

Optimizing PRRT-based therapy in NETs

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Erasmus MC
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Disclosures

Speaker fees AAA, PrimeOncology

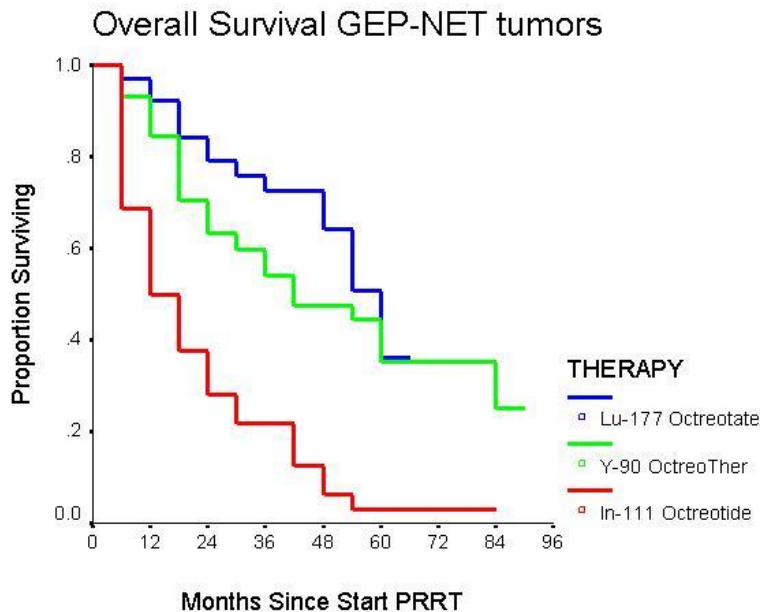
PRRT at Erasmus MC

- 1992 ^{111}In -octreotide therapy
- 1997 ^{90}Y -DOTATOC and amino acids
- 2000 ^{177}Lu -DOTATATE

- 2018 >1500 patients treated with ^{177}Lu -DOTATATE

PRRT with somatostatin analogues

Overall Survival



Median survival

In-111 Octreotide: 12 mo

(31 dead, 1 (3%) alive)

Y-90 OctreoTher: 36 mo

(34 dead, 24 (41%) alive)

P < 0.001 vs In-111 Octreotide

Lu-177 Octreotate: >48 mo (?)

(55 dead, 319 (85%) alive)

Preliminary, many patients
censored with short follow-up:
not yet reliable!



*Granisetron or
Ondansetron*

- *4 Cycli; 8 week interval*
- *hospitalisation 1 night*

*200 mCi
¹⁷⁷Lu-DOTATATE*



4 hours

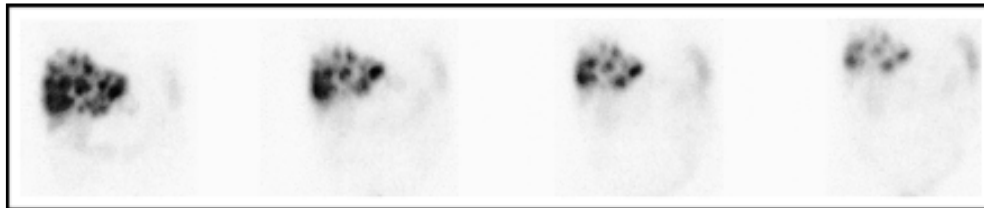
Erasmus MC



Peptide Receptor Radionuclide Therapy (PRRT)

Success

- Good tumor response rate
- Extended progression free survival
- Improvement of quality of life

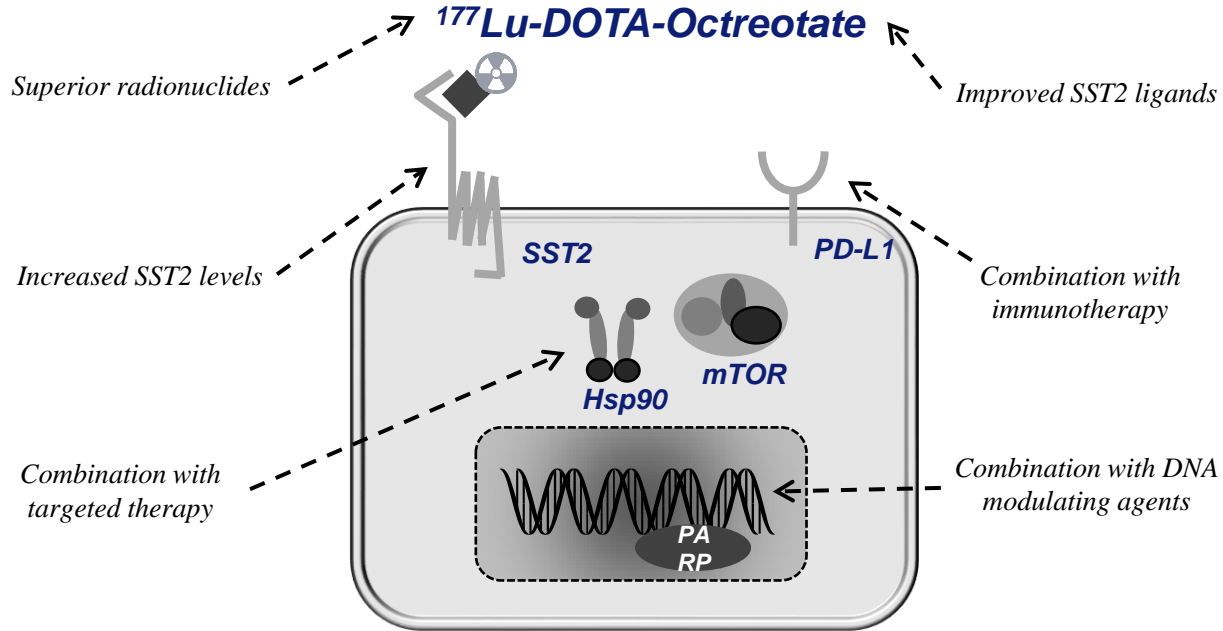


Partial remission of a GEP-NET with massive hepatic metastases with ¹⁷⁷Lu-DOTA-TATE

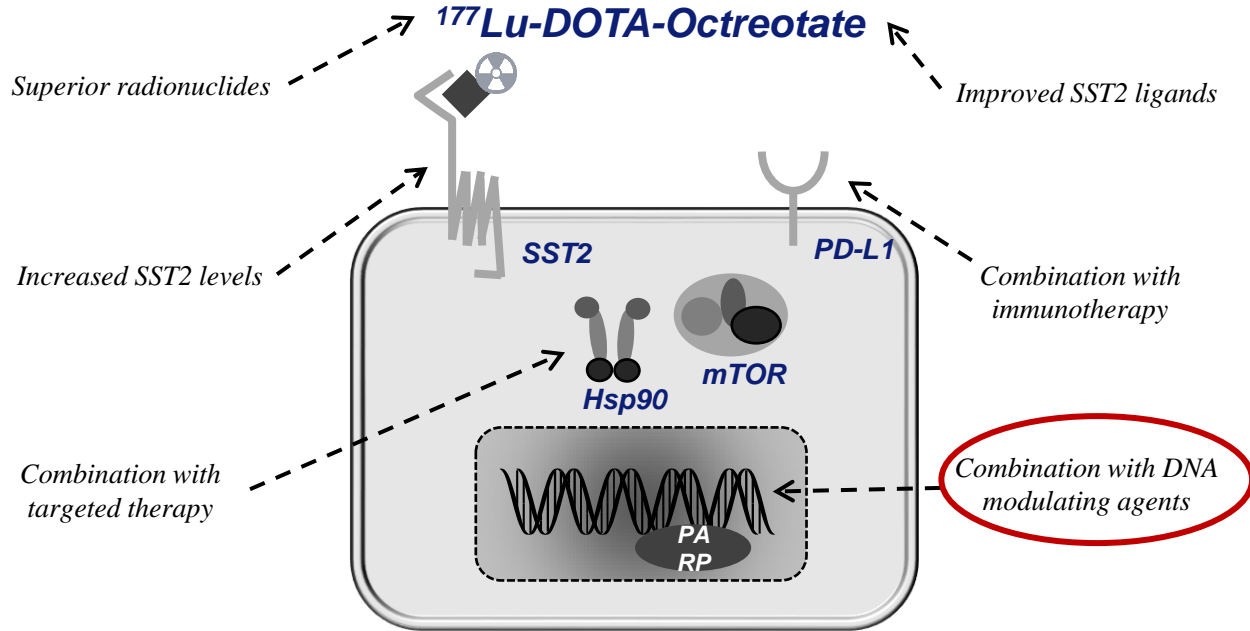
Drawback

- Partial response
- Normal tissue toxicity (kidneys and bone marrow)

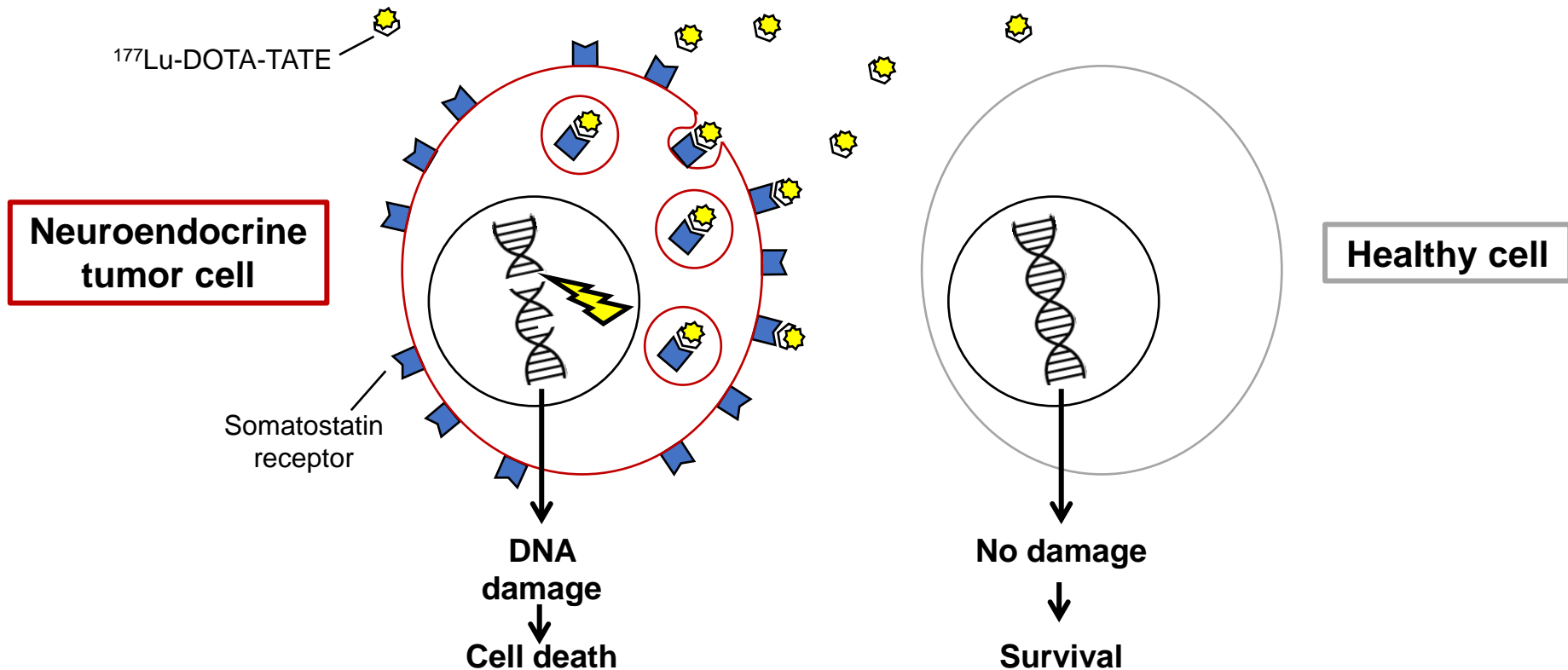
Optimizing PRRT



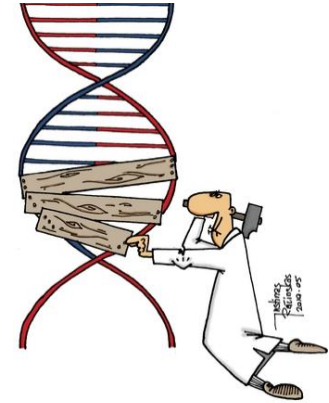
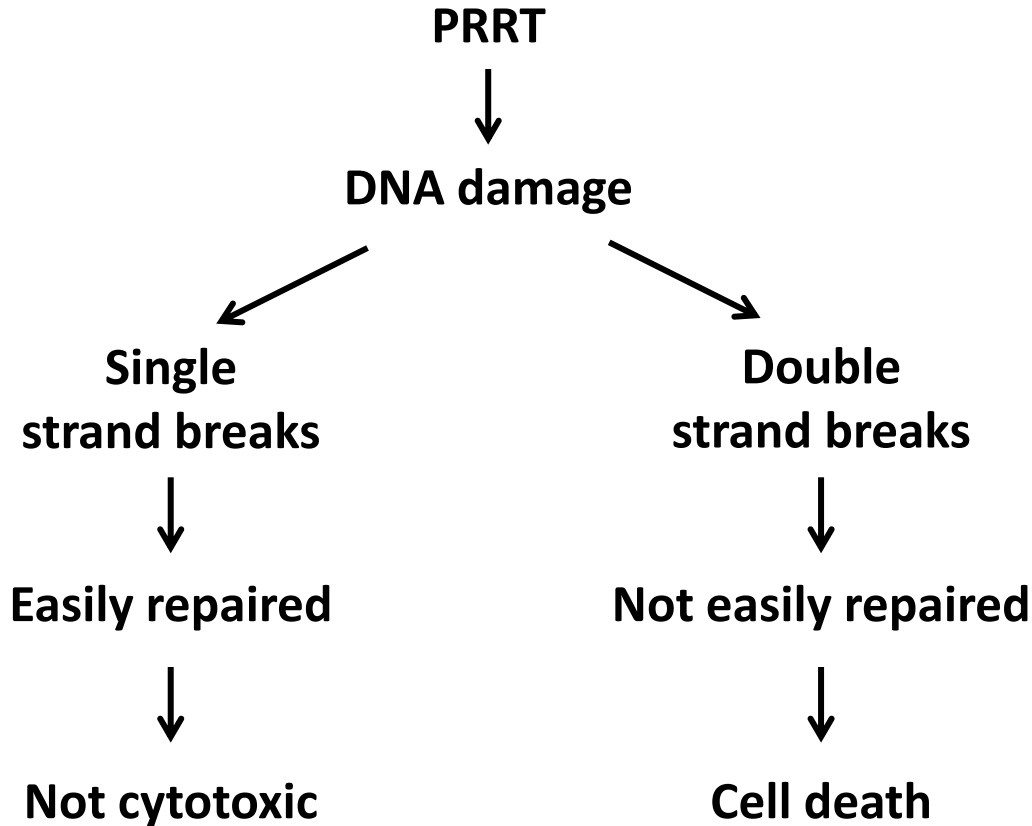
Optimizing PRRT



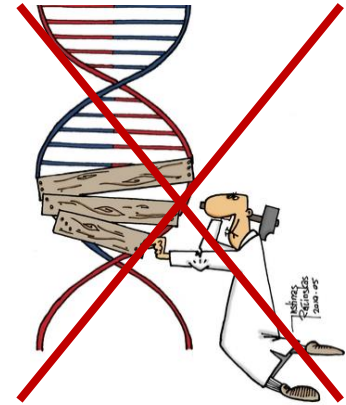
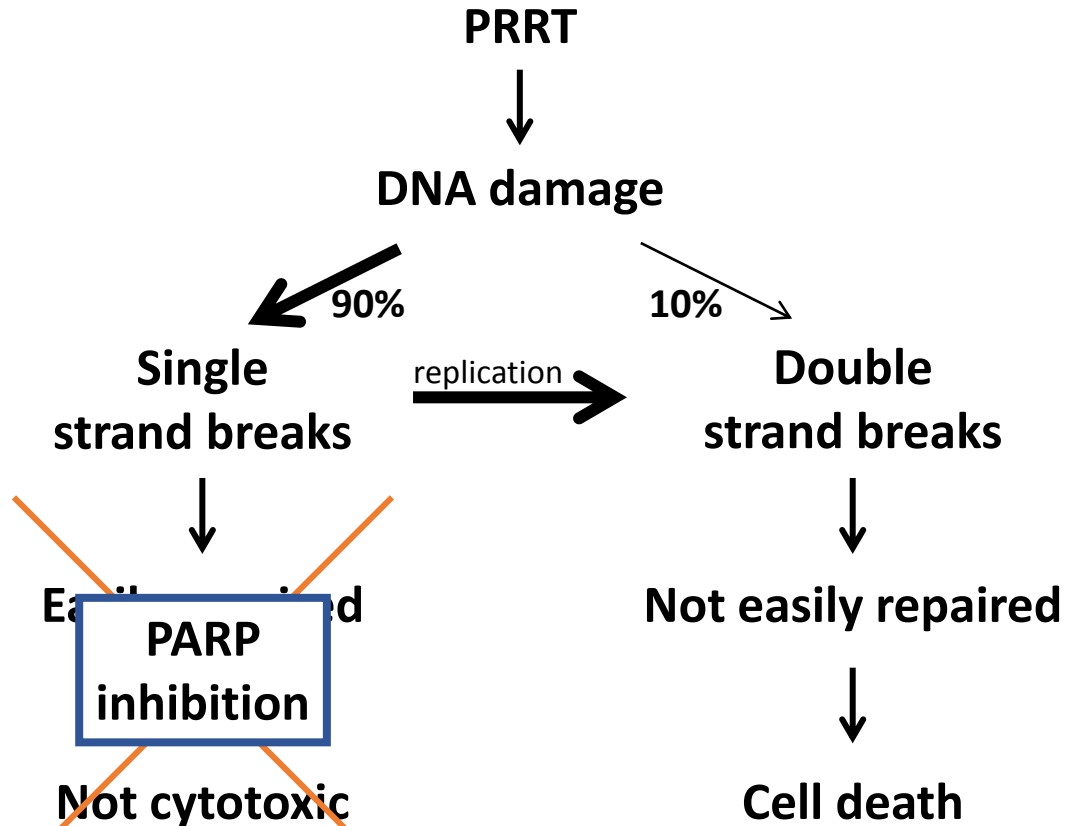
Peptide Receptor Radionuclide Therapy (PRRT)



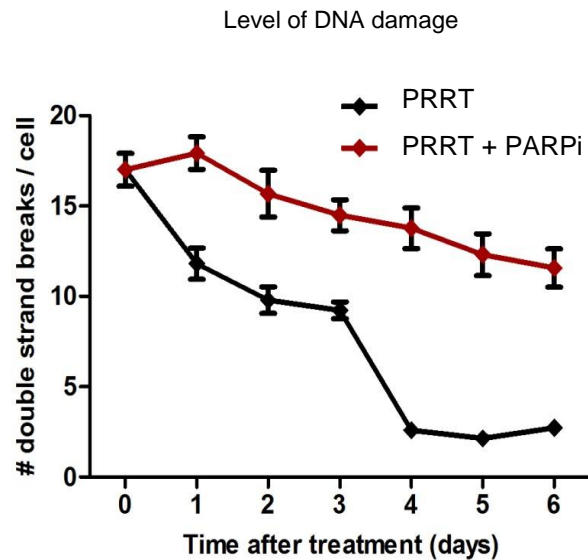
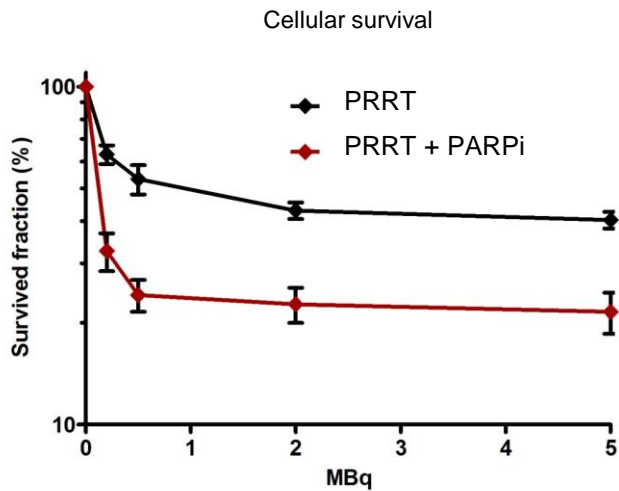
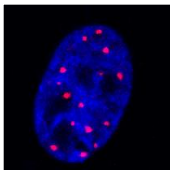
Combination therapy



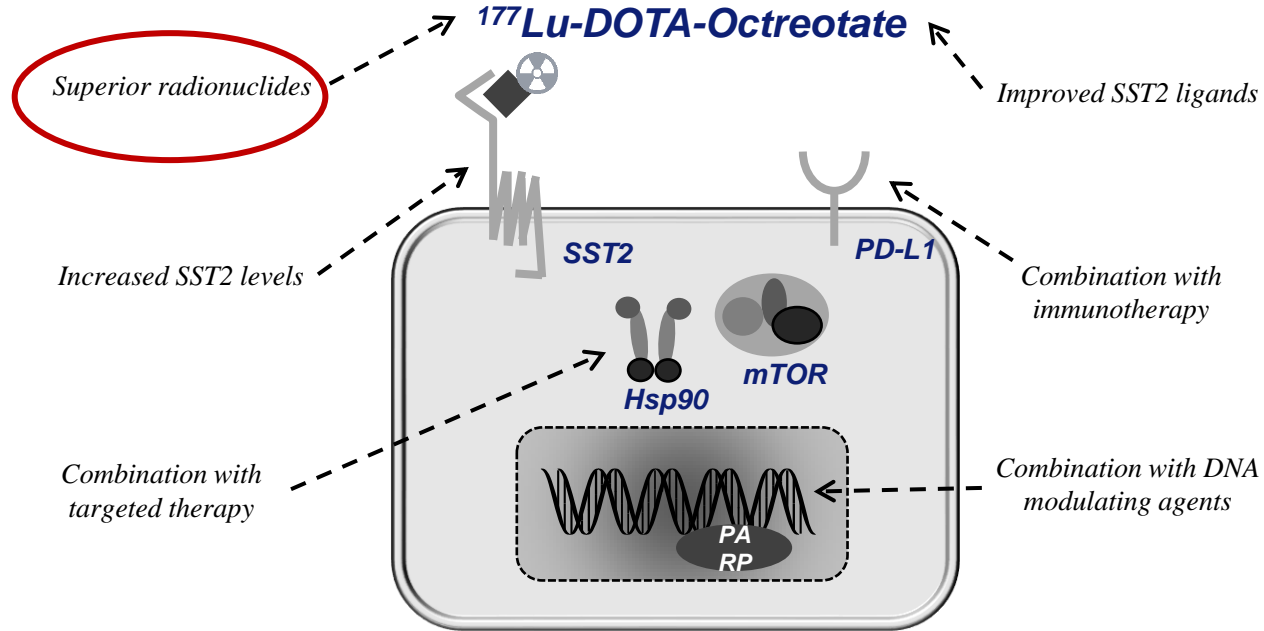
Combination therapy



Results



Optimizing PRRT



Radionuclides

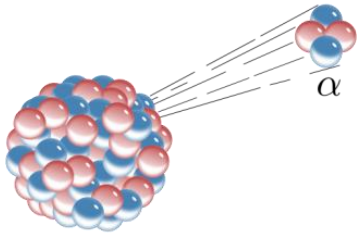
Alpha and beta radiation for therapy

Alpha emission:

High ionizing power

Short range

Stopped by paper

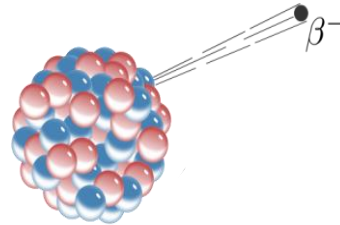


Beta emission:

Moderate ionizing power

Moderate range

Stopped by 5 cm aluminum

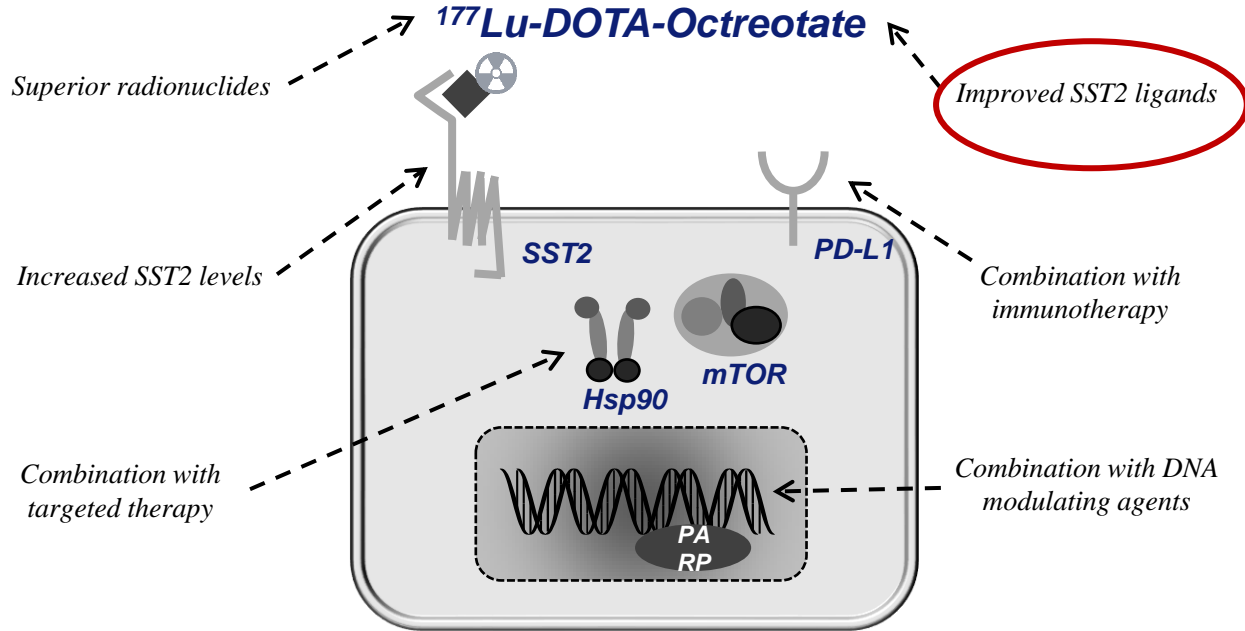


Radionuclides

- Bismuth-213:
 - ^{213}Bi -DOTATOC (Kratochwil et al. EJNMMI 2014)
 - 7 patients with a response and favorable acute and mid-term toxicity

- Lead-212:
 - ^{212}Pb -DOTAMTATE (Stallons et al. Mol Can Ther 2019)
 - 79% of animals were tumor free after 31 weeks
 - Phase 1 trial in patients is running

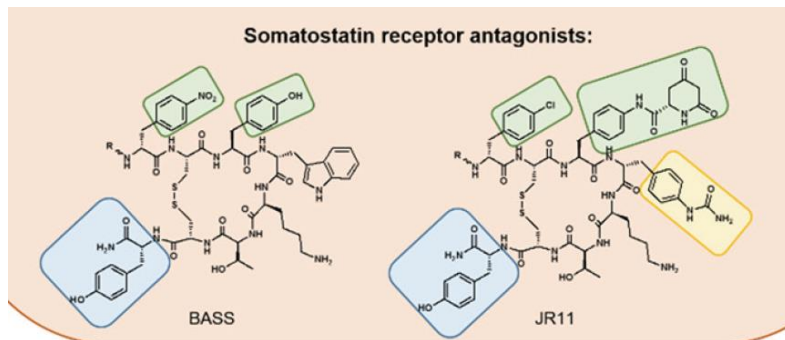
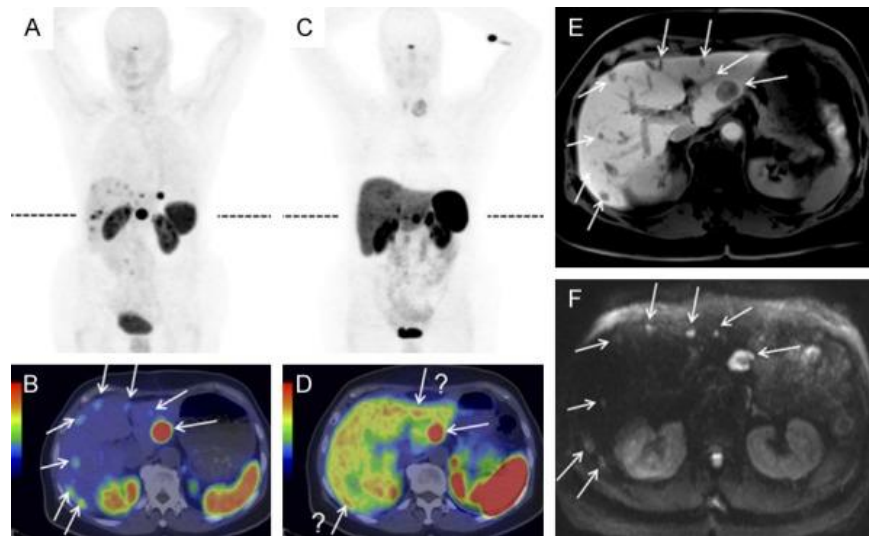
Optimizing PRRT



Antagonist

No internalisation

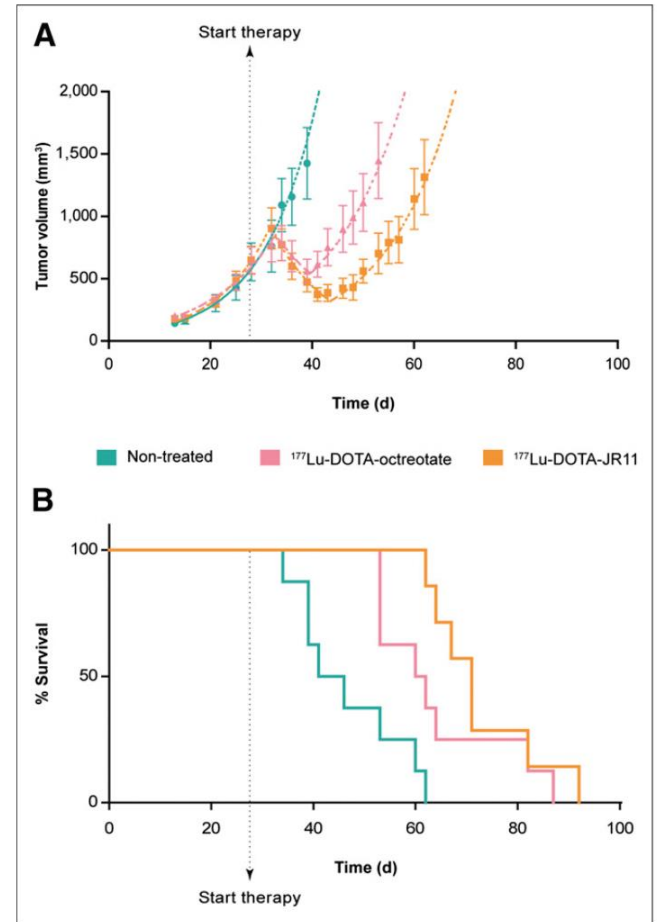
Higher tumor uptake



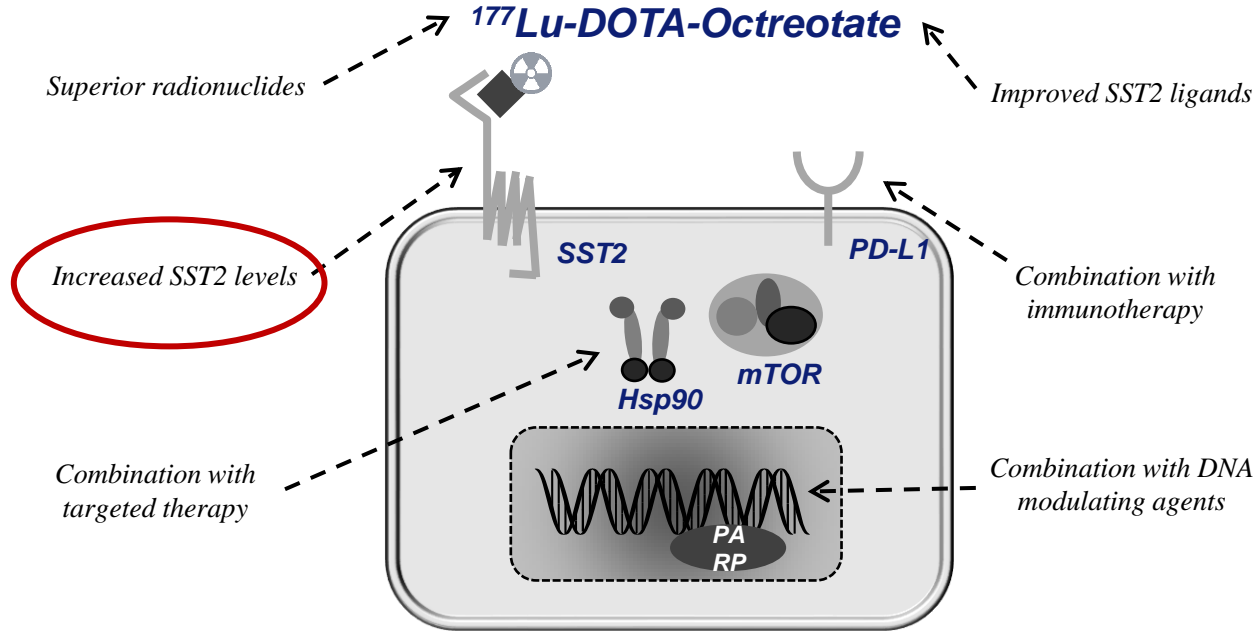
Elin Pauwels et al. AM J Nucl Med Mol Imaging 2018;8(5):311-331

Antagonist

- ^{177}Lu -DOTA-JR11 vs ^{177}Lu -DOTA-octreotate
- 4.4 higher radiation dose
- Delay in tumor growth and longer median survival

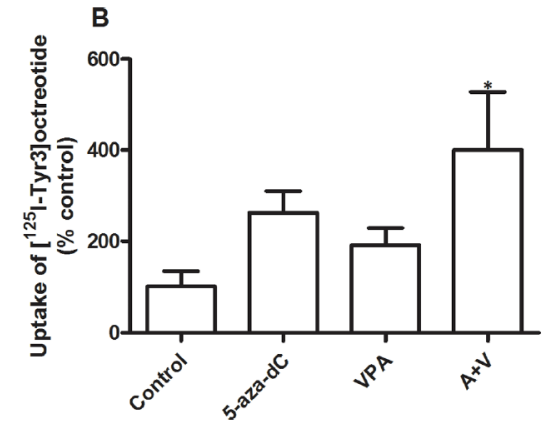
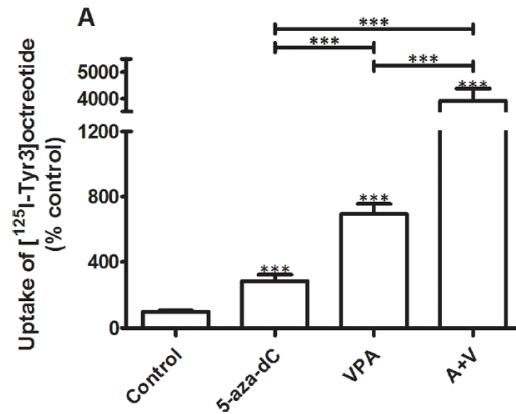


Optimizing PRRT



Upregulation SSTR

- Epigenetic regulation is a mechanism of cells to regulate gene expression
- Epidrugs can induce epigenetic modification resulting in upregulation of the SSTR
 - 5-aza-2'-deoxycytidine (5-aza-dC)
 - Valproic acid (VPA)
- In vitro uptake increased 3820% and 300% in different cell lines
- Clinical trial is running at EMC

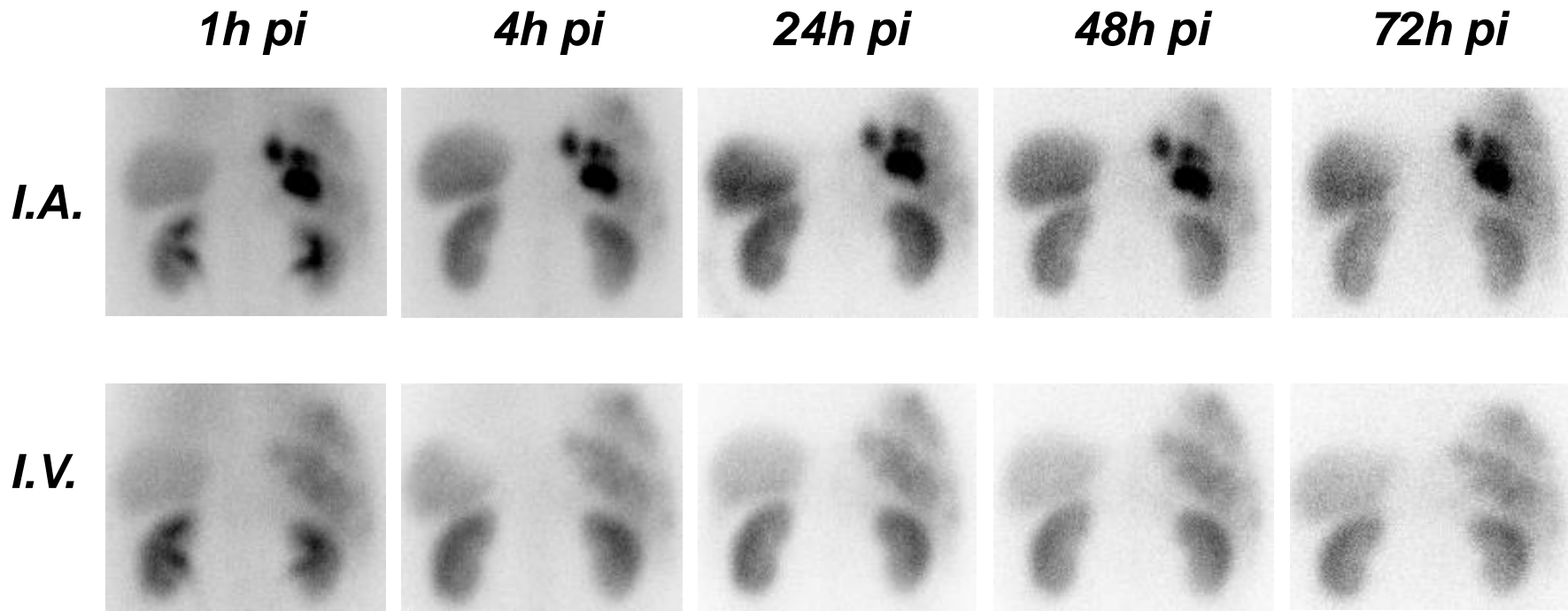


Other methods

- Intra-arterial administration
- More cycles of ^{177}Lu -DOTATATE

IA-treatment

- Intra arterial ^{177}Lu -DOTATATE can increase uptake



More cycles

- Erasmus MC: Retreatment in 181 patients, PFS >18 months after first therapy
- PFS after R-PRRT 14.6 months and after RR-PRRT 14.2 months
- No additional toxicity

- Uppsala: in 200 patients dosimetry based on planar whole-body scans and SPECT-CT of abdomen
- In 50% of patients >4 cycles of 7.4 GBq (up to 10 cycles)

Conclusions

- Results of ^{177}Lu -DOTATATE are favorable, but there is room for improvement
- New developments in radioligands, receptor expression and combination therapy
- Majority is in preclinical stages
- Good clinical trials are needed

Thank you for the attention

