Preclinical development of Th-227 labeled molecules for tumor therapy

Sabine Zitzmann-Kolbe

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EURADOS Webinar

Disclosure Information

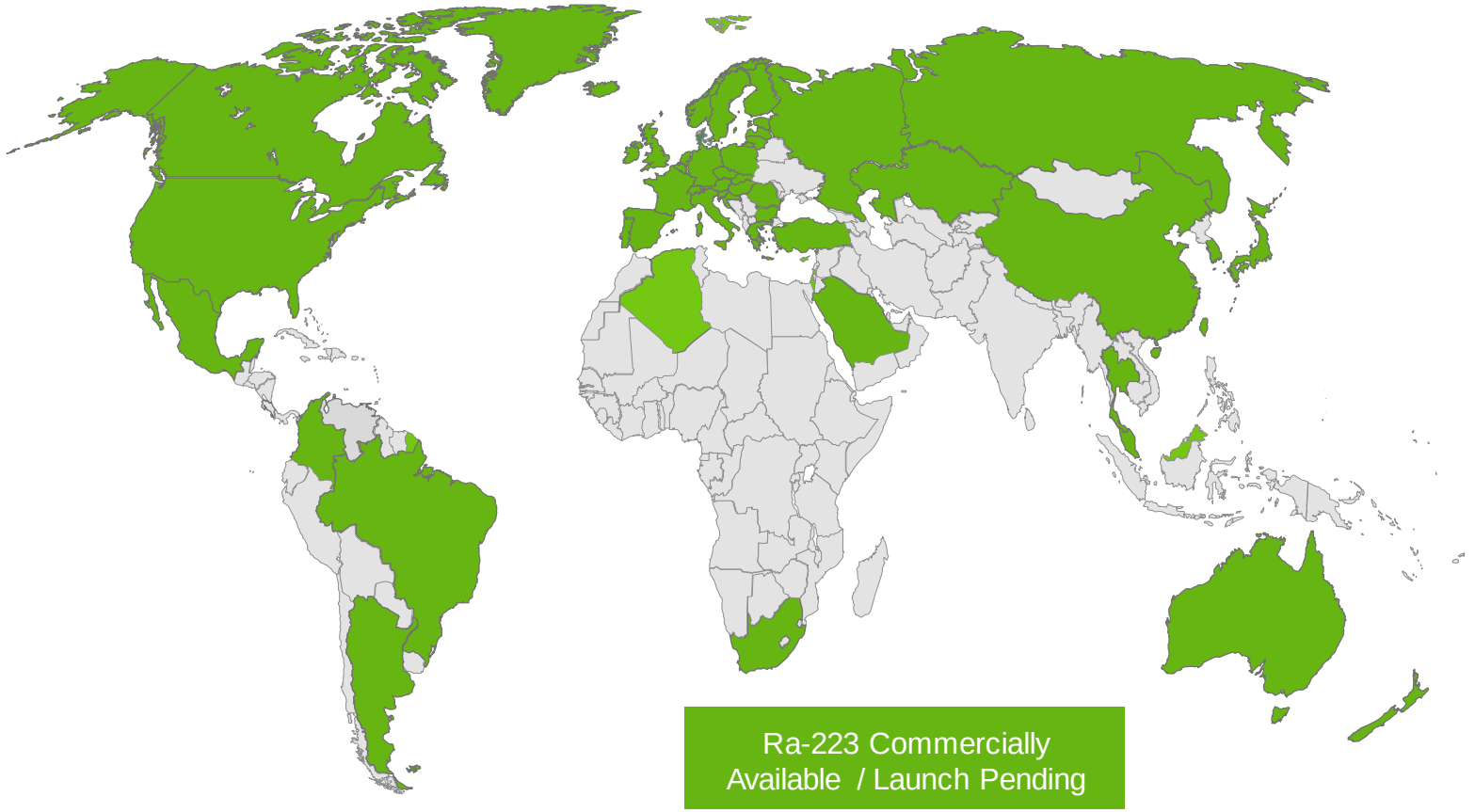
Sabine Zitzmann-Kolbe

- I have the following financial relationships to disclose:
- Employee of Bayer AG, Germany
- I will not discuss off label use and/or investigational use in my presentation
- I am co-author of patents presented within this presentation

Bayer Focuses on three Innovative Oncology Research Platforms Targeted Alpha Therapy (TAT) is one of them

Bayer Oncology

- Targeted Alpha Therapy (TAT)
- Oncogenic Signalling
- Immuno-Oncology

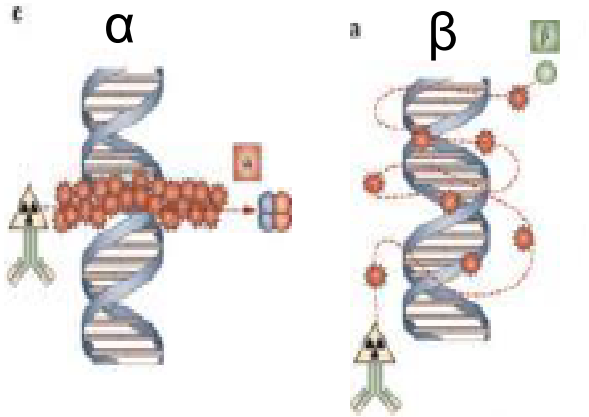


// Targeted Alpha Therapy is an emerging new modality within the field of radiotherapy
// Radium-223 (Xofigo®) first and only approved alpha therapy, for treatment of mCRPC, now approved in >50 countries
// Extending the TAT portfolio with MAb-like alpha therapies by leveraging the established manufacturing and supply chain

Targeted Alpha Therapy (TAT): Utilizing the therapeutic attributes of alpha particles for systemic targeted radiation therapy

Alpha radiation

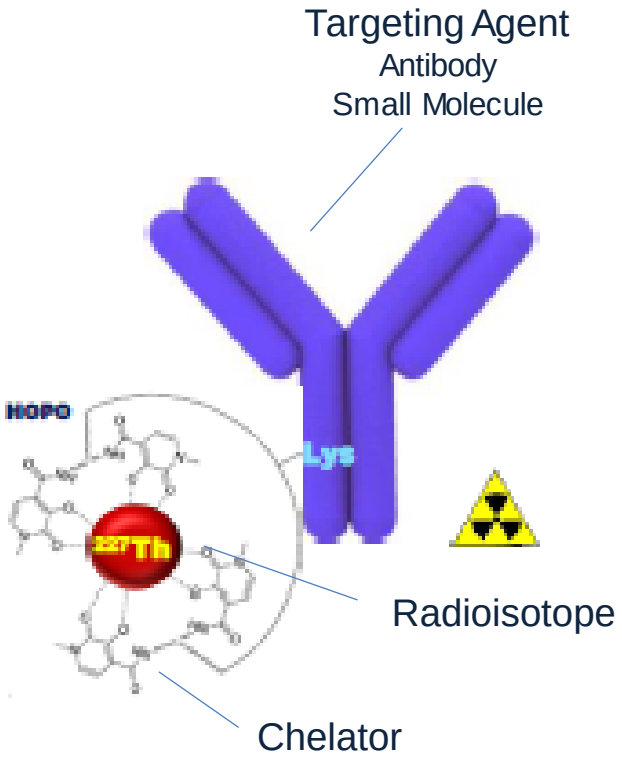
- Lethal double strand DNA breaks
- Limits exposure to surrounding tissues
- Uses >1000X lower doses of radioactivity



Parameter	α	β
Energy/decay (MeV)	5-30	0.1-0.5
Range (mm)	< 0.1	1–10
Hits for cell killing	2 – 10	~2000

Targeted Alpha Therapy

- Three component compound
- Systemic tumor targeting using antibodies (Ab) and small molecules (smol)
- Biologic, chemical and nuclear properties of the three components must be synergistic



