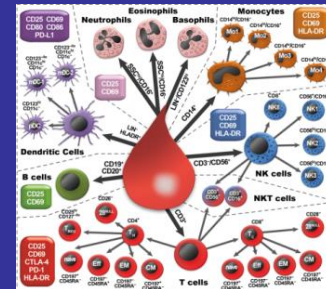




Foto: Strahlenklinik Erlangen



Zhou, Donaubaauer et al.,
J Immunother Cancer, 2021, Feb;9(2)

Do the immunological effects of hyperthermia and FLASH-RT go together?

Prof. Dr. Udo S. Gaipf

Head of Translational Radiobiology -
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DEGR LUNCH SYMPOSIUM

FREITAG, 14. JUNI 2024 | 12:30 - 13:30 UHR | ROSENAAAL

► QUALITÄTSGESICHERTE HYPERTHERMIE UND
FLASH-RADIODTHERAPIE



@translatradbio



**Universitätsklinikum
Erlangen**



Conflict of interest disclosure



Berater- und Gutachtertätigkeiten

AstraZeneca, BMS, Dr. Sennewald Medizintechnik

Honorare

AstraZeneca, BMS, Dr. Sennewald Medizintechnik , Merck

Forschungsfinanzierung

AstraZeneca, MSD

Eigentümerinteressen (Patent, Urheberrecht, Verkaufslizenz)

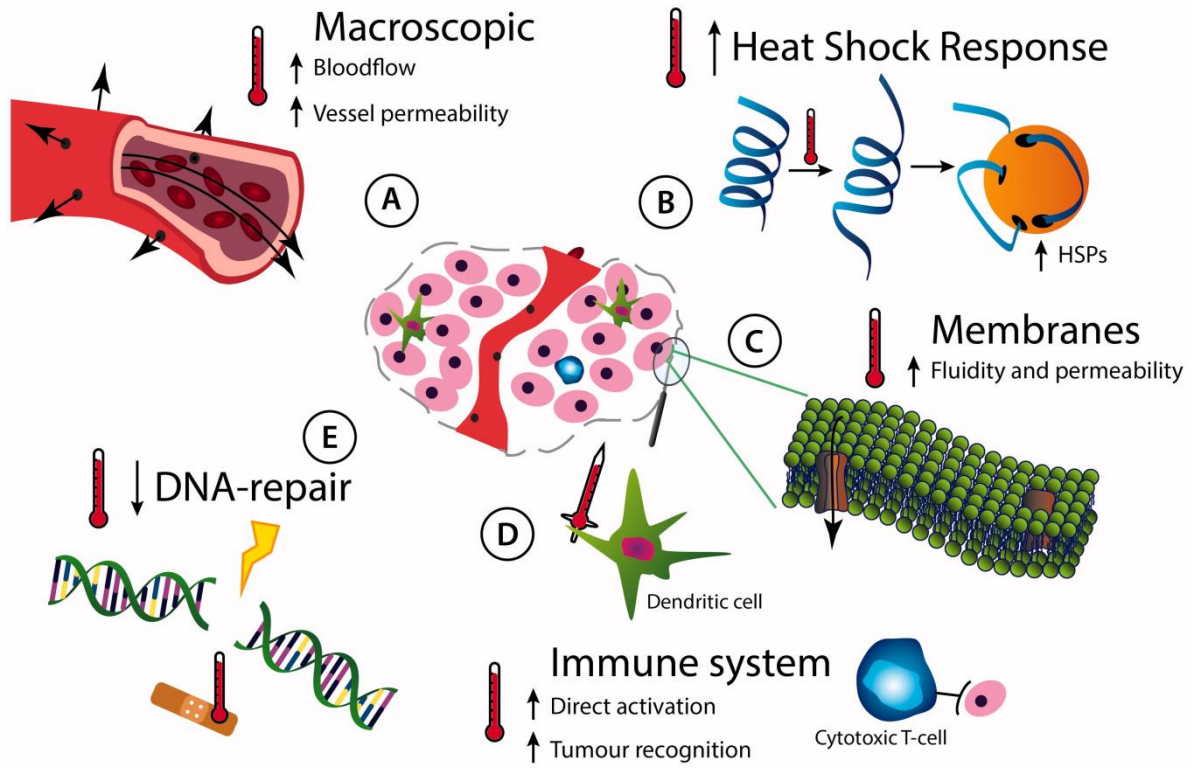
Nein

Geschäftsanteile, Aktien, Fonds

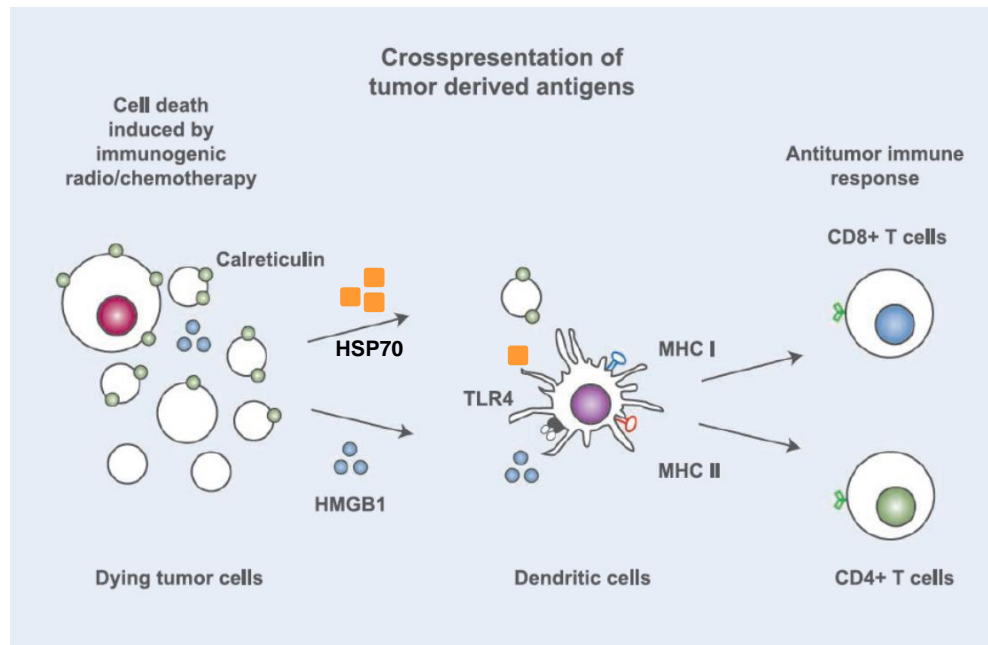
Nein



Hyperthermia affects the tumor and the tumor micro-environment (TME)



Why immune modulation by hyperthermia: triggering of immunogenic forms of tumor cell death

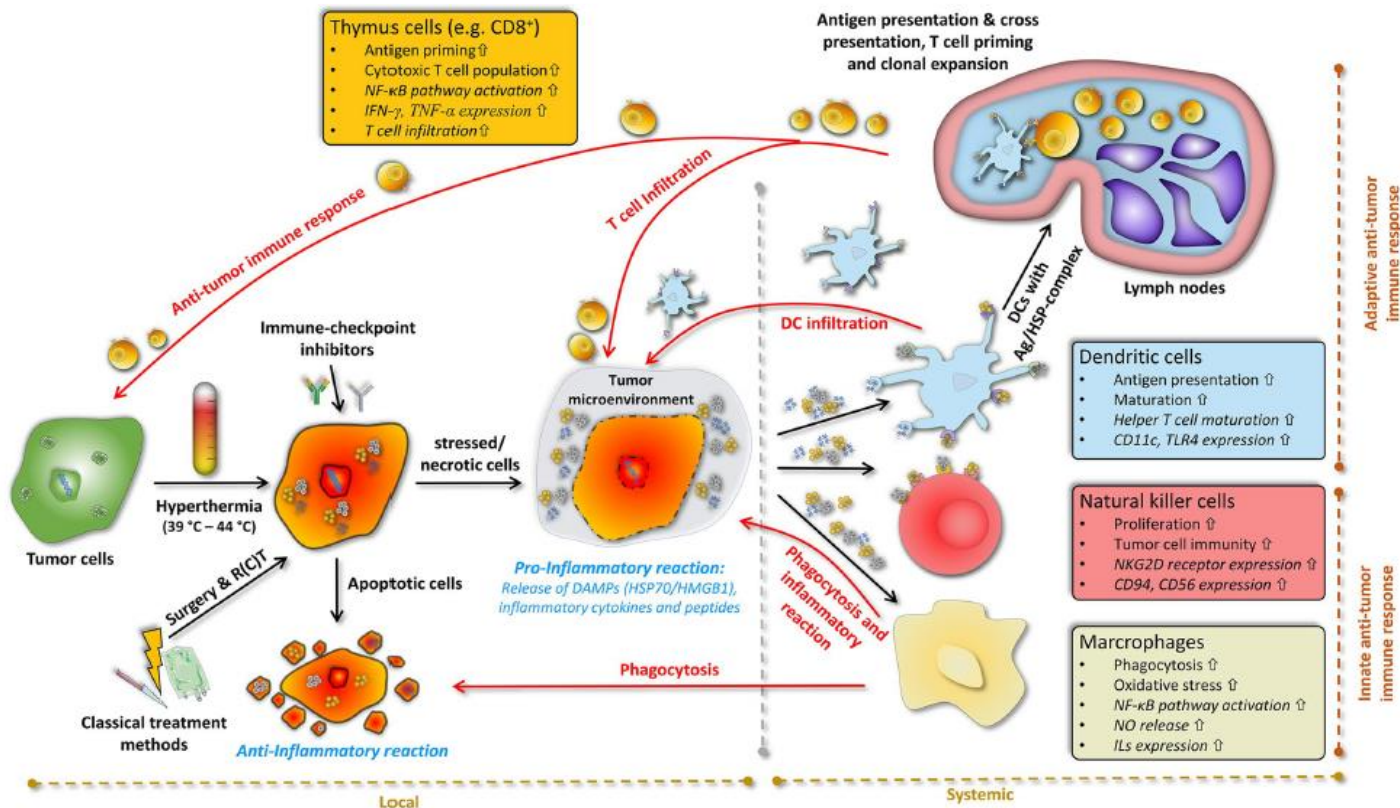


CRT: binding of dying tumor cells to dendritic cells (DCs)

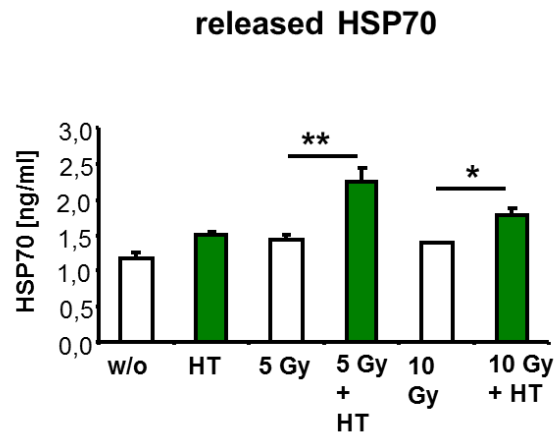
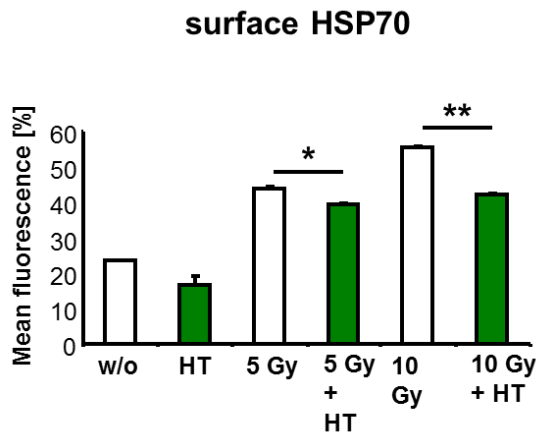
HMGB1: enhances DC maturation and MHC I-based antigen presentation, particularly to CD8+ cytotoxic T lymphocyte (CTL)

HSP70: delivery of antigens and activation of immune cells

Hyperthermia affects the innate and the adaptive immune system – local and systemic effects



RT in combination with HT induces the release of HSP70 - local treatments can become