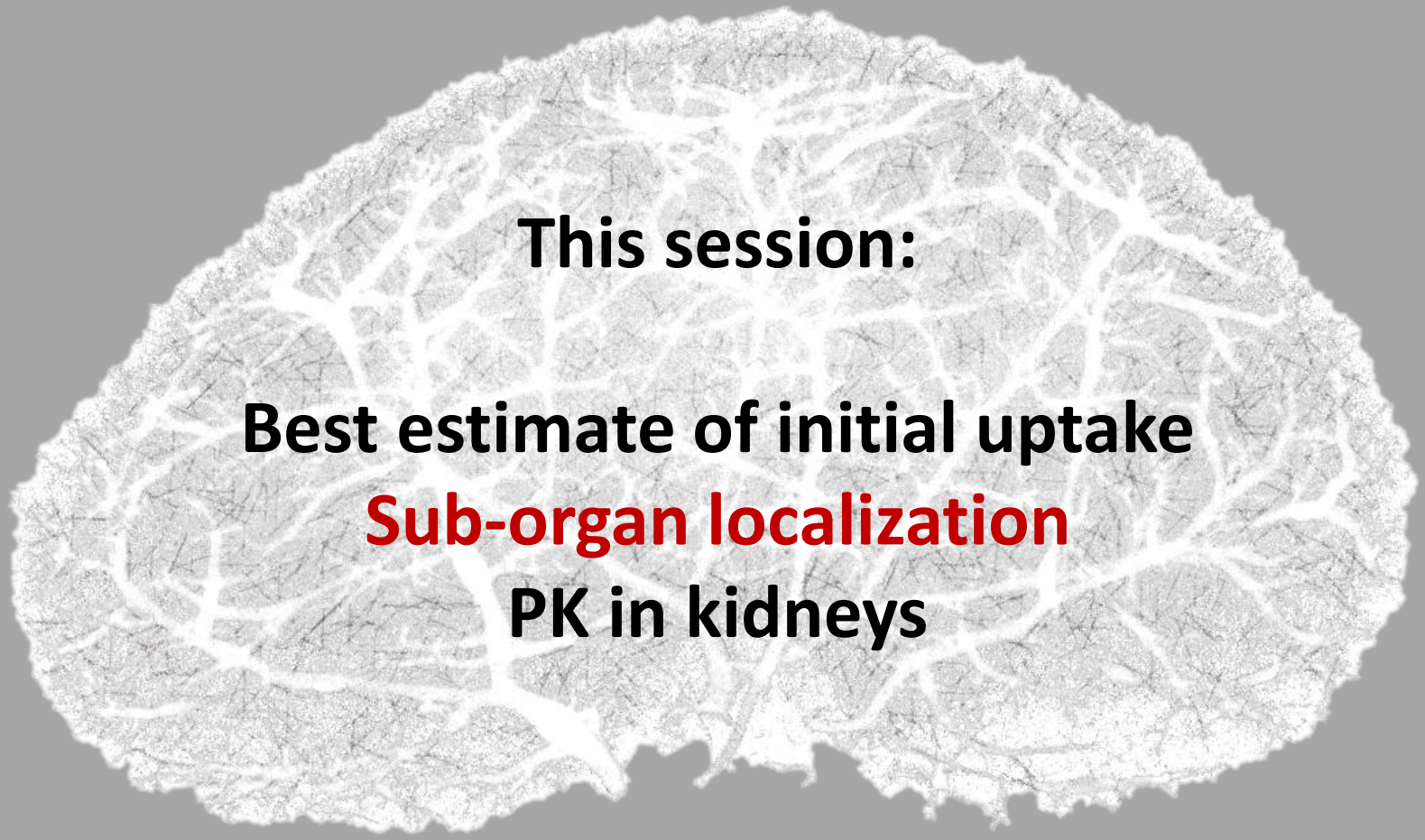
NTCP for kidneys in RPT



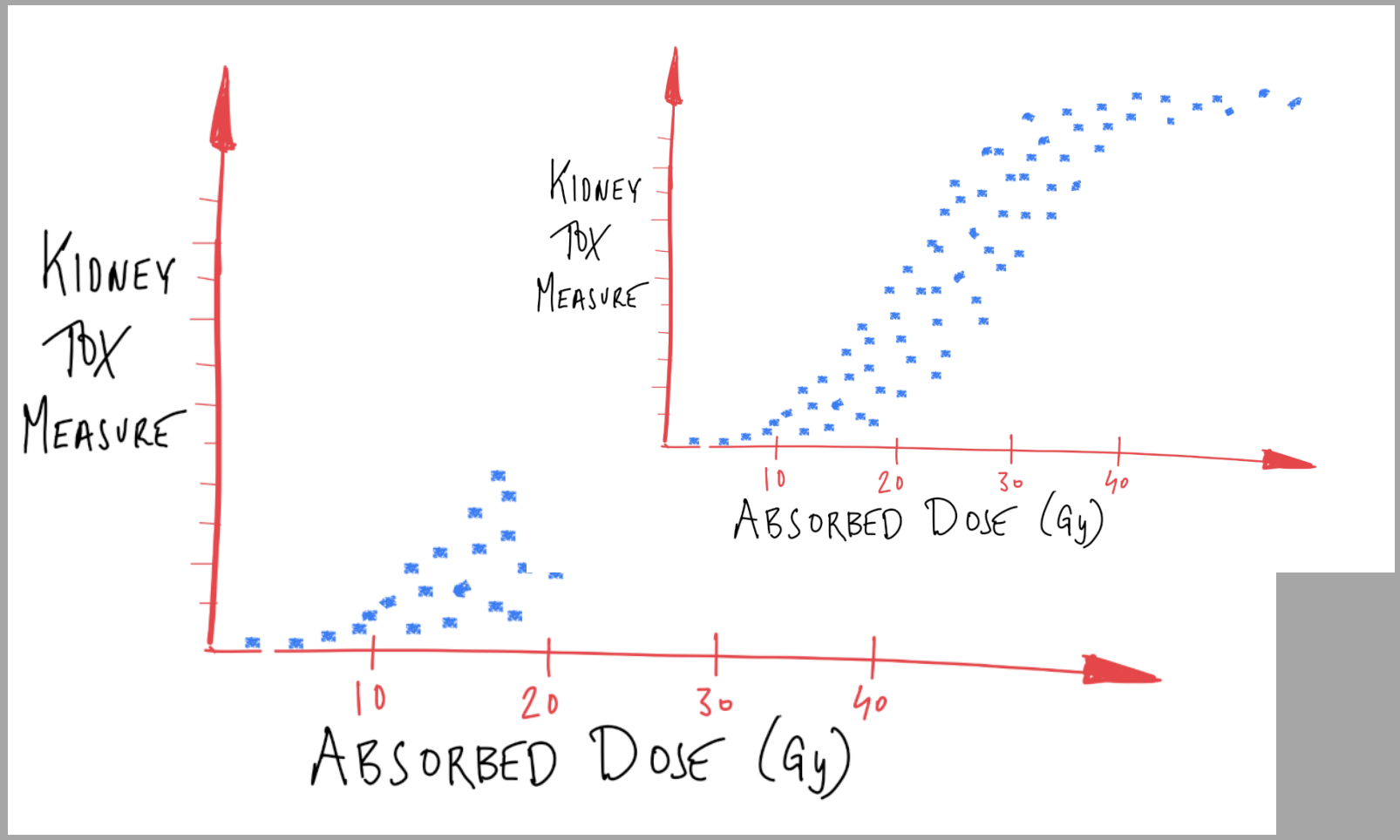
This session:

Best estimate of initial uptake

Sub-organ localization

PK in kidneys

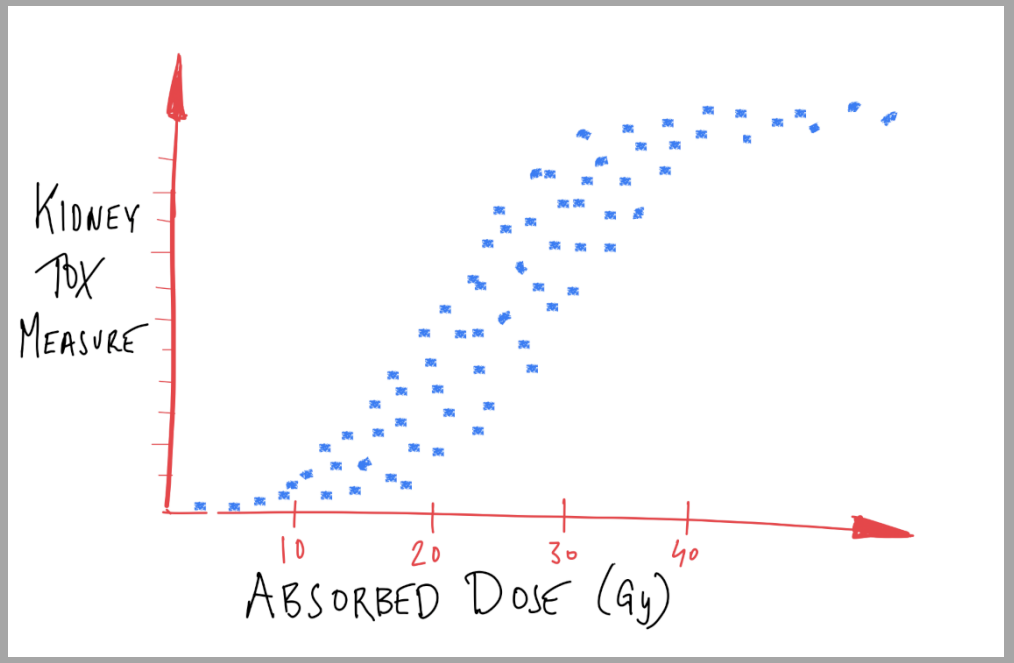
NTCP for kidneys in RPT



NTCP for kidneys in RPT

But….which endpoint?
Serum Creatinine?
Cystatine C?
eGFR? BUN? HCt? EVF?
$eGFR_{cr}$? $eGFR_{cy}$? $eGFR_{cr+cy}$?
Measured GFR? (mGFR)
MAG-3 scint?

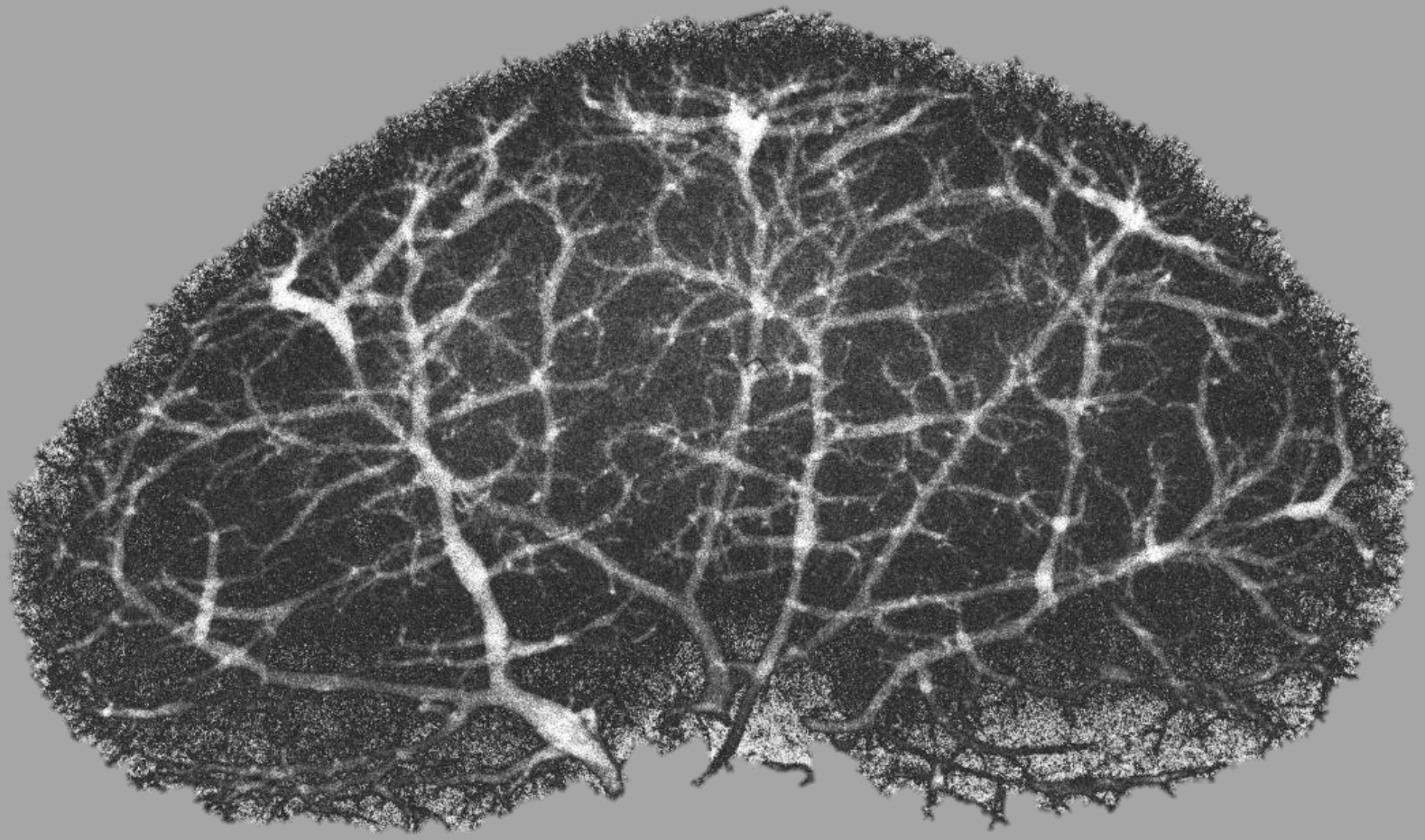
At what follow-up time?



To which volume/compartment?
Whole kidney?
Cortex?
Proximal tubules?
Glomerulii?

Calculated how?
Mean absorbed dose?
BED?
EUD?

Acute and long-term kidney toxicity in mice after i.v. alpha-RIT with ^{211}At-MX35-F(ab')$_2$



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Fractionated i.v. alpha-RIT with ^{211}At-MX35-Fab$_2$

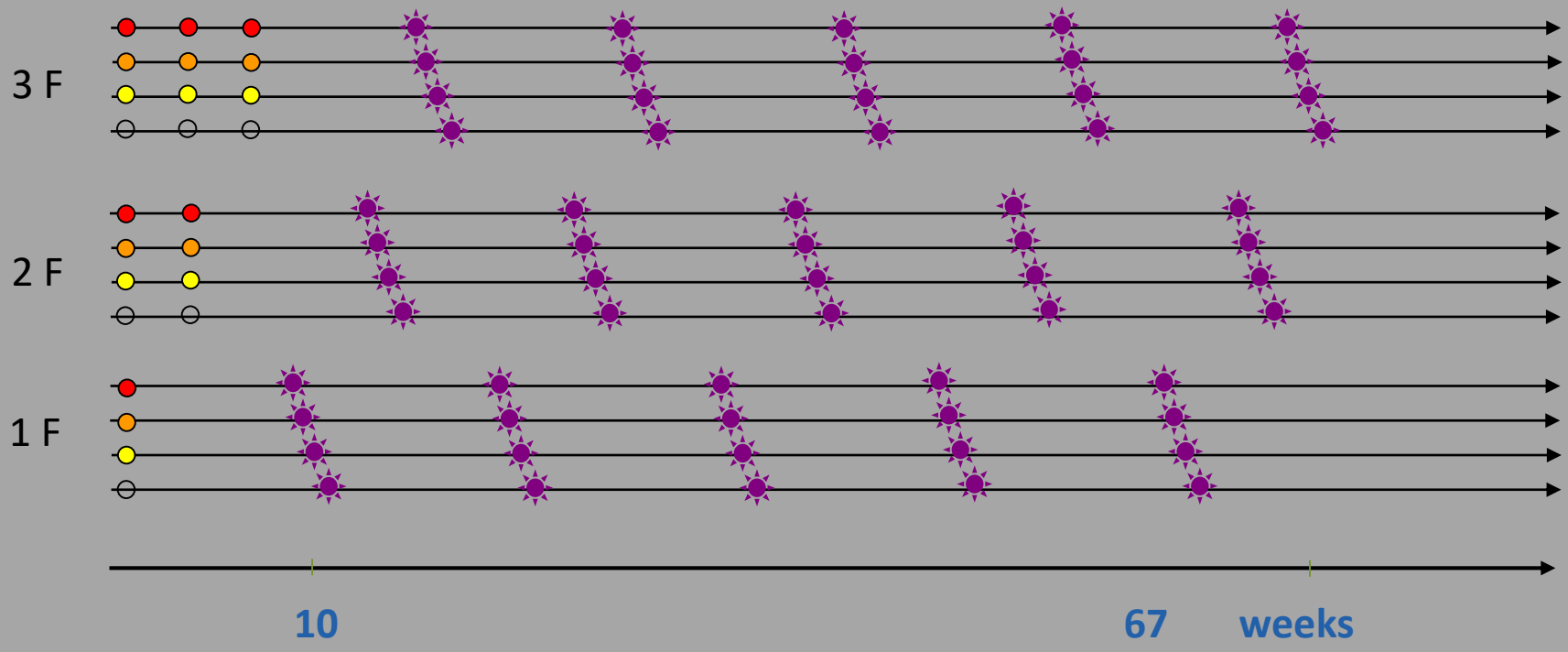
TABLE 1. STUDY GROUPS AND EXPERIMENTAL DESIGN

Group[a]	Number of injections	Administered activity in injection				Mean absorbed dose to the kidney[b]
		1 (kBq)	2 (kBq)	3 (kBq)	Total (kBq)	(Gy)
1	3	1340	1460	1100	3900	15
2	3	870	630	770	2270	8.8
3	3	360	460	480	1300	4.7
4	3	—	—	—	—	0
5	2	1530	1430	—	2960	12
6	2	1020	600	—	1620	6.3
7	2	500	450	—	950	3.7
8	2	—	—	—	—	0
9	1	1100	—	—	1100	4.3
10	1	770	—	—	770	3.0
11	1	380	—	—	380	1.5
12	1	—	—	—	—	0
13	3	1000	910	1060	2970	12
14	3	500	440	420	1360	5.3
15	2	1000	1140	—	2140	8.3
16	2	500	610	—	1110	4.3
17	1	1530	—	—	1530	6.0
18	1	1020	—	—	1020	4.0
19	1	500	—	—	500	1.9
20	1	—	—	—	—	0

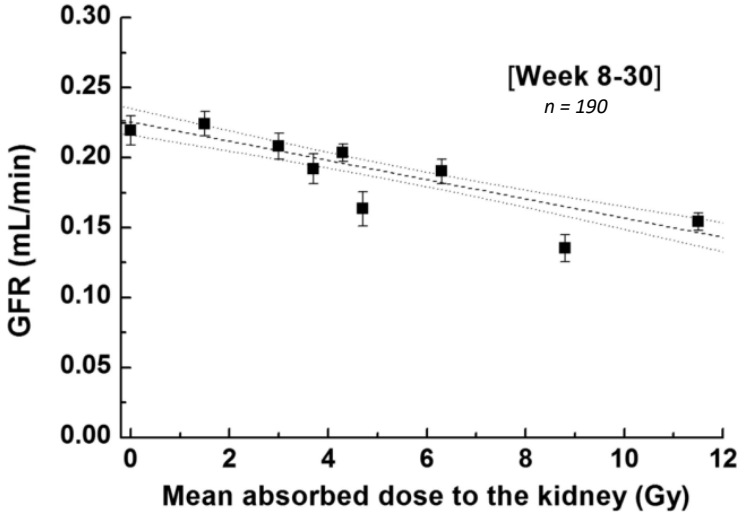
[a]Six to 10 animals per group. Groups 1 through 12 were initially tumor carriers.
[b]Total dose from all injections.

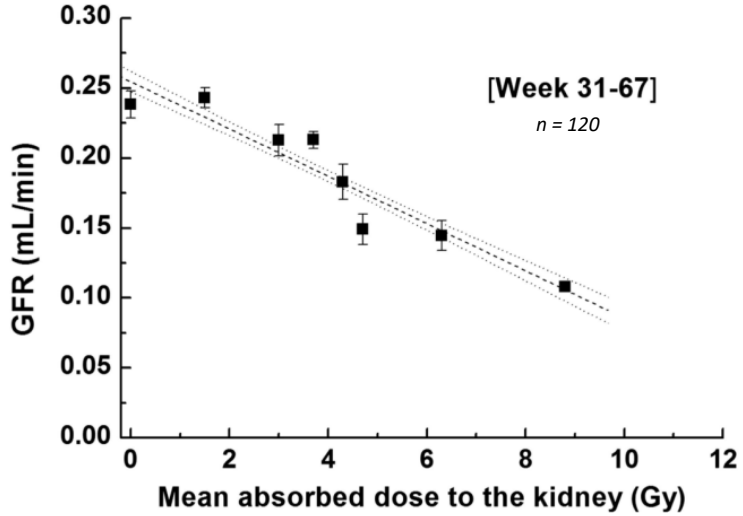
*For repeated injections,
the absorbed doses were summed

Repeated GFR -measurements
(mGFR with ^{51}Cr-EDTA)

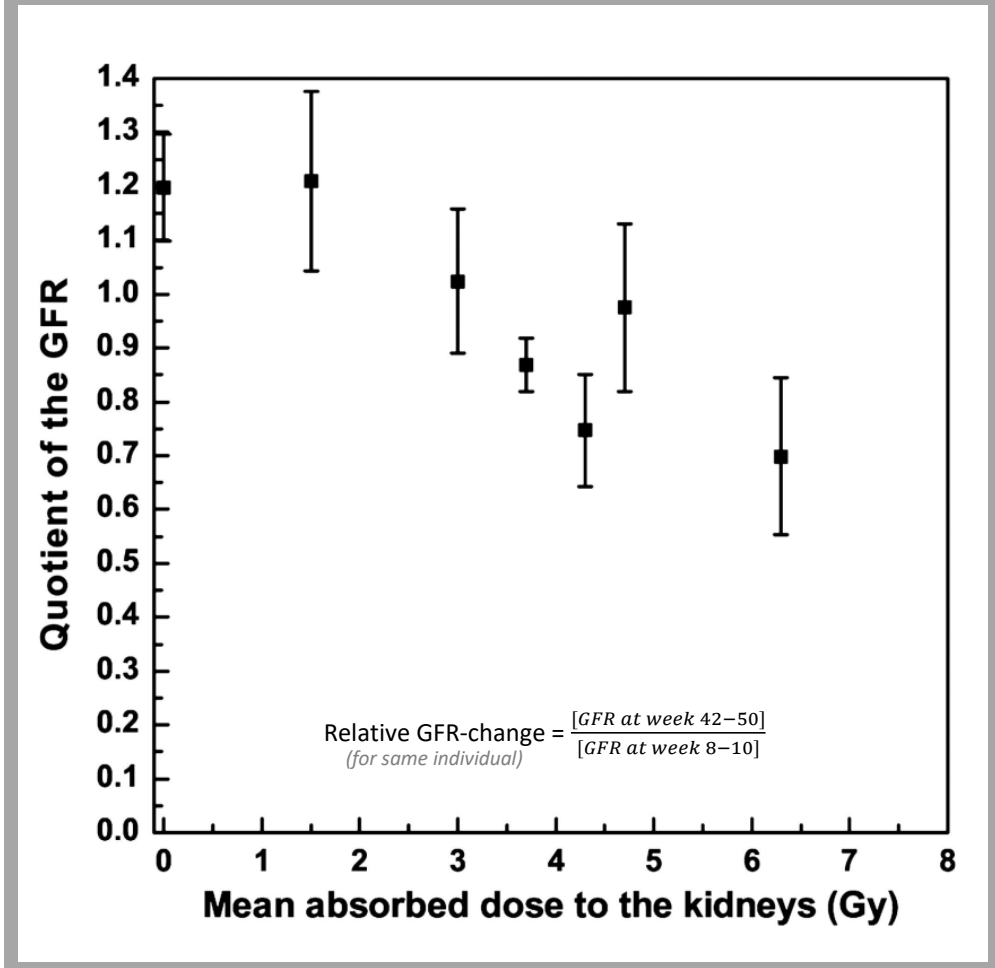


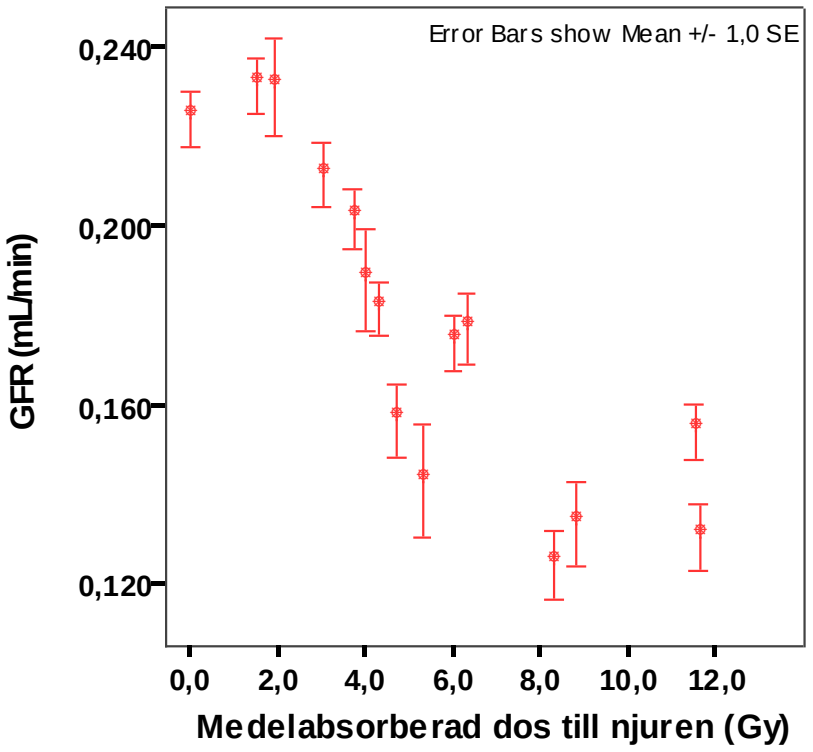
Dose-dependent reduction in GFR after i.v. TAT

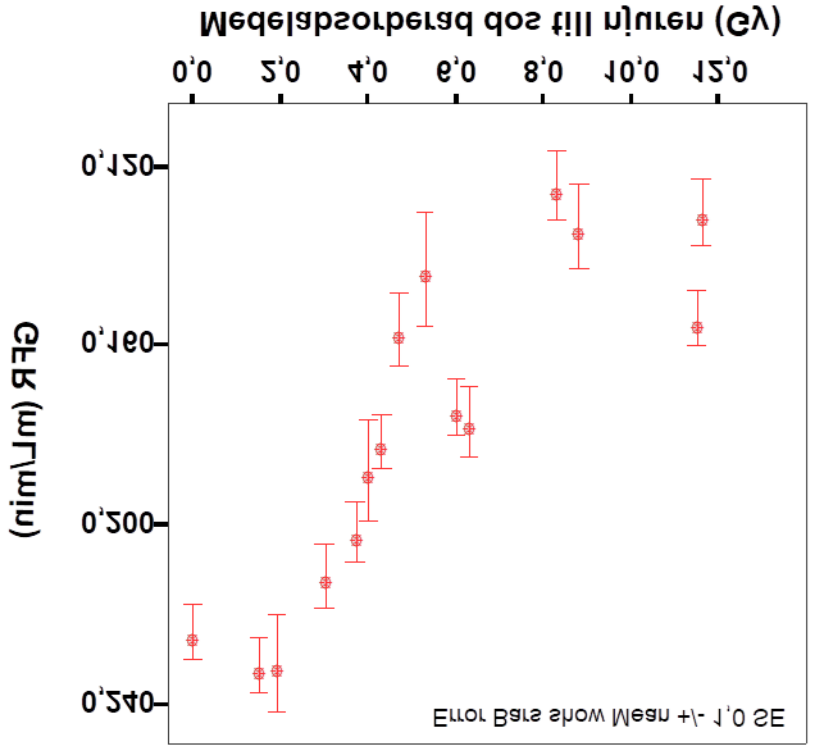




Time-progressive kidney toxicity




Error Bars show Mean +/- 1,0 SE
GFR (mL/min)
0,240
0,200
0,160
0,120
0,0
2,0
4,0
6,0
8,0
10,0
12,0
Medelabsorberad dos till njuren (Gy)


Medelabsorberad dos till njuren (Gy)
0,0
2,0
4,0
6,0
8,0
10,0
12,0
GFR (mL/min)
0,240
0,200
0,160
0,120
Error Bars show Mean +/- 1,0 SE

RBE?

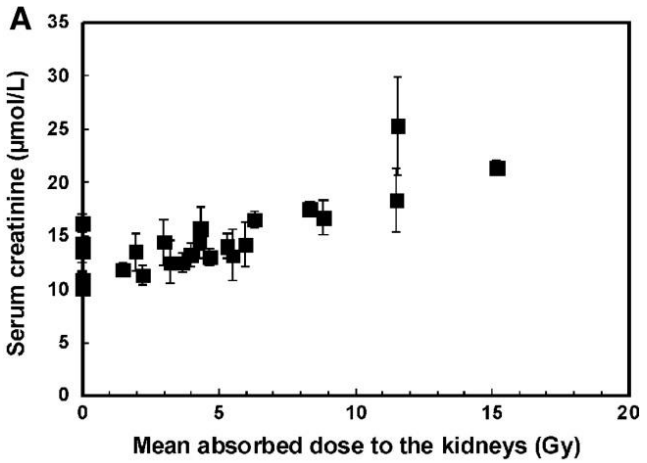
XRT: 240 kV X-rays
@ 25 weeks: 50% reduction in clearance at 16.6 Gy (dose rate 2 Gy/min)
-> EDQD2 (α/β: 3) = 65 Gy

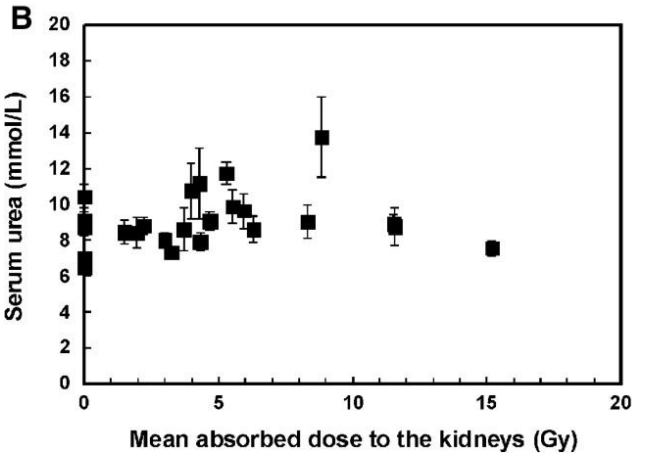
i.v. alpha-RIT with ^{211}At-MX35-Fab$_2$
@ similar time (30 weeks):
50% reduction in clearance at 14 Gy
-> **RBE** = 65 Gy/14 Gy = **~ 5**

Williams MV, Denekamp J. Sequential functional testing ofradiation-induced renal damage in the mouse. Radiat Res 1983;94:305.

Denekamp[30] used ^{51}Cr-EDTA to estimate clearance in a study of renal damage in mice after local external irradiation (240 kV X-rays) of both kidneys. Twenty-five (25) weeks after irradiation, they found that the absorbed dose causing a 50% reduction in clearance was 16.6 ± 0.5 Gy. The absorbed doses to the kidneys in their study were homogeneous and the dose rate was high (2 Gy/min), corresponding to 65 Gy, if recalculated to total equivalent dose in 2-Gy fractions (EQD2), assuming an α/β ratio (the dose at which both components in the LQ model of cell killing are equal) of 3 Gy for the kidneys. At approximately the same time postirradiation (8–30 weeks), we found that an absorbed dose of 14 Gy, delivered during ~12 hours (as estimated from absorbed dose calculation for the first 12 hours), caused a 50% reduction in GFR. As they produce the same biologic effect, these absorbed doses can be used to estimate a theoretic relative biologic effect (RBE) for functional renal damage. With the above X-ray radiation (recalculated to EQD2) as the reference, the estimated RBE for the alpha radiation in our study would be approximately 5.

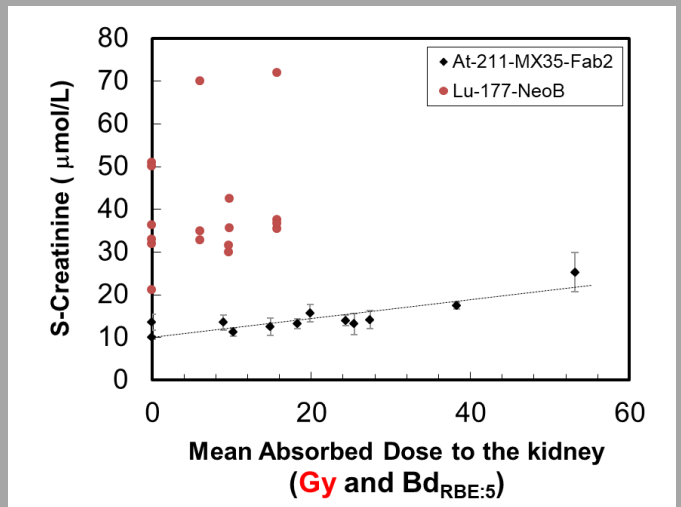
Alpha vs Beta? Serum creatinine & Urea

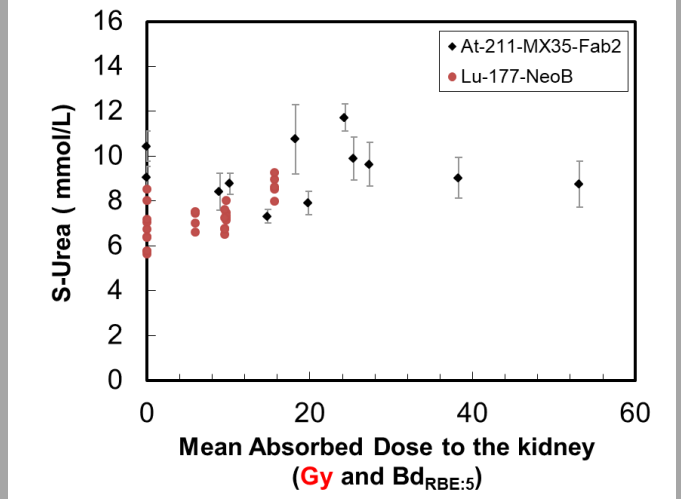




RBE= 5

RBE= 5

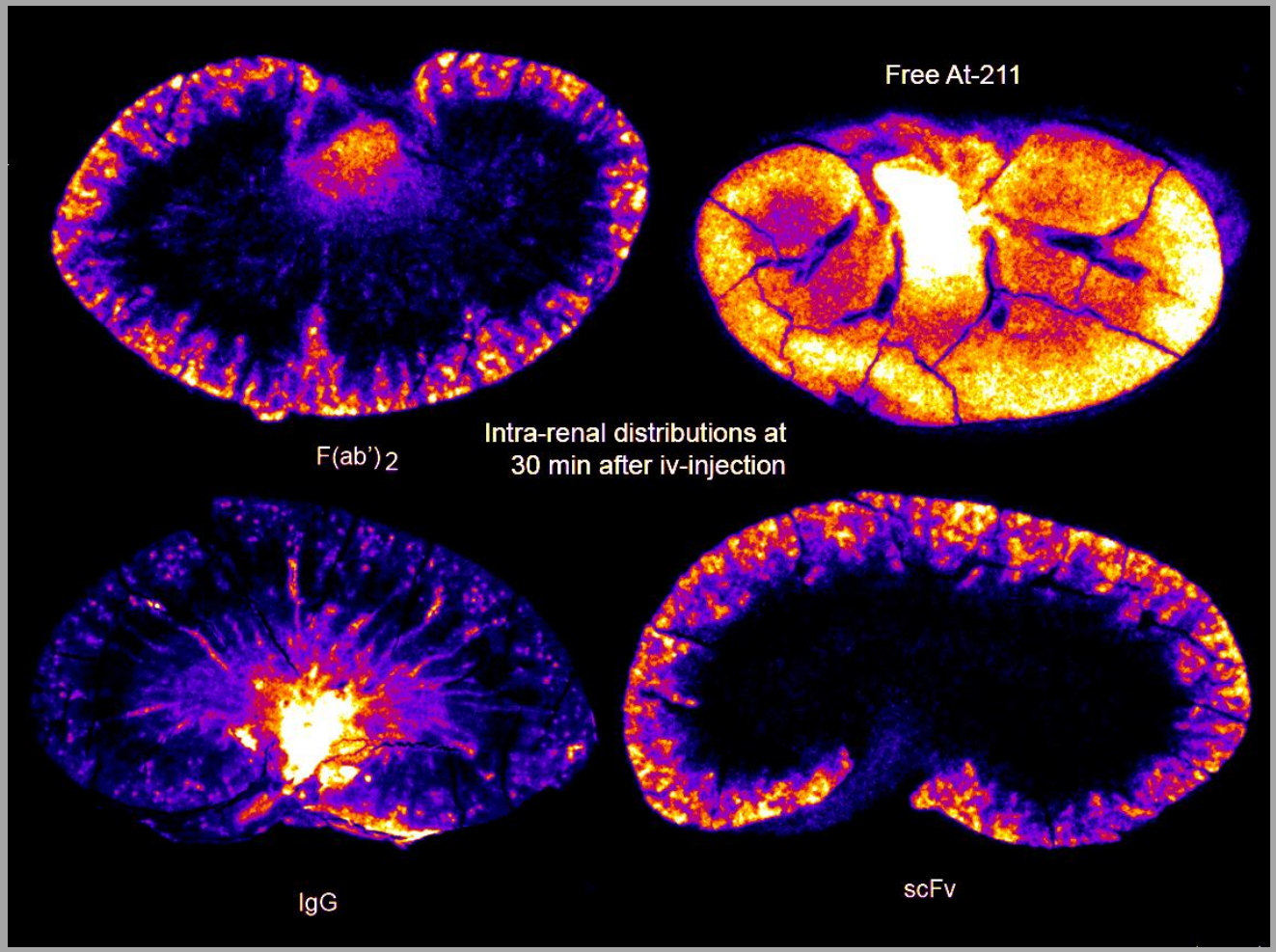




Targeted Alpha Therapy

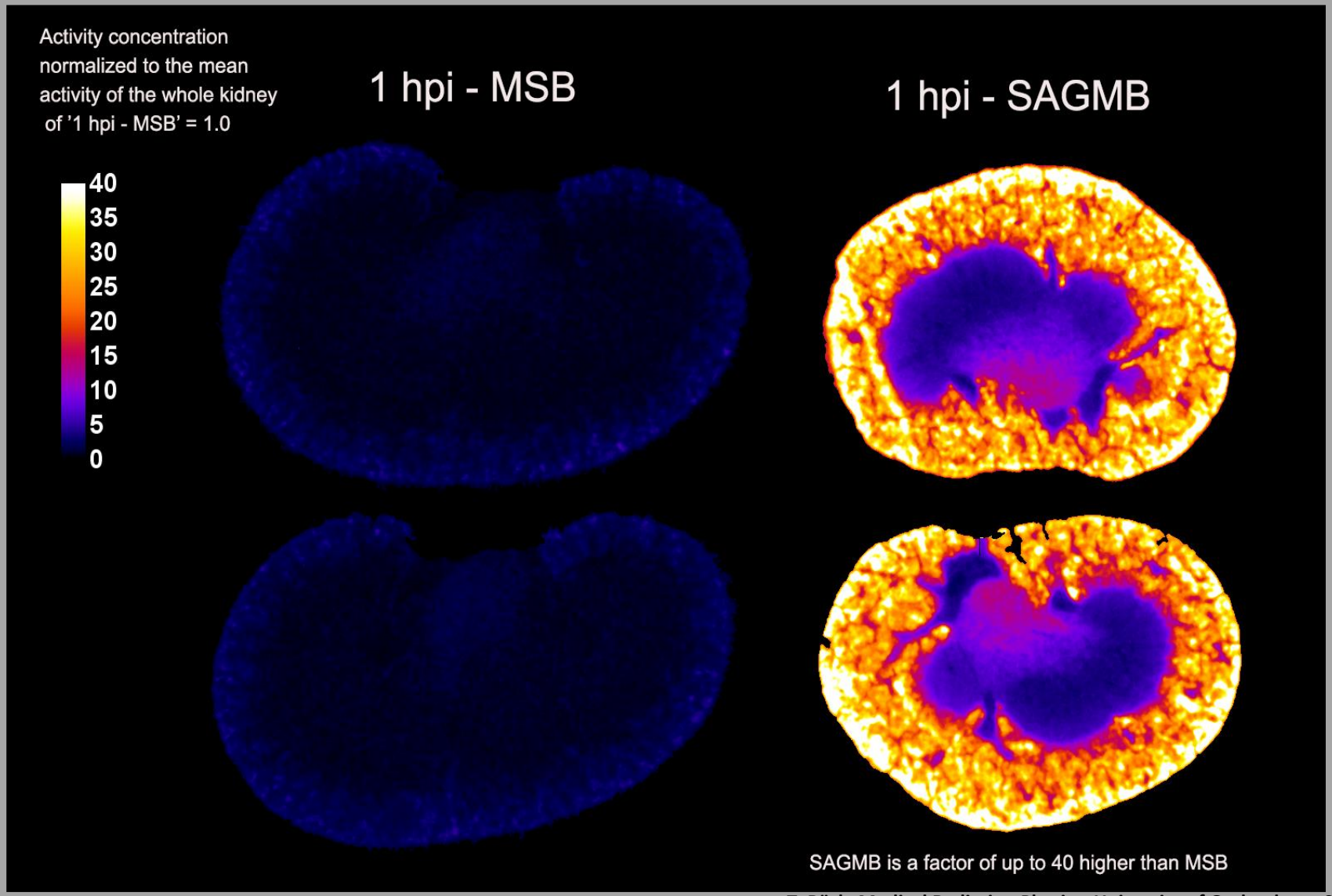
LOCATION! **LOCATION!** **LOCATION!**

The kidneys in alpha-RIT – Alpha Camera imaging

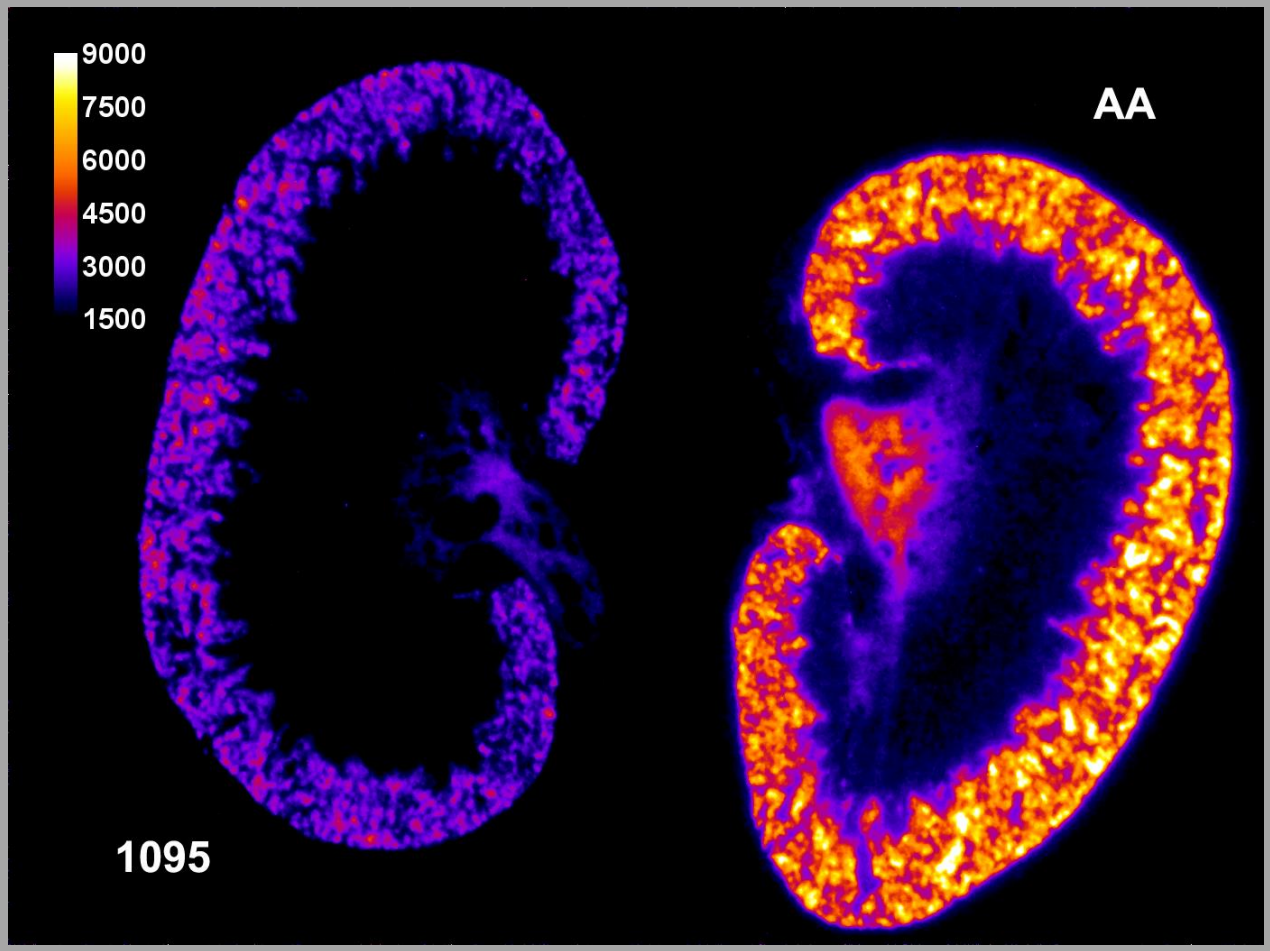


Influence of molecular weight; 4 different sizes, 30 mpi

At-211-Nanobodies using two different labeling methods



At-211-PSMA: Two different versions of the ligand



a-camera imaging of the intra-renal distribution of At-211-labeled AA versus 1095 at 3 hours after i.v.-injection.
LUT bar indicates relative activity (au). Kidney cryosections from female Balb C nu/nu.

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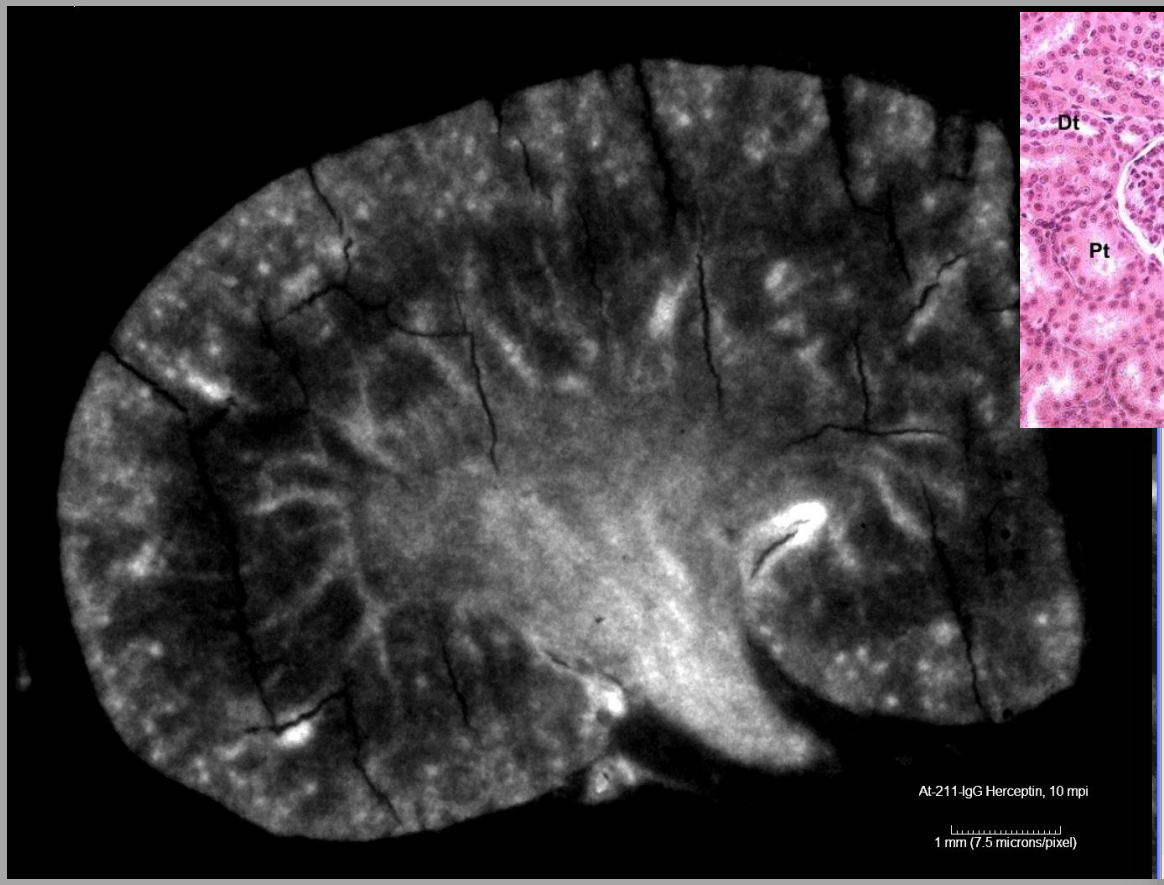
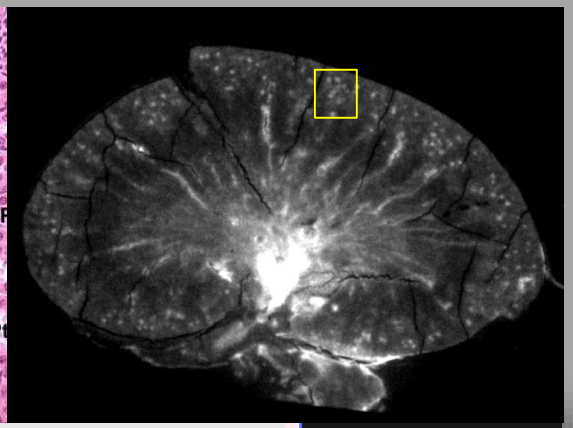
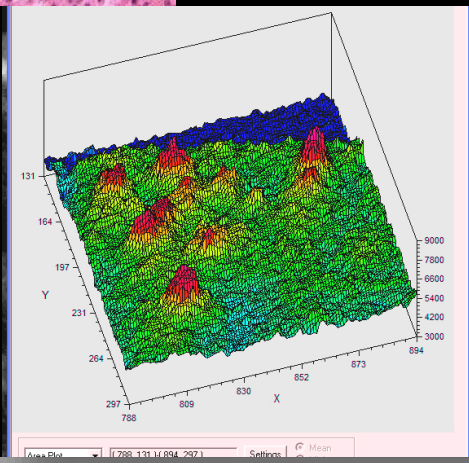
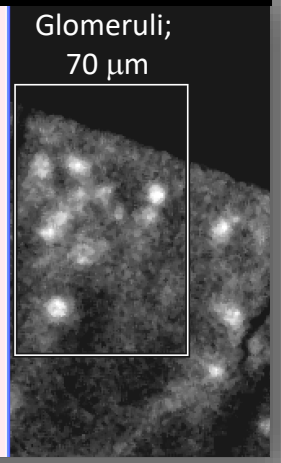
At-211-Trastuzumab i.v.









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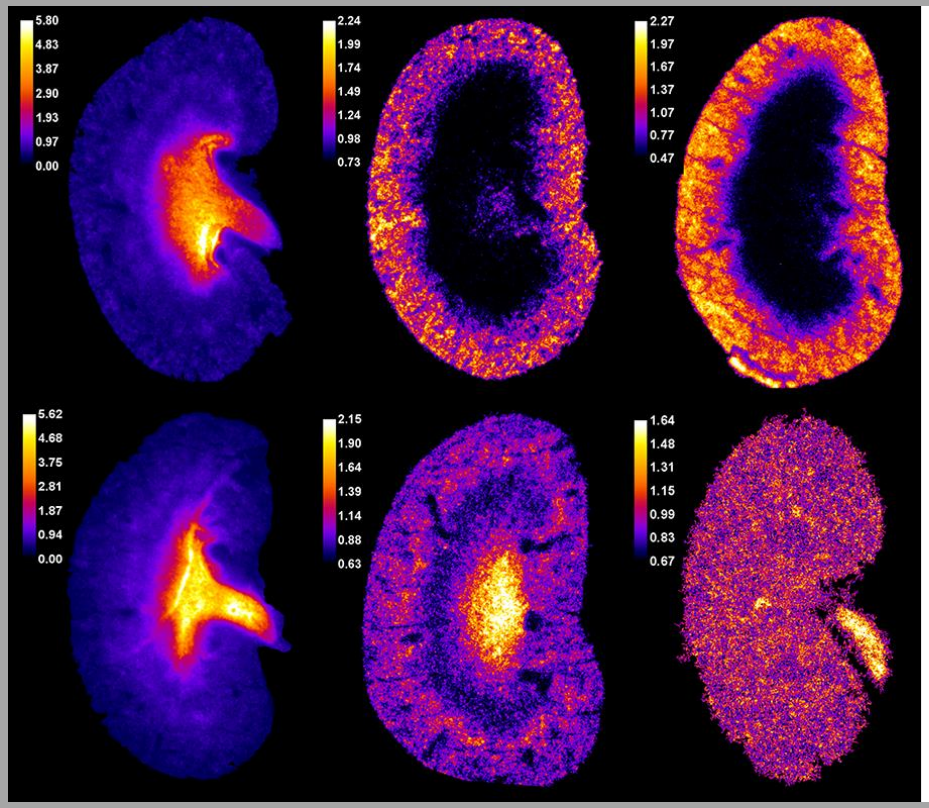
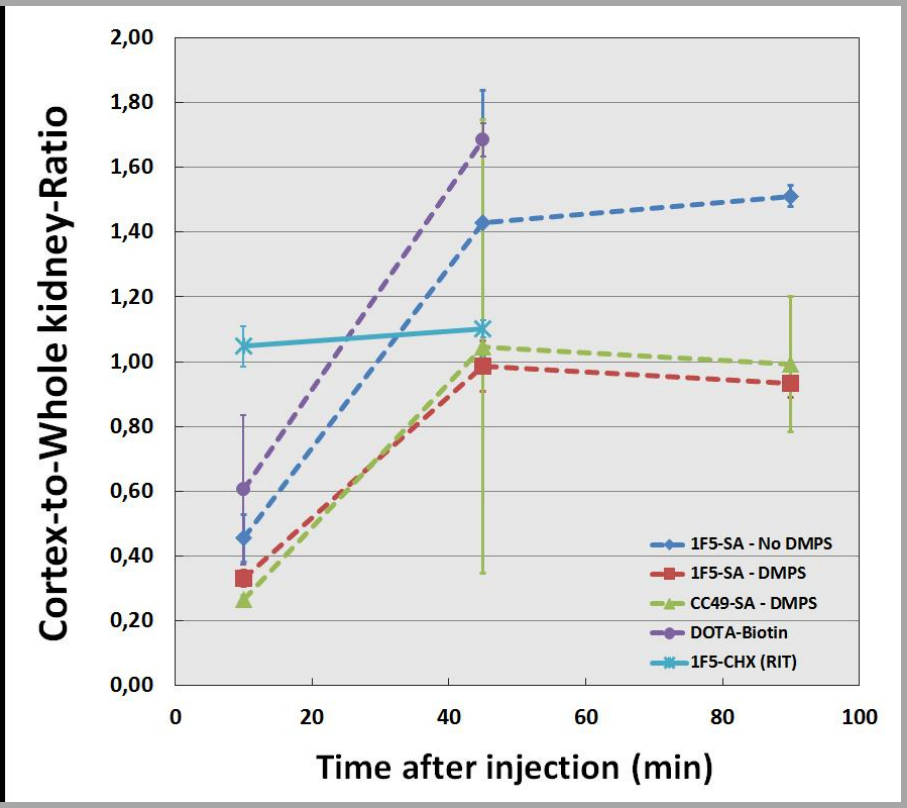
Blockers to reduce kidney retention: DMPS and Bi-213

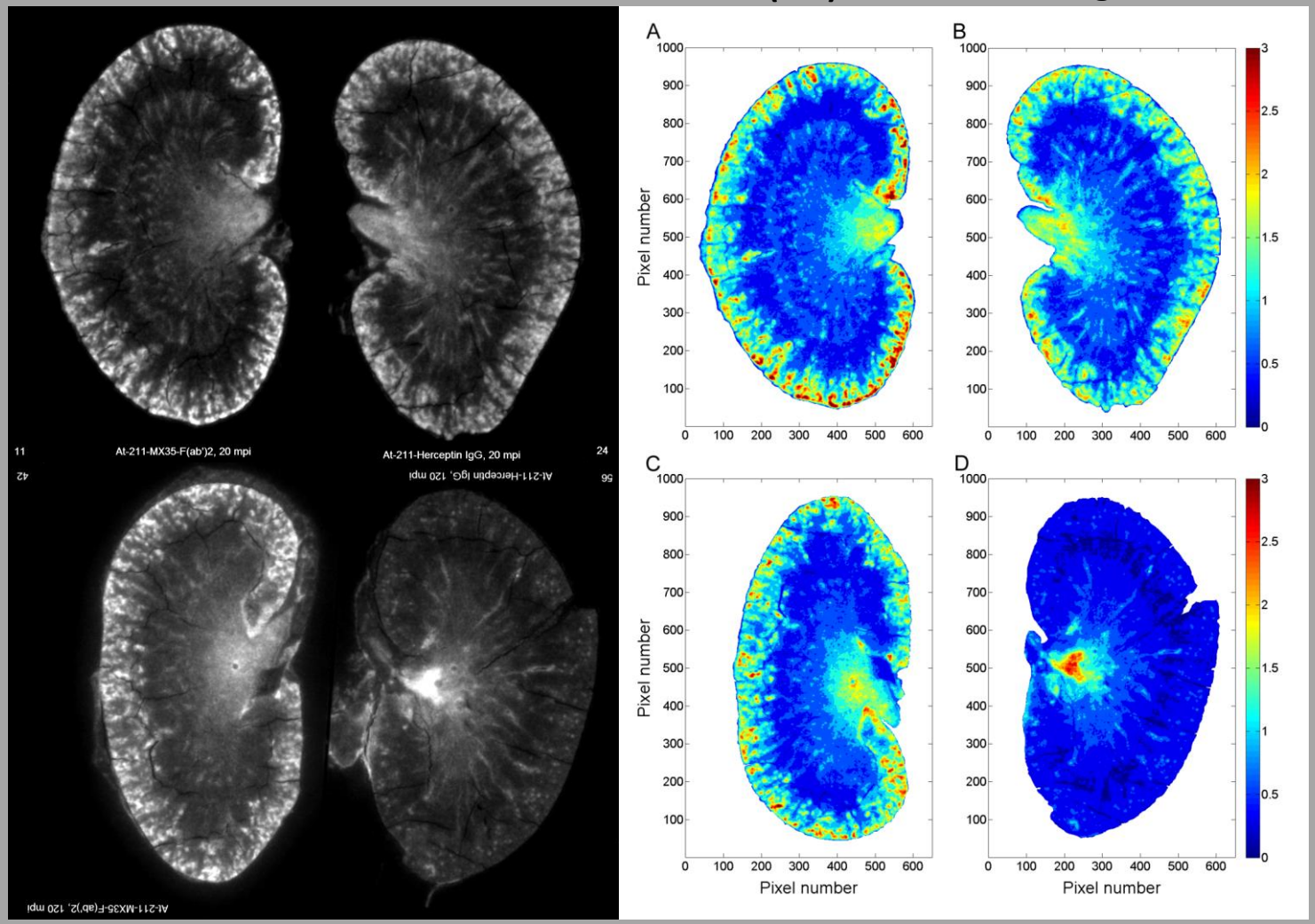
10 mpi 45 mpi 90 mpi





Left Panel: Activity distribution in the kidneys at 10, 45 and 90 mpi (left to right) following PRIT with 1F5-SA and Bi-213-DOTA-Biotin, without DMPS (top row) or with DMPS (bottom row). Images visualize the different intrarenal activity uptake with a strong retention in cortex for a unblocked kidney. Right panel: Quantification of the Cortex-to-Whole kidney-ratios for different regimens and times.

Activity distribution: ^{211}At-labeled IgG vs F(ab')2



NTCP for kidneys in RPT

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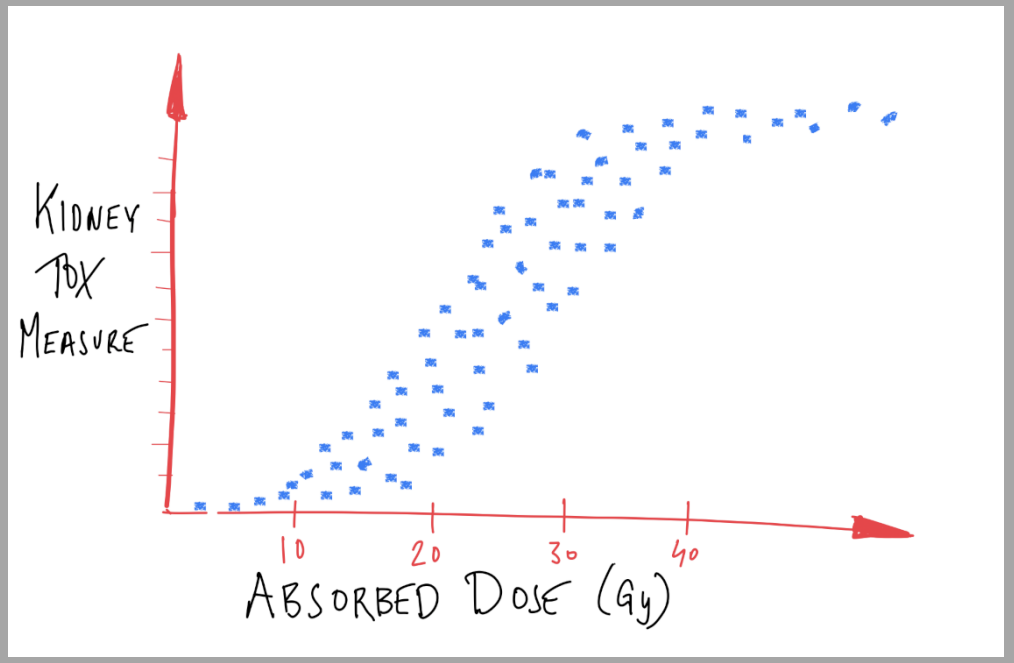

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Glomerulii?

Calculated how?
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BED?
EUD?