Antibody targeting HER2

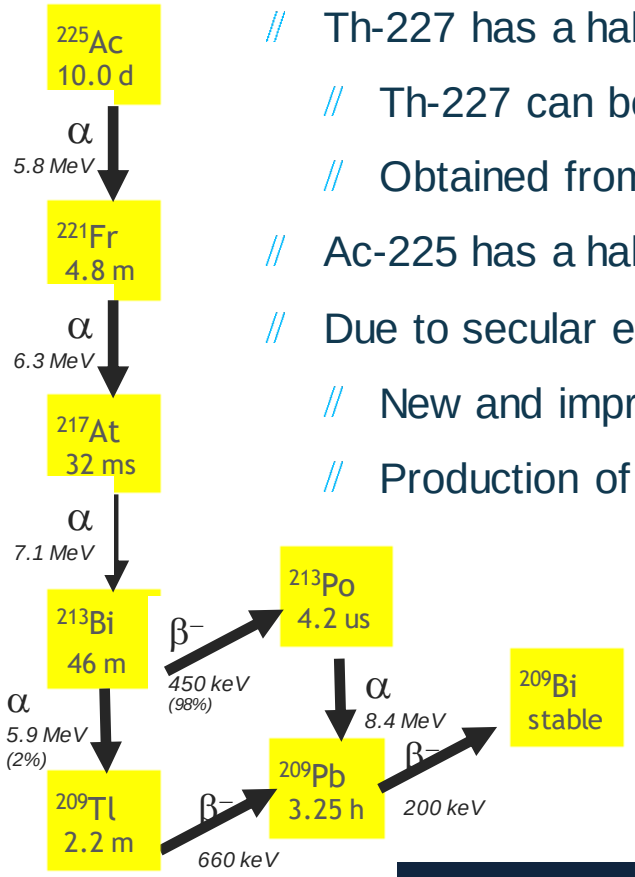
Antibody targeting PSMA

Peptide targeting PSMA

Targeted Alpha Therapy at Bayer

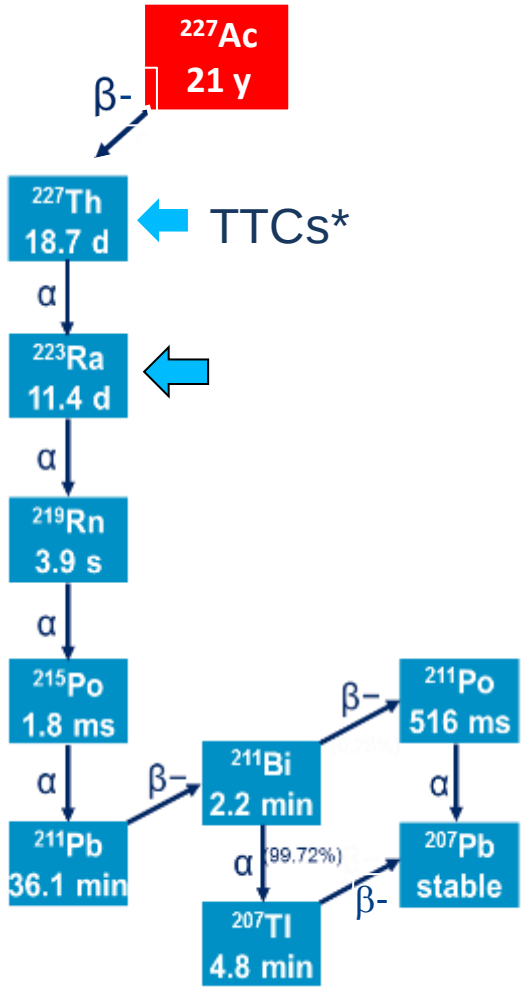
Ac-225

- Initial programs focusing on Thorium-227 (Th-227)
- Th-227 has a half-life of 18.7 days with a total emission of 32.4 MeV days
  - Th-227 can be stably complexed to 3,2-HOPO chelators
  - Obtained from the same supply chain as Radium-223 (Xofigo®)
- Ac-225 has a half-life of 10 days with a total emissions of 27.7 MeV
- Due to secular equilibrium, Ac-225 delivers a faster dose rate to the tumor
  - New and improved chelators required
  - Production of Ac-225 at sufficient scale and purity



Per decay of ^{225}Ac:
Total α emission = 27.7 MeV (97%)
Total β emission = 0.86 MeV (3%)
Secular equilibrium at 6h
= faster dose rate

Th-227, Ra-223



Per decay of Th-227:
Total α emission = 32.4 MeV
Total β emission = 0.96 MeV
Secular equilibrium at 50d

Targeted Thorium-227 Conjugates

Through the acquisition of "Noria and PSMA Therapeutics", Bayer is extending its portfolio in prostate cancer and Ac-225[#]

[#]*Published on Thursday, 03 June 2021 14:10*
https://pipelinereview.com/index.php/2021060378309/More-News/Bayer-acquires-Noria-and-PSMA-Therapeutics-to-expand-portfolio-in-prostate-cancer.html

Bayer has currently two active TTC projects in Ph1 dose escalation

PSMA-TTC (Progenics Pharmaceuticals antibody)

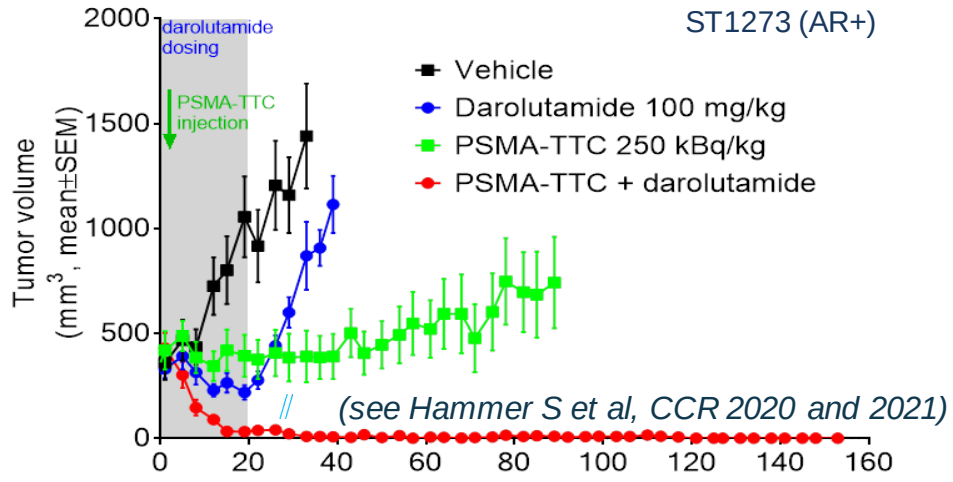
- PSMA-TTC showed strong preclinical efficacy in cell line and patient derived xenograft models in monotherapy and in combination with the androgen receptor inhibitor darolutamide
- PSMA-TTC is currently in Ph1 dose escalation for the treatment of patients suffering from Metastatic Castration Resistant Prostate Cancer (NCT03724747; monotherapy and combination with Darolutamide)

HER2-TTC (trastuzumab biosimilar)

- HER2-TTC showed strong preclinical efficacy in cell line and patient derived xenograft models, either being HER2-low expressing or resistant to SOC therapies
- HER2-TTC is currently in Ph1 dose escalation for the treatment of patients suffering from HER2-expressing cancers (NCT04147819; BrCa & GaCa)

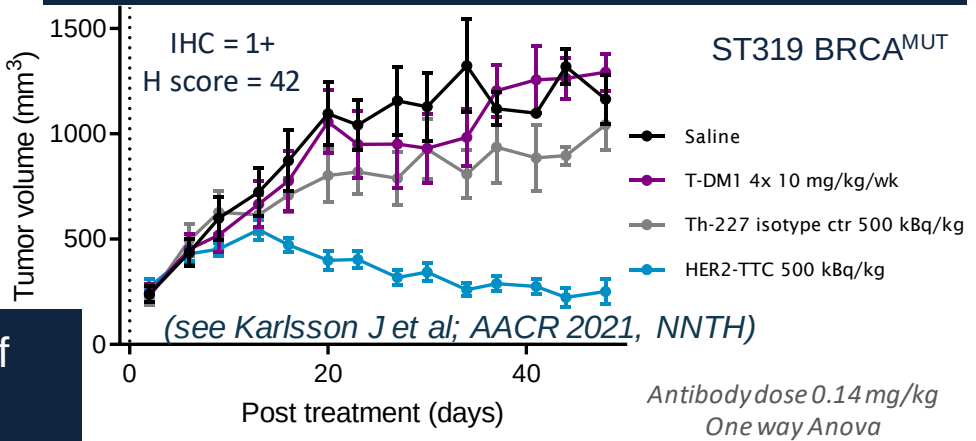
- Current clinical stage TTC projects are designed to address indications of high unmet medical need
- Additional TAT assets in early research & preclinical development at Bayer

PSMA-TTC shows strong efficacy in the hormone sensitive PDX models ST1273 in combination with Darolutamide



(see Hammer S et al, CCR 2020 and 2021)

HER2-TTC shows specific efficacy in HER2-low expressing cancers

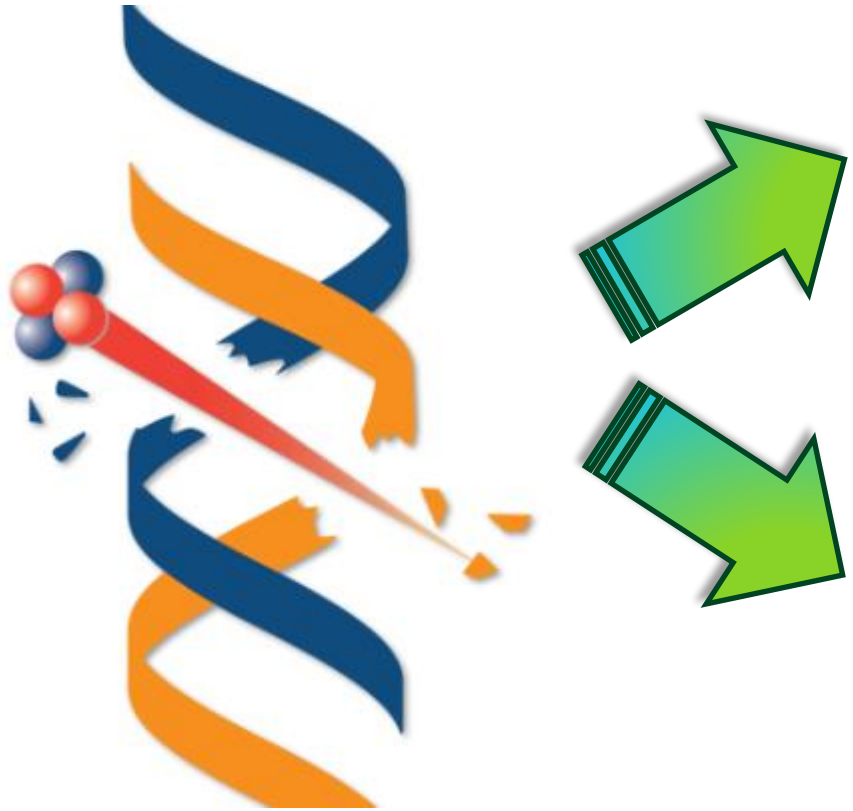


(see Karlsson J et al; AACR 2021, NNTH)

Antibody dose 0.14 mg/kg
One way Anova

*: p<0.05; **: p<0.01; ***: p<0.001; ****: p<0.0001

Areas of investigations within preclinical research

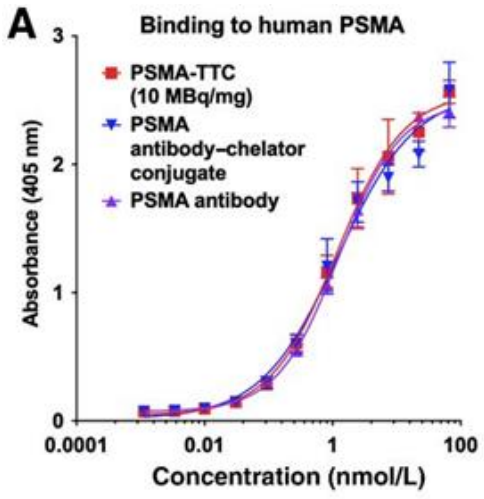


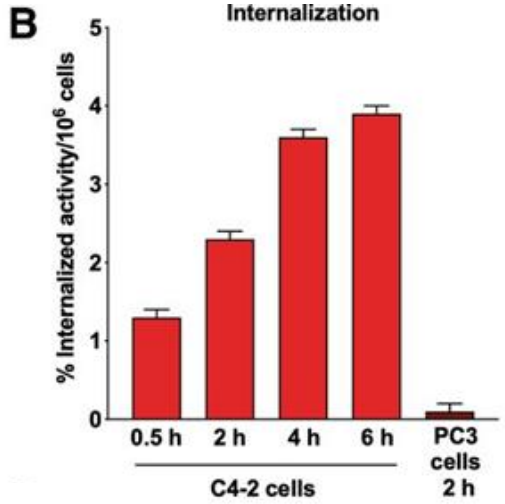
// **Development of new TAT therapeutics**

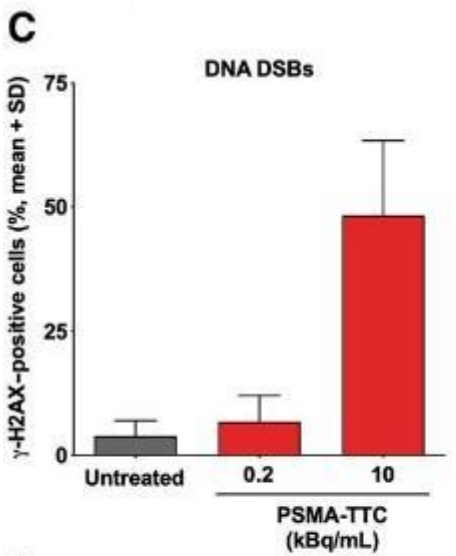
// **Effects of TAT /Sensitivity of cells to TAT**

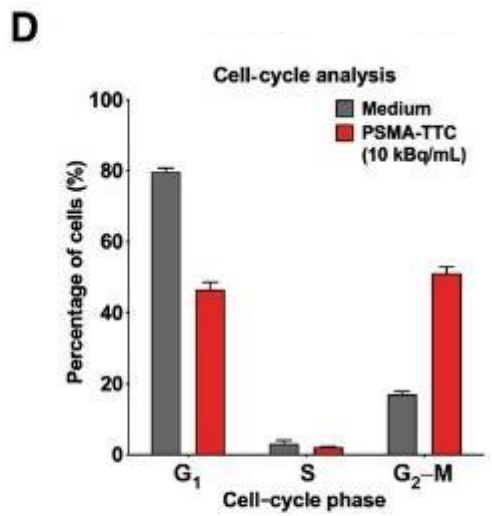
Stages of developing new TAT therapeutics

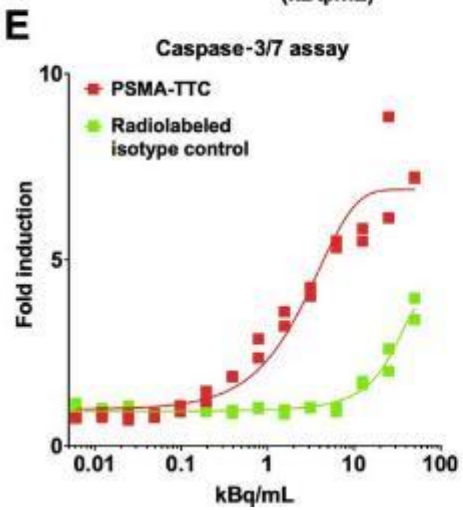
- 1. Find a good target!
- 2. Find a good targeting molecule!
  - Test for desirable in vitro characteristics (specific binding, internalization, damaging effects on target expressing cells)

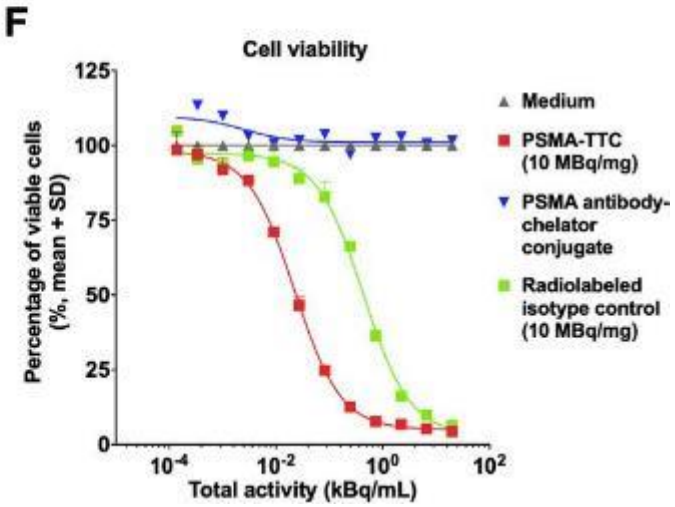








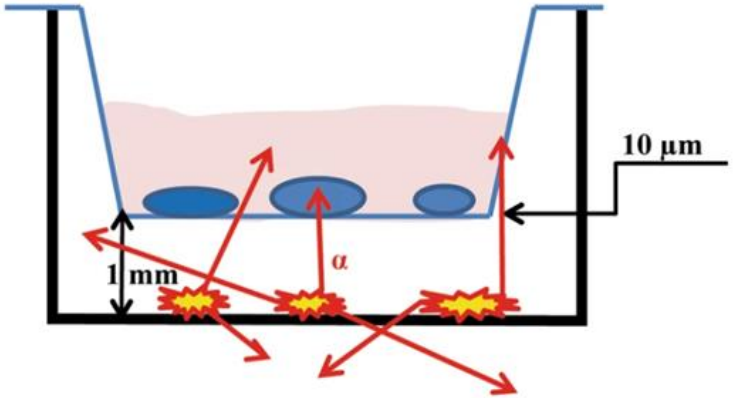


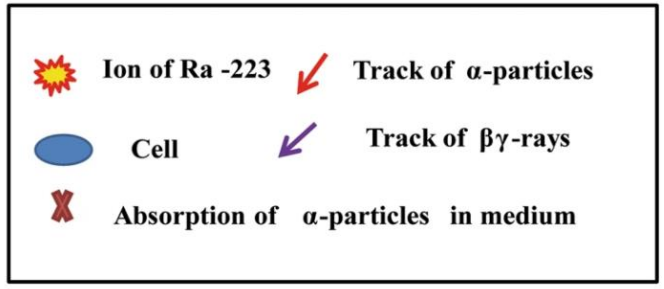


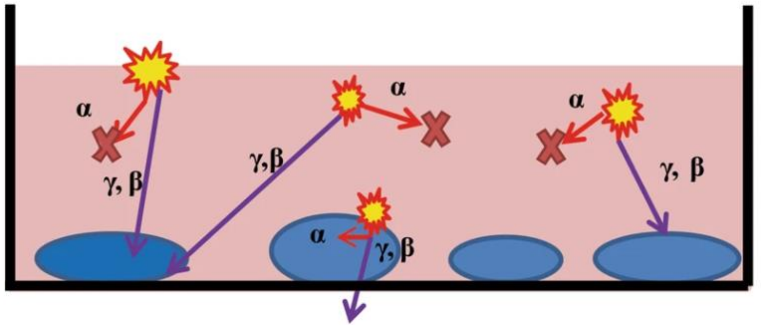
Stefanie Hammer et al. Clin Cancer Res 2020;26:1985-1996

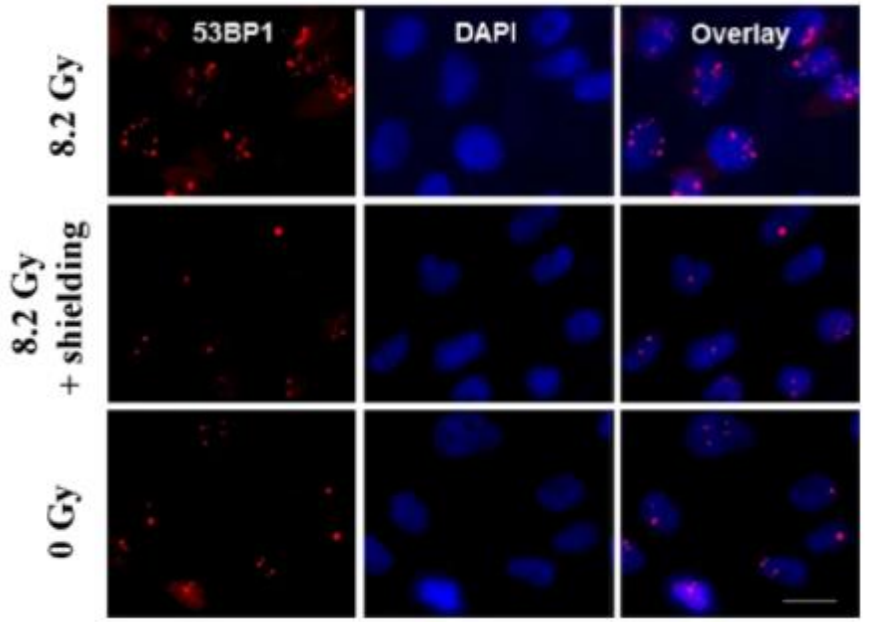
Investigating alpha radiation effects on cells in vitro

- Special considerations for alpha radiation:
  - Not just one decay but many daughters
  - Not just alpha but also beta and gamma
  - Alpha is easily shielded, so many experimental restrictions







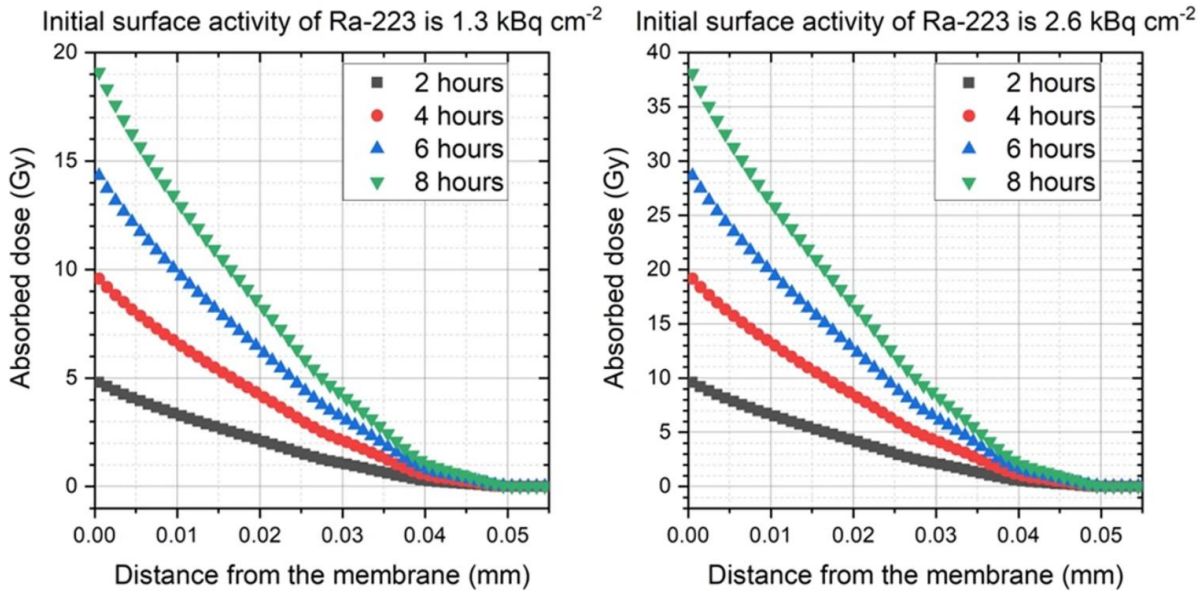


Kristina Bannik et al. Sci Rep 2019;9: 18489-18499

Investigating alpha radiation effects on cells in vitro

- and how much dose is actually delivered to the cells?

Cell line		Length, µm	Width, µm	Height, µm
H460	cell	20	16	9
	nuclei	12.5	8.5	7
OVCAR-3	cell	18	15.7	14.7
	nuclei	13	10	10.3
COV362	cell	34.3	19.8	14.1
	nuclei	16.6	12.8	8.9
COV644	cell	32.6	17	9.8
	nuclei	14	9.7	3.2



Cell line	2 h	4 h	6 h	8 h
H460	4.1 ± 1.3 Gy	8.16 ± 1.7 Gy	12.2 ± 2.1 Gy	16.2 ± 2.4 Gy
OVCAR-3	3.86 ± 0.9 Gy	7.73 ± 1.4 Gy	11.50 ± 1.8 Gy	15.37 ± 1.9 Gy
COV644	4.30 ± 0.8 Gy	8.75 ± 1.2 Gy	13.16 ± 1.5 Gy	17.58 ± 1.7 Gy
Average dose delivered	4.1 ± 0.2 Gy	8.2 ± 0.4 Gy	12.3 ± 0.7 Gy	16.4 ± 0.9 Gy

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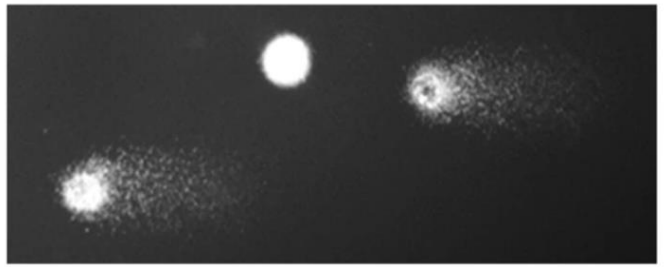
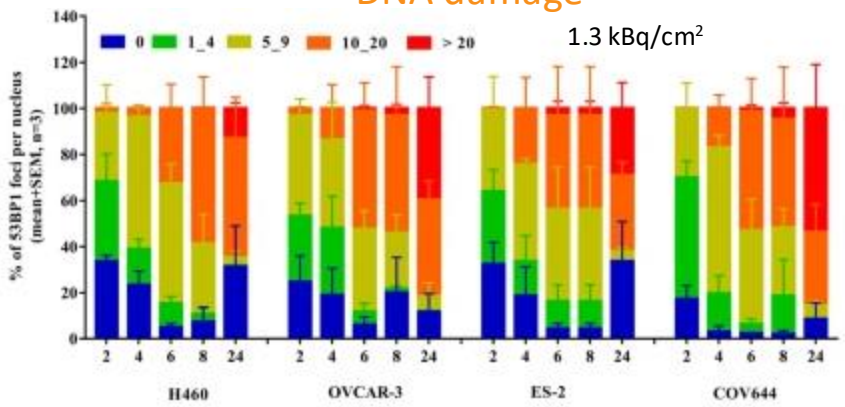
Investigating alpha radiation effects on cells in vitro

- Cells show variable sensitivity and reactions towards alpha radiation

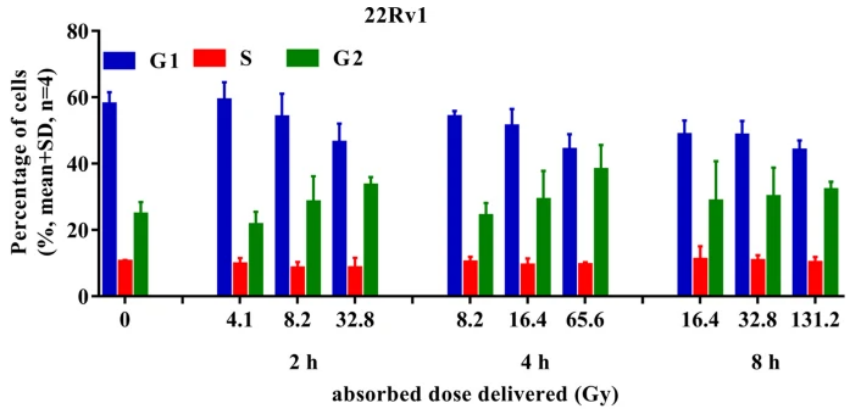
DNA breaks



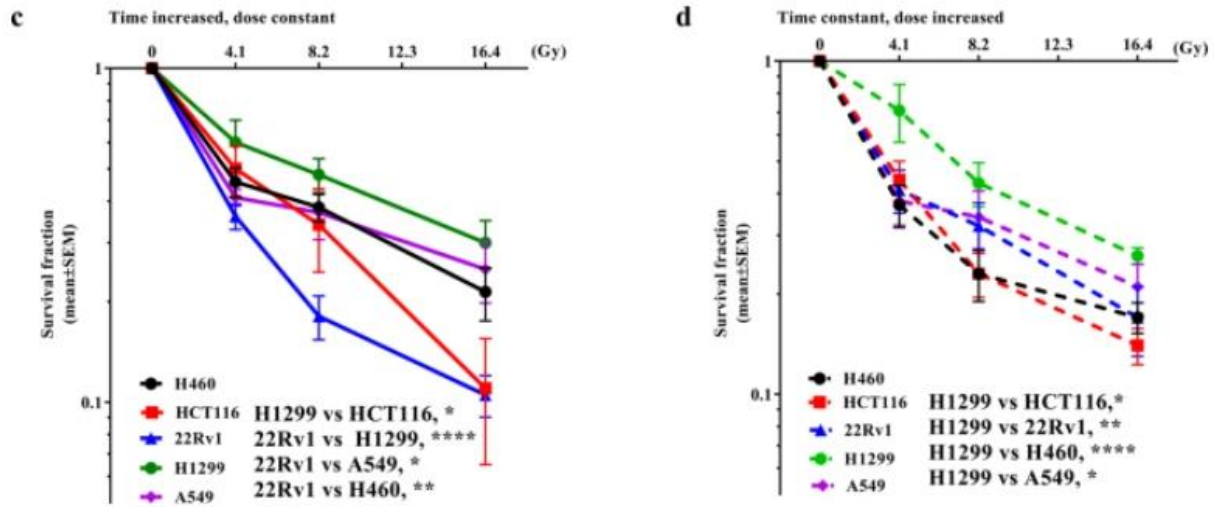
DNA damage

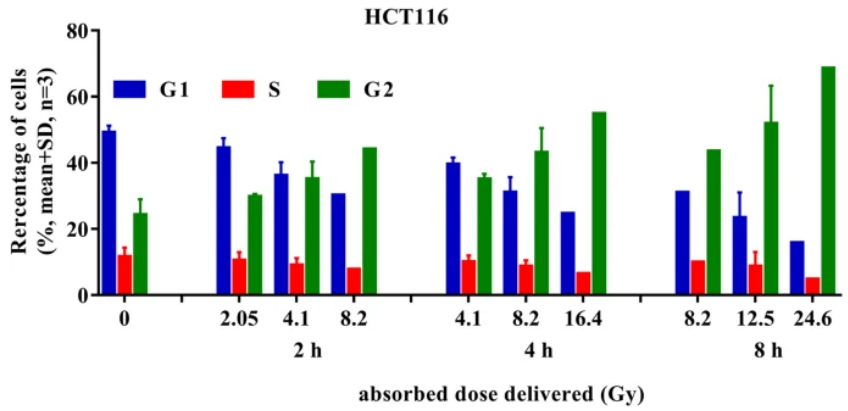


cell cycle arrest



cell death





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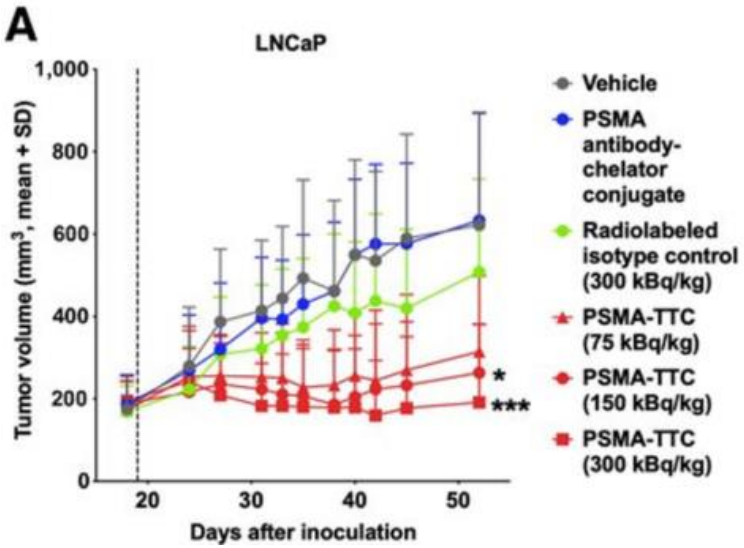
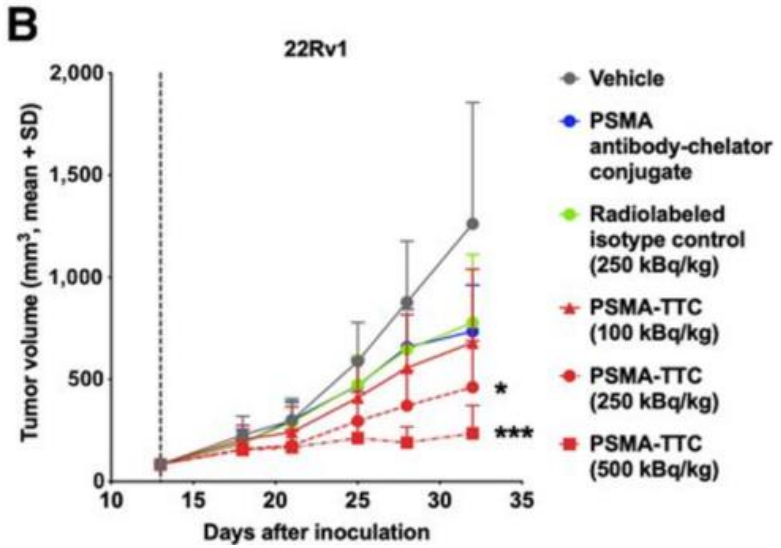
Stages of developing new TAT therapeutics

- 2. Find a good targeting molecule!
  - Test for in vivo characteristics (efficacy vs tumors, effects of target expression, effect on body weight)

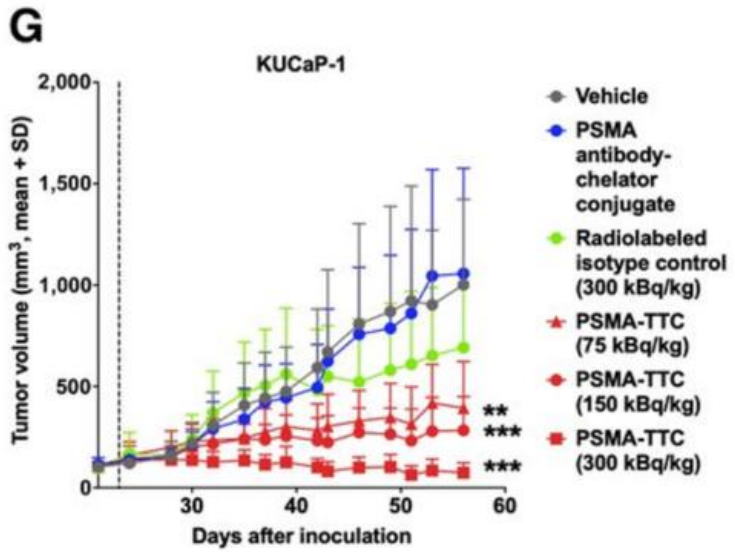
high expressing model



low expressing model



PDX model

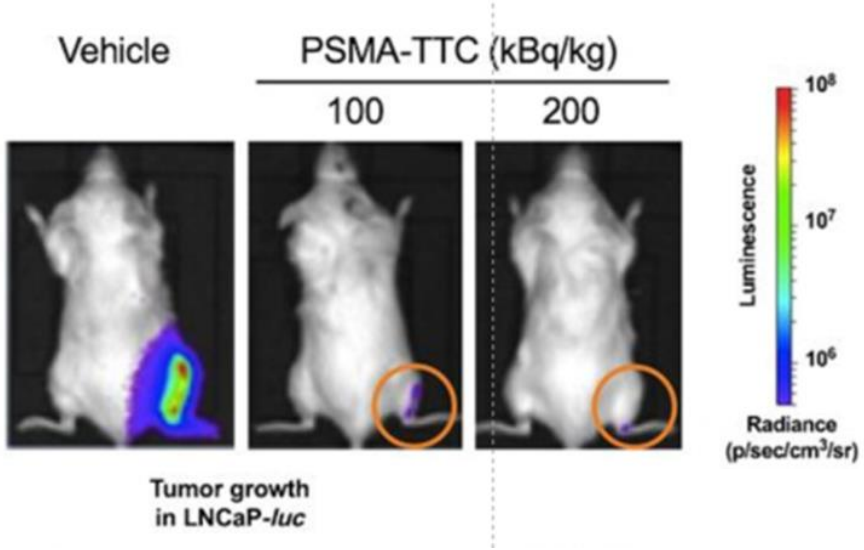


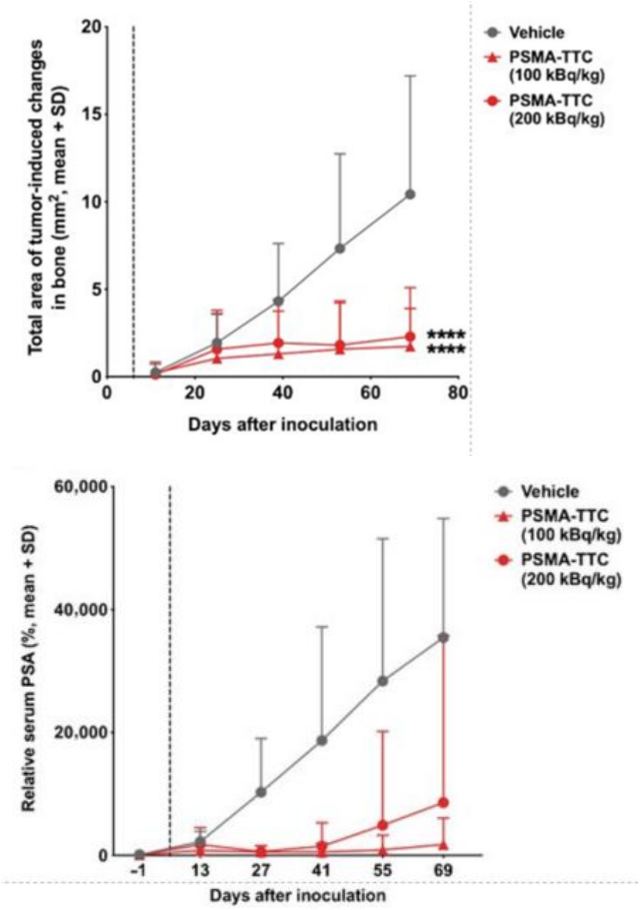
Stefanie Hammer et al. Clin Cancer Res 2020;26:1985-1996

Stages of developing new TAT therapeutics

- 2. Find a good targeting molecule!
  - Test for in vivo characteristics (efficacy vs tumors, effects of target expression, effect on body weight)

Bone metastasis model





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Stages of developing new TAT therapeutics

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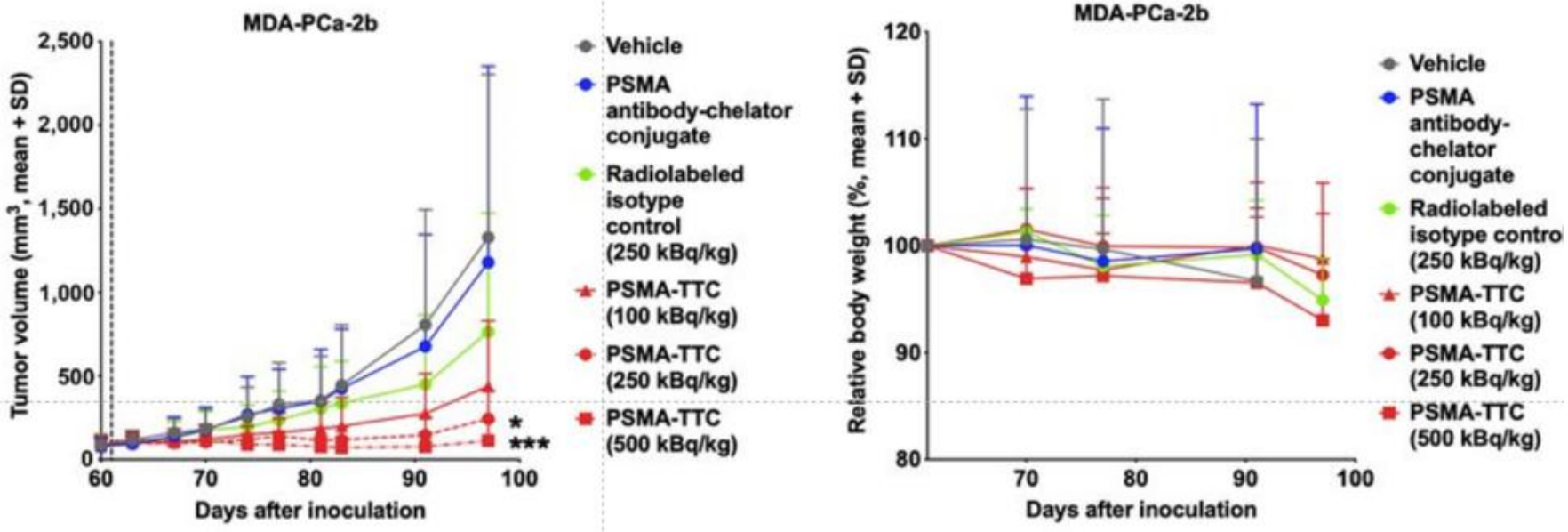
high expressing model



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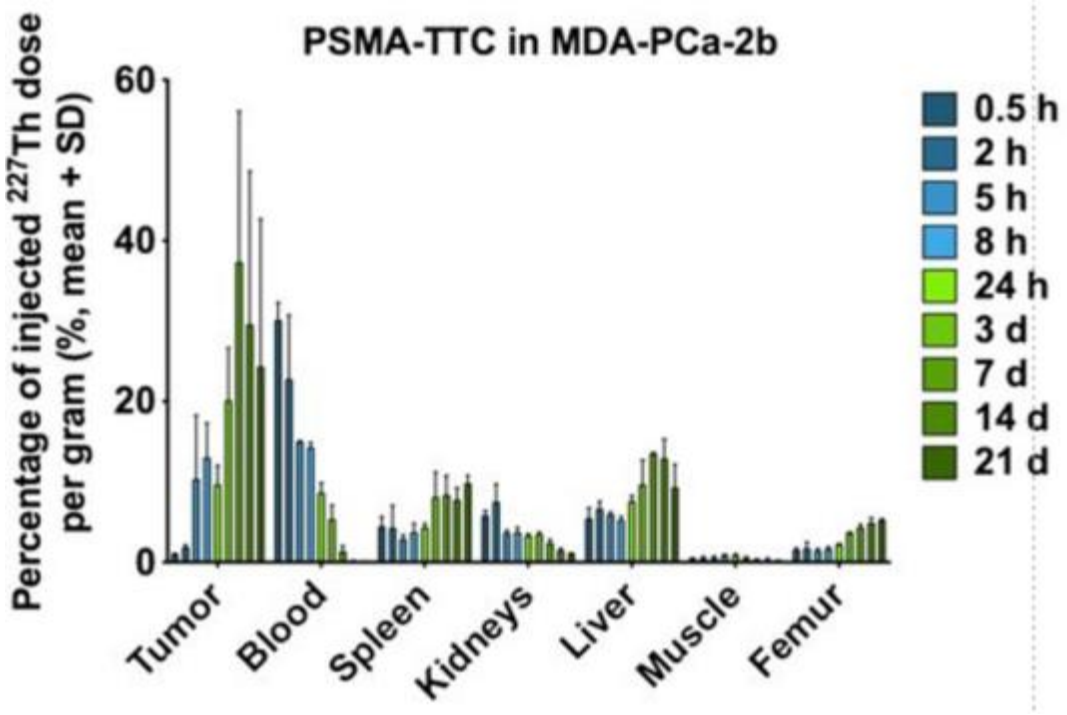
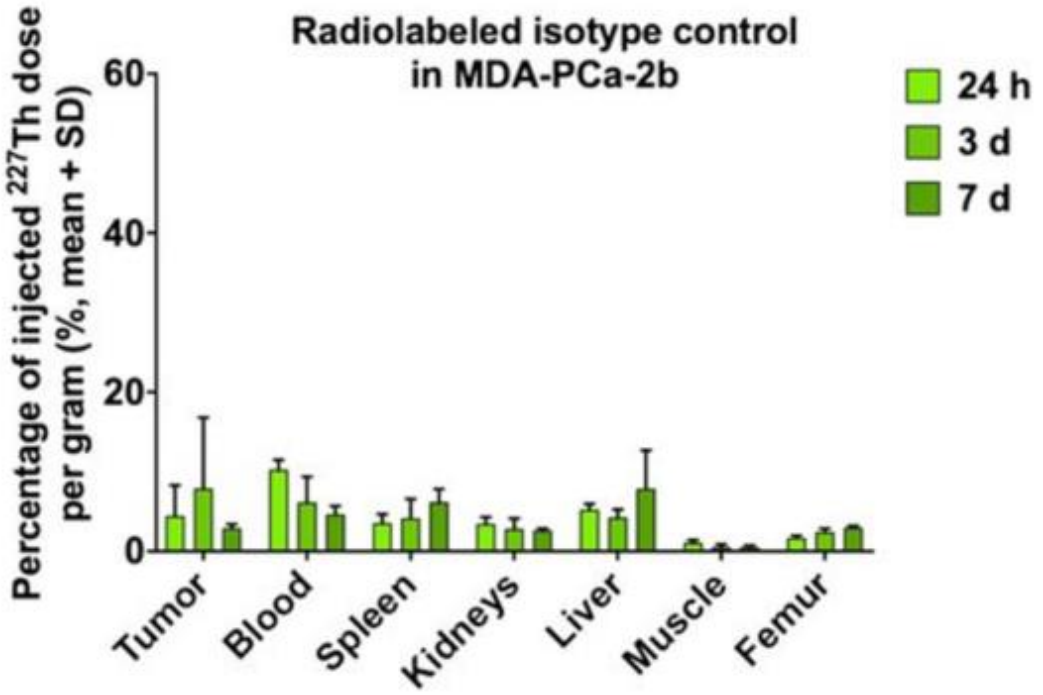
Stages of developing new TAT therapeutics

- 2. Find a good targeting molecule!
  - Test for biodistribution

high expressing model





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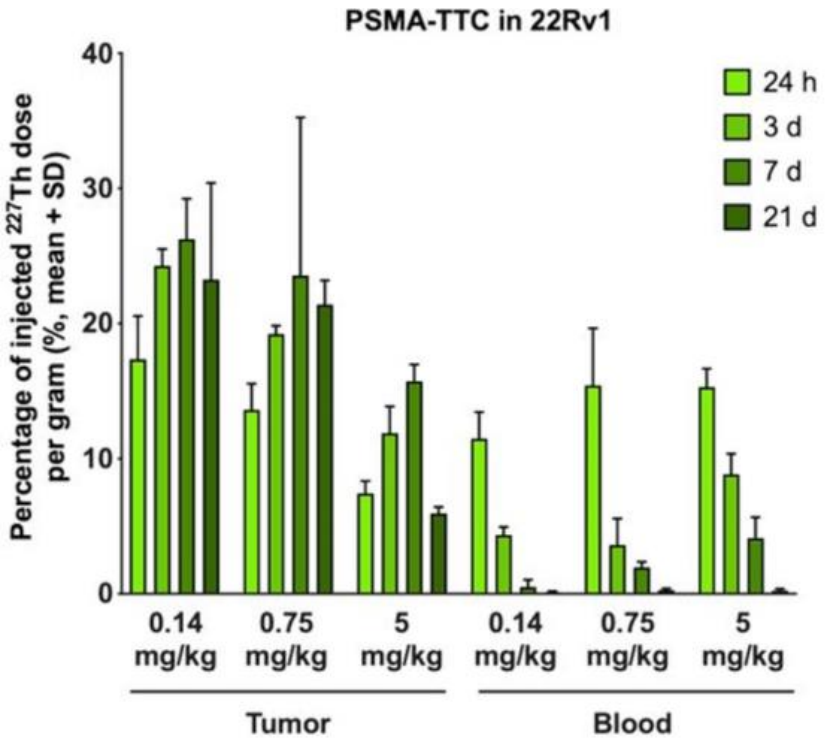
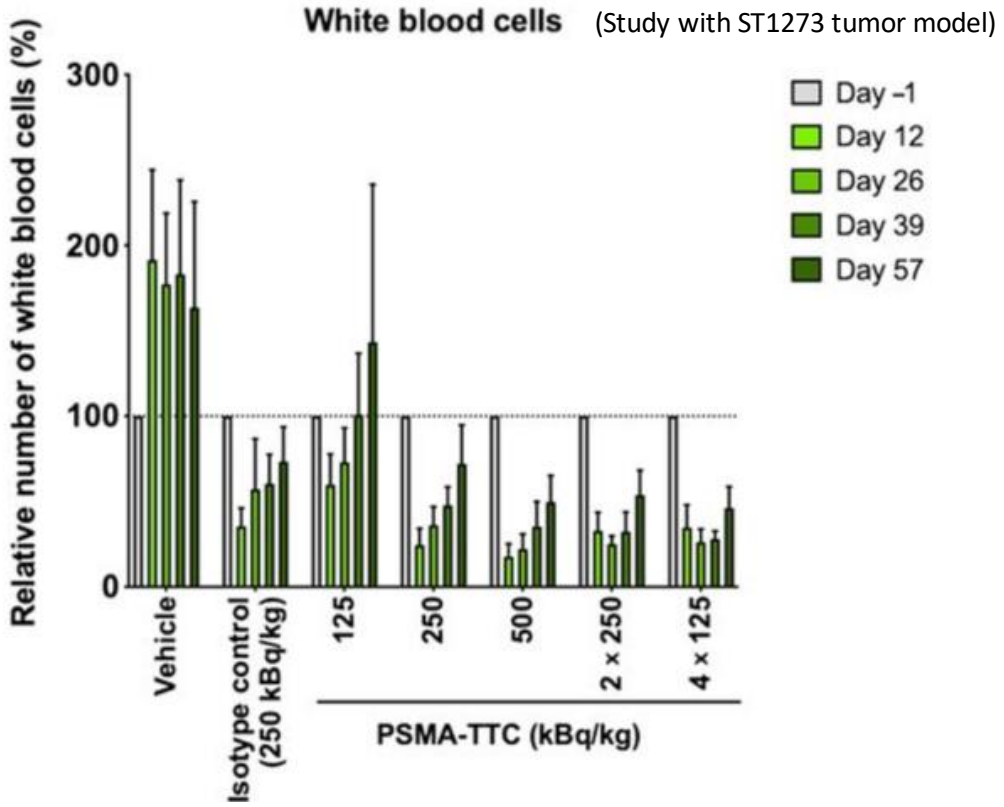
Stages of developing new TAT therapeutics

- 2. Find a good targeting molecule!
  - Test for biodistribution

effect of protein dose





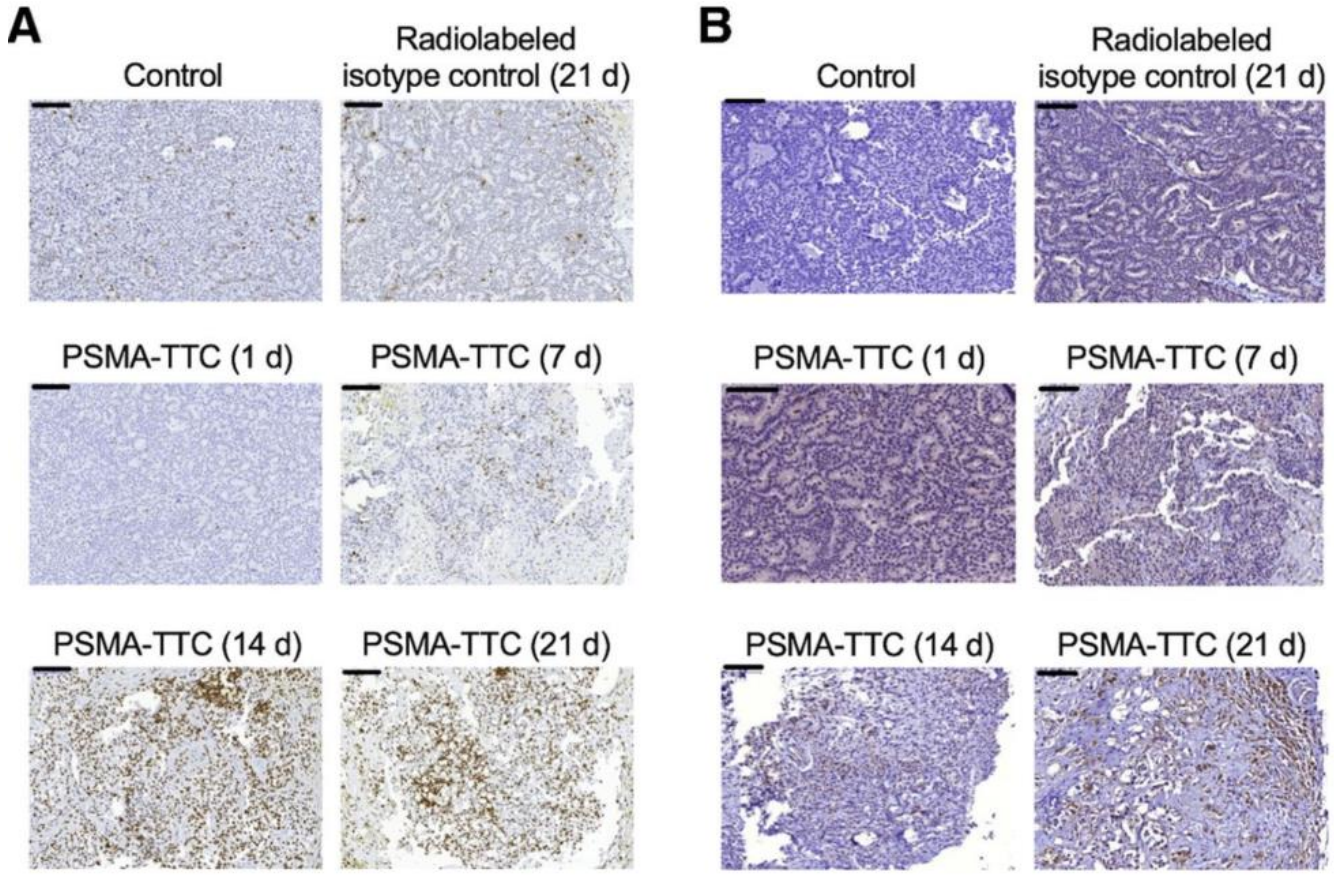
Stefanie Hammer et al. Clin Cancer Res 2020;26:1985-1996

Stages of developing new TAT therapeutics

- 3. Detailed look into effects and side effects of the targeting molecule
  - Immunohistochemistry

DNA damage γH2AX

Apoptosis induction



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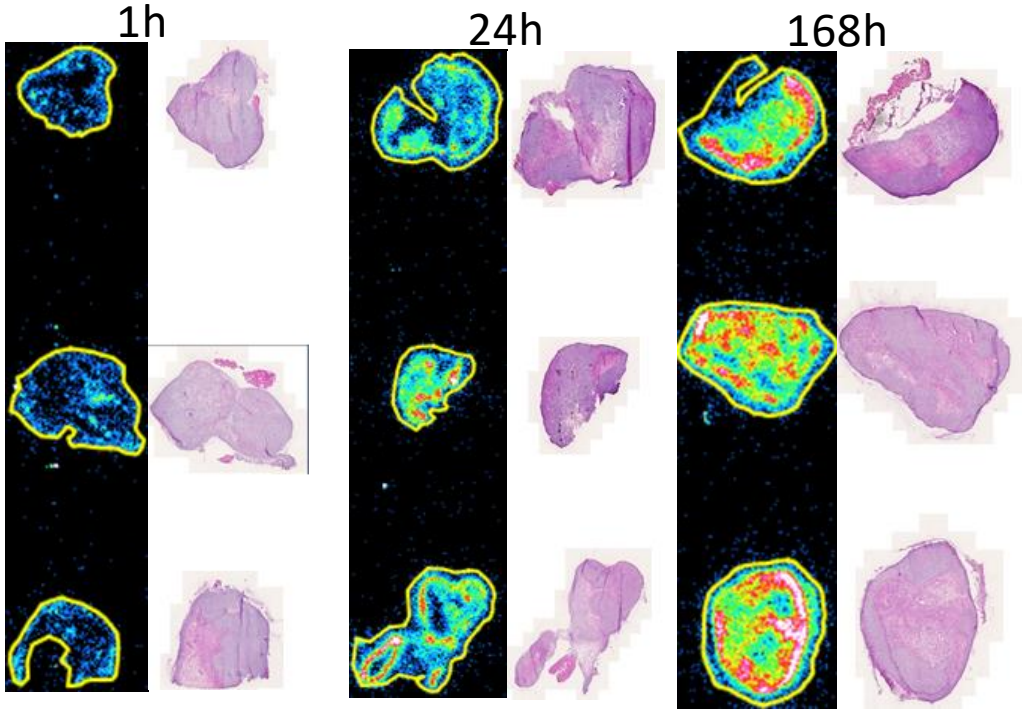
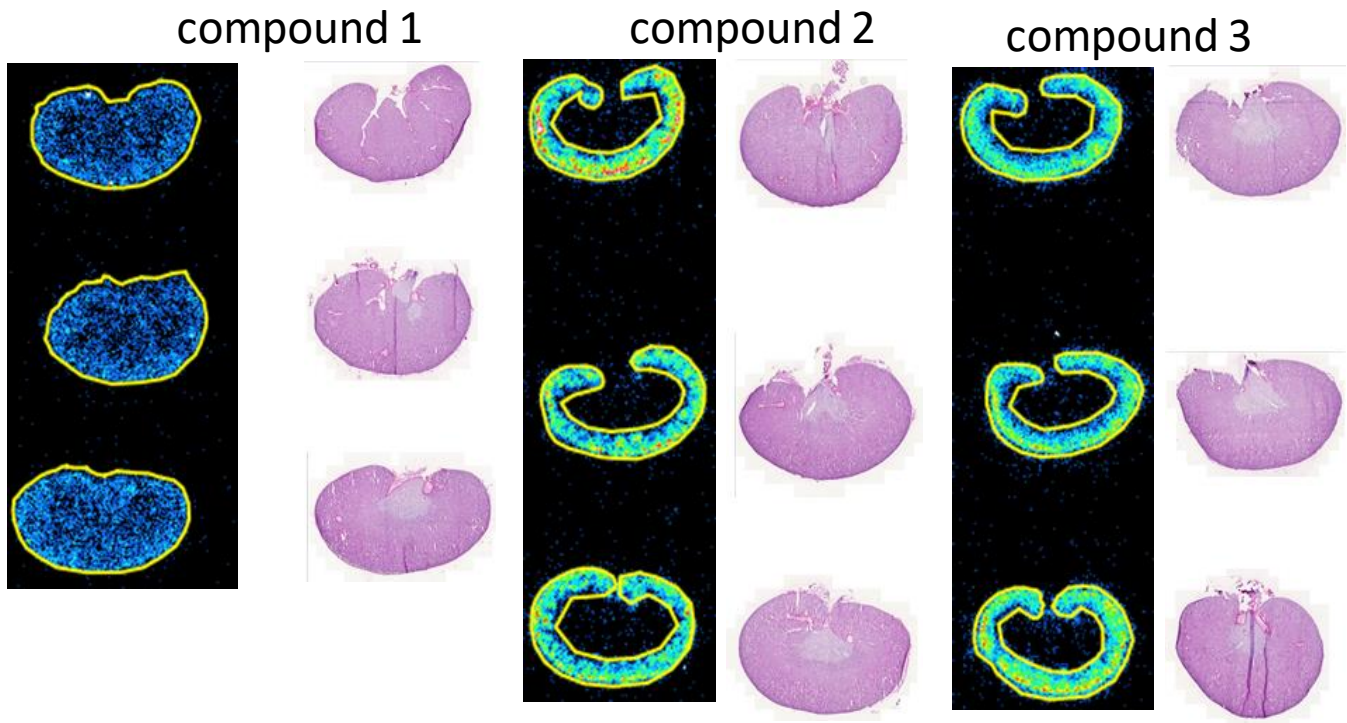
Stages of developing new TAT therapeutics

- 3. Detailed look into effects and side effects of the targeting molecule
  - autoradiography by a gas detectors for real-time

Tumor distribution over time



Kidney localisation of different compounds



Summary

- Bayer has currently two clinical TTC programs in Ph1 dose escalation
- Bayer is expanding its radionuclide portfolio into Ac-225 based molecules

- Preclinical research is focusing on:
  - 1. Find a good target!
  - 2. Find a good targeting molecule!
    - Test for desirable in vitro characteristics (specific binding, internalization, damaging effects on target expressing cells)
    - Special considerations for alpha radiation (not just one decay but many daughters, not just alpha but also beta and gamma, Alpha is easily shielded, so many experimental restrictions)
    - Test for in vivo characteristics (efficacy vs tumors, effects of target expression, effect on body weight)
  - 3. Detailed look into effects and side effects of the tracer (Immunohistochemistry, autoradiography)

Acknowledgements

// **Research & Development team in Oslo & Berlin**

TARGETED ALPHA THERAPY

Thank You