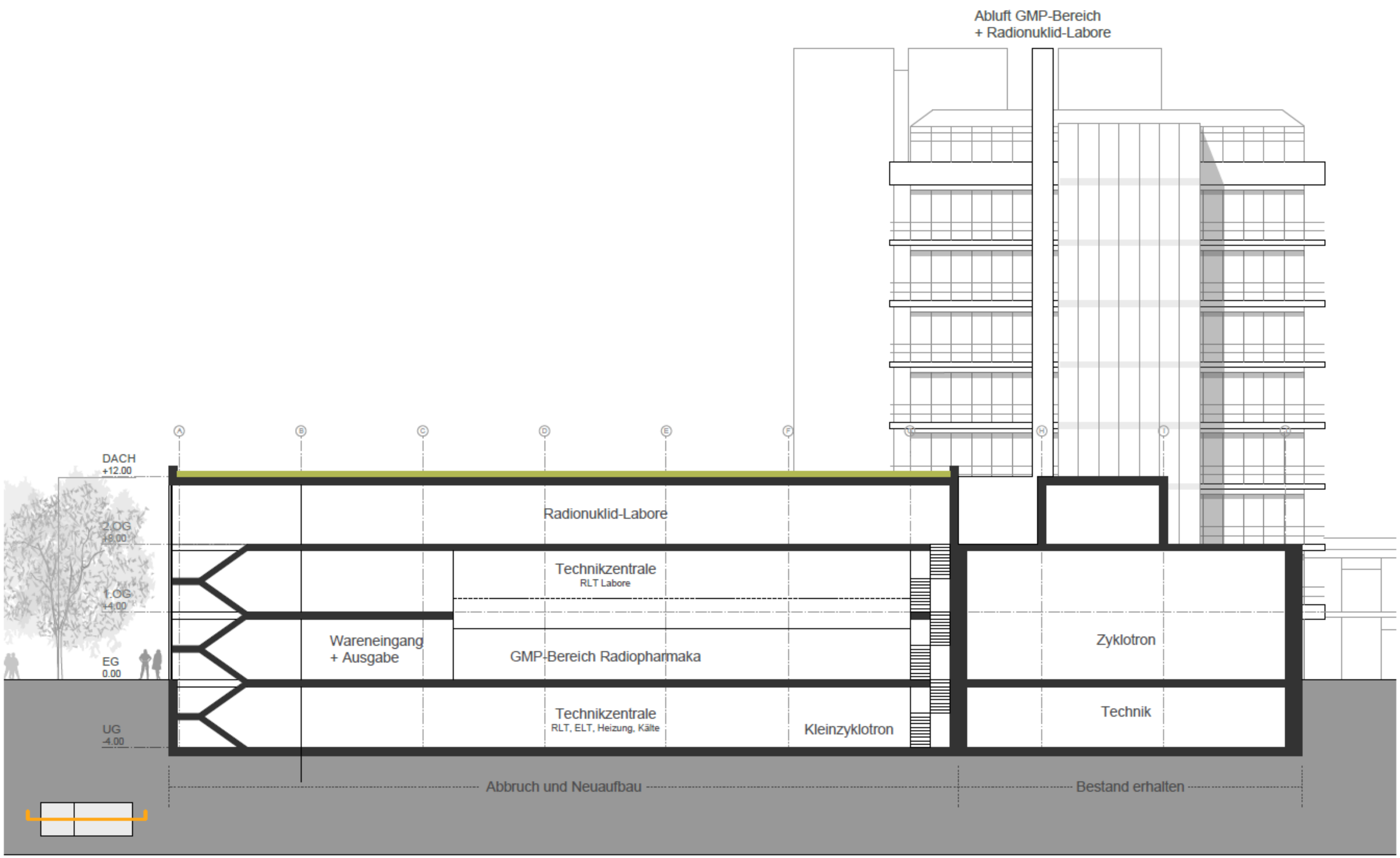
Proposal for Research and Development Center for Radiopharmaceutical Chemistry (FER)

dkfz.
50 Years – Research for A Life Without Cancer



Courtesy: Prof. Dr. Heinz-Peter Schlemmer

50 Years – Research for A Life Without Cancer



Forschungs- und Entwicklungszentrum für Radiopharmazeutische Chemie

Schnitt A
1:200

18. Juni 2014
Heinle, Wischer und Partner
Freie Architekten

Viplav Gupta
DKFZ,
Heidelberg

Proposal for Research and Development Center for Radiopharmaceutical Chemistry (planned …)

dkfz.

50 Years – Research for A Life Without Cancer

Radiology Research Center (starts 2014…)

50 Years – Research for
A Life Without Cancer

Massive problems since Feb’17

- 1) Leakage in the cooling room – defective valves, vacuum pumps
  - *Consequences*: Flood of water everywhere in the hall,
    - Danger of short circuits,
    - Alarms
- 2) Defective pressure sensors and flow regulators
  - *Consequences*: No monitoring of the cooling water possible leading to the damage of cooling tubes of the devices and power supplies for main magnet, RF, vacuum pump etc.
- 3) Automatic filling system in copper and aluminum circulation circuit
  - *Consequence*: Manual refilling of the 800 liters tank every 2-3 days
- 4) Software bug
  - *Consequences*: handling of radioactivity due to increased manual work
- 5) And so on…the list is long enough for this session ☺

Problems continue…

Reasons :

- i) Aging
- ii) Absence of maintenance contract, no expert support was available
- iii) Upgrades, maintenances, repairs not done periodically
- iv) Bad Luck, bad timing..?? Has to happen sometime..
- v) Tremendous pressure of routine production for clinics
- vi) Lack of spare parts and expert companies

- Needed → Money, time, resources

Viplav Gupta
DKFZ,
Heidelberg

Intent for future w.r.t. to radionuclides production from cyclotron

- Radionuclide production and Radiopharmceuticals development is and will be proceeding further towards Theranostic approach.

Diagnostic

- Theranostic

+

Therapeutic

- Goal:
- There are dozens of matched-pair combinations suited for theranostic approach.
- The idea is to buy those radionuclides readily and commercially available on the market,
- produce those which are not available from cyclotrons
- And to make their matched pair and go for theranostic approach !

Intent for future continued…..

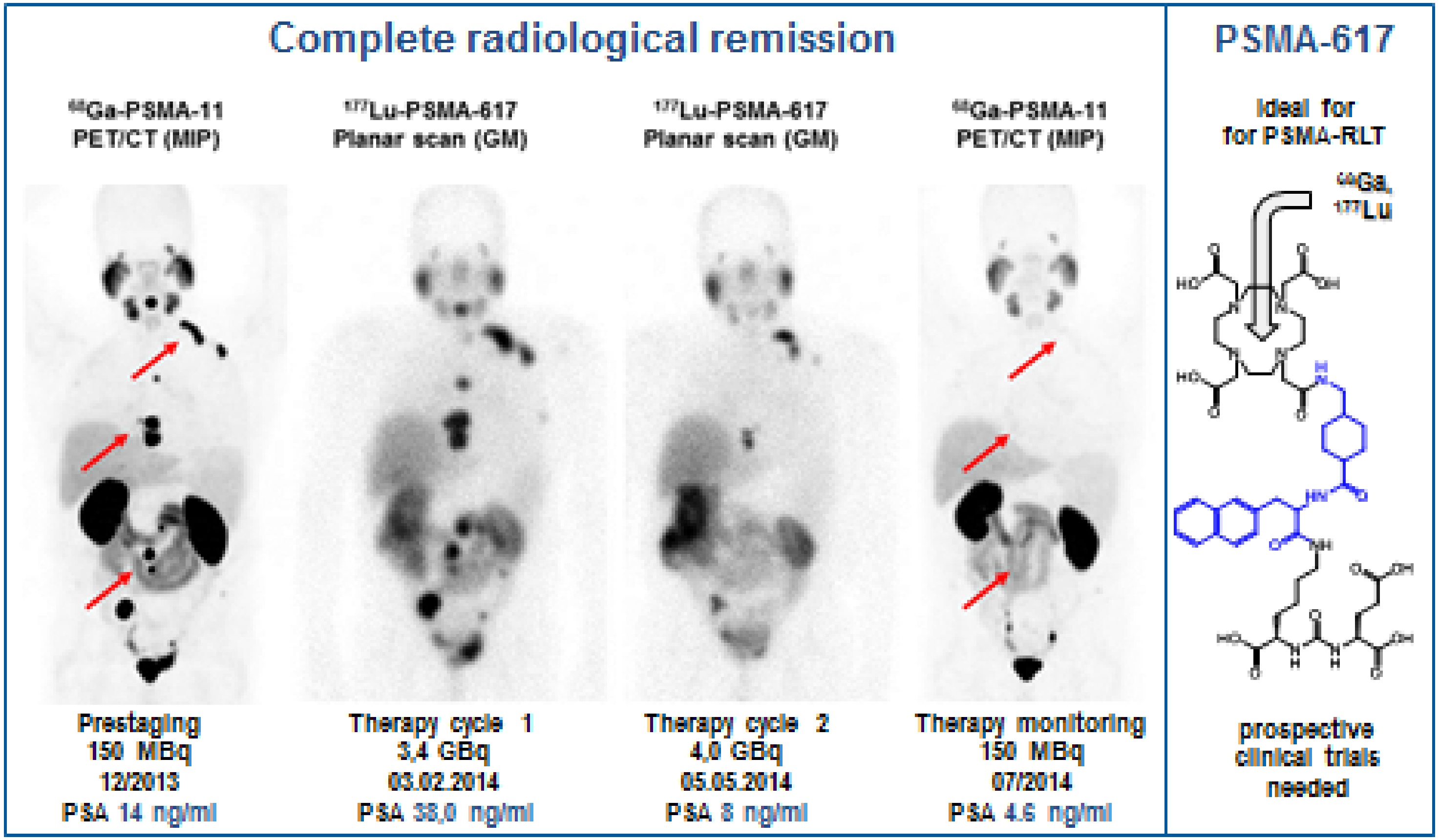
Theranostic Pairs	Half Life ($t_{1/2}$)	Decay mode	Nuclear reactions	Beam energy
$^{99m}Tc^*/^{186}Re$	6h/3.72d	γ=0.141 MeV (99%)/ β^-=1.07 MeV (71%), γ=137.2 keV (9.42 %)	$^{186}W(d,2n)^{186}Re$ $^{99m}Tc^*$ = commercially available	Deuterons ≈14MeV
$^{177}Lu^*/^{86}Y$	6.7d/14.7h	β^-= 0.49 MeV, γ=208 keV (11 %), 113keV (6.6%)^2 / β^+ = 1.2 MeV	$^{nat}Rb(d,2n)^{86}Y$ $^{86}Sr(p,n)^{86}Y$	d ≈ 16 MeV p ≈ 20 MeV
$^{90}Y^*/^{86}Y$	64.1h/14.7h	β^-= 2.28 MeV/ β^+ = 1.2 MeV	Do	-Do
$^{131}I^*/^{124}I^2$	8d/4.2d	β^-= 0.61 MeV/ β^+_{max}= 2.1 MeV	$^{124}Te(p,n)^{124}I$ $^{124}Te(d,2n)^{124}I$	p ≈ 15 MeV d ≈ 14-15 MeV
$^{90}Y^*/^{103}Pd^{**}$	64.1h/17d	β^-= 2.28 MeV/ γ=0.357 MeV, Auger electron = 20- 22 keV	$^{103}Rh(p,n)^{103}Pd$ $^{103}Rh(d,2n)^{103}Pd$	P ≈ 21 MeV P ≈ 15 MeV

*^{99m}Tc, ^{177}Lu, ^{90}Y, ^{131}I: very good commercial availability; ** Being an Auger electron emitter like ^{125}I, we suggest e.g. ^{103}Pd as rare alternative Auger electron emitter and good replacement for ^{125}I which itself is a reactor based nuclide.

•Zhanga, X et al., Appl. Rad. and Isot. 2001; 54(1); 89-92
•Schmitz, J., EJNMMI 2011
•Cyclotron Produced Radionuclides: IAEA TRS 468

E.g.: The in vivo theranostic approach: ^{177}Lu-PSMA-617

The in vivo theranostic approach: ^{177}Lu-PSMA-617



Kratochwil C et al. Eur J Nucl Med Mol Imaging 2015; 42: 987-988. IMAGE OF THE MONTH: January.
Benešová M et al. J Nucl Med 2015; 56: 914-920. SNMMI IMAGE OF THE YEAR 2015

Possible Scenarios for future…..

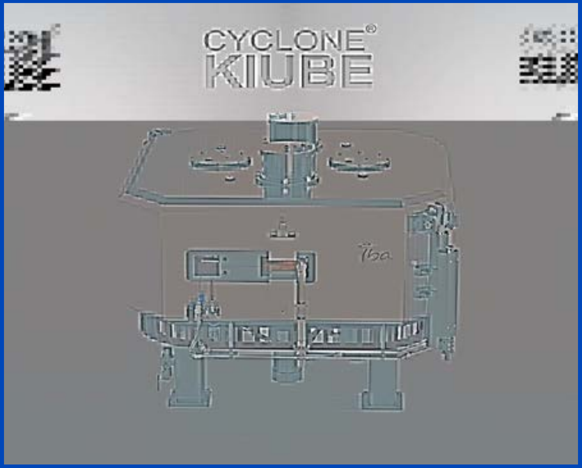
- *Case 1*
- Holding MC32NI for theranostic radionuclides and purchasing another small compact cyclotron (18/9 MeV) for meeting routine demands of clinics (^{18}F, ^{11}C, ^{15}O etc..)
- Downtime ≤ 1%
- Space requirement : 40 – 50 m^2
- Could easily be accomodated in FER
- Major manufacturers : GE Healthcare, Ion Beam Applications (IBA),
    - Advanced Cyclotron System Incorporations (ACSI)

P.S.: In a big research center like DKFZ two cyclotrons are not a luxury but a necessity if both (research and routine) concepts have to be gained.

Viplav Gupta
DKFZ,
Heidelberg

Case 1 (MC32NI + Compact cyclotron)

GE PETtrace 880

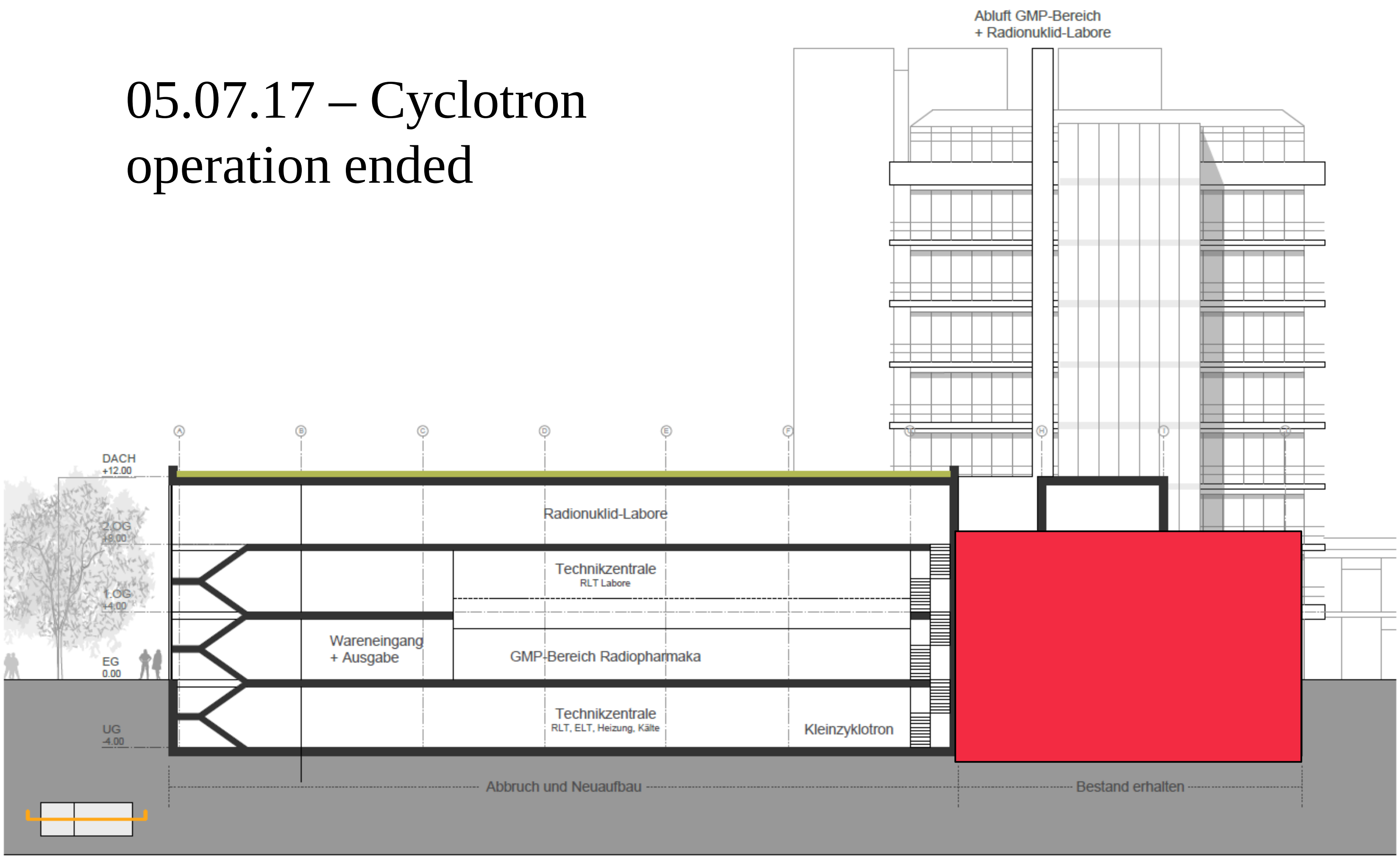


IBA Cyclone Kiube

ACSI TR 19/9

Installation in FER ??

05.07.17 – Cyclotron operation ended



Forschungs- und Entwicklungszentrum für Radiopharmazeutische Chemie

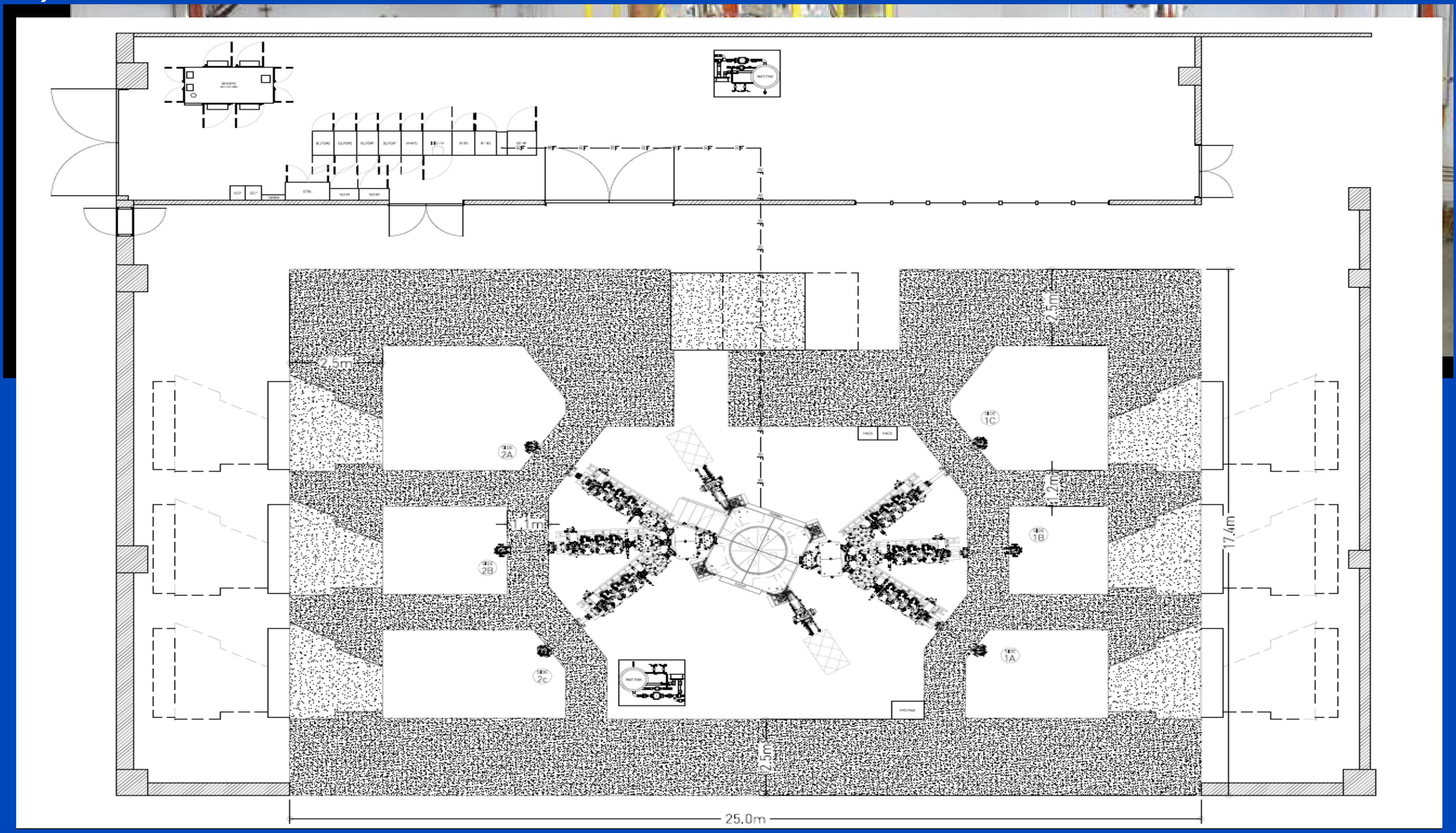
Schnitt A
1:200

18. Juni 2014
Heinle, Wischer und Partner
Freie Architekten

Viplav Gupta
DKFZ,
Heidelberg

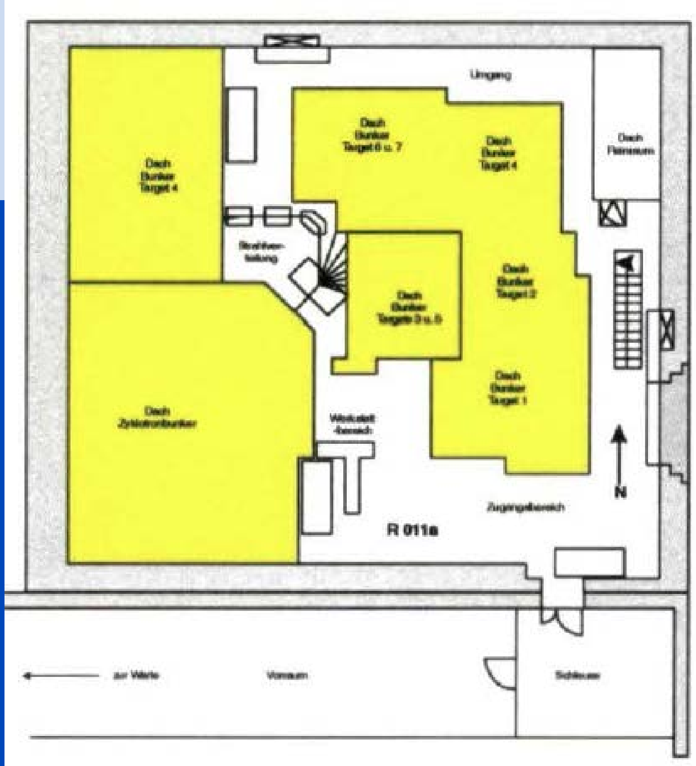
Case 2: Cyclotrons available on the market

- 1) ACSI TR 30/15



Decommissioning

ensity of Concrete	2400	kg/m3								
	Objekt	Form	Upper breadth (cms)	Lower breadth (cms)	length (cms)	height (cms)	Volume (cubic meters)	Weight (tonnes)	Number	Total Weight (tonnes)
	A	Trapezium	49	32	595	52	1,25307	3,007368	48	144,353664
	A1	Trapezium	49	32	830	52	1,74798	4,195152	43	180,391536
	B	Cuboid	50	0	500	50	1,25	3	41	123
	C	Cube	50	0	50	50	0,125	0,3	122	36,6
	D	Cuboid	98	0	100	197	1,9306	4,63344	5	23,1672
	E	Cuboid	100	0	50	100	0,5	1,2	161	193,2
	F	Cuboid	50	0	24	12	0,0144	0,03456	14	0,48384
	G	Cuboid	50	0	200	50	0,5	1,2	205	246
	H	Cuboid	50	0	100	50	0,25	0,6	350	210
	I	Cuboid	50	0	400	50	1	2,4	21	50,4
	K	Cuboid	50	0	250	50	0,625	1,5	41	61,5
	L	Cuboid	25	0	100	50	0,125	0,3	18	5,4
	M	Cuboid	30	0	50	100	0,15	0,36	5	1,8
	N	Cuboid	20	0	28	15	0,0084	0,02016	61	1,22976
	O	Cuboid	20	0	14	15	0,0042	0,01008	4	0,04032
	P	Cube	20	0	20	20	0,008	0,0192	34	0,6528
	Q	Cuboid	25	0	25	12,5	0,0078125	0,01875	31	0,58125
	R	Cuboid	50	0	50	75	0,1875	0,45	7	3,15
	Y	Cuboid	50	0	50	175	0,4375	1,05	1	1,05
	Z	small stones	15		25	25	0,009375	0,0235	592	13,912
							Total		1804	1296,91237


R 011a
N


R5

Predicted Time Frame

- Dec 2018/Jan 2019 – Movement to REZ, stop production, decay time.
- Dec 2019 – 2024 ?? Demolishing the existing building and building a complete new Building with GMP Compliant
- 2022 – 2024 – Application for a new Cyclotron, commissioning
- 2025 onwards – After acceptance test, restart of new cyclotron operation
- In the meantime, constant looking for interim solutions to carry forward our research program. Getting protons from somewhere ☺

Promising Radionuclides for future

- ^{18}F – Godfather. Cant be replaced
- ^{68}Ga – Needs production from cyclotrons. Solid targets ?
- ^{225}Ac – Targeted Alpha therapy. Has to come sooner or later. Long story. Finance ? Radiochemists?
- ^{44}Sc – Could also provide back up to our cooperators in PSI. Transportation is feasible due to ≈ 4h $t_{1/2}$

Thank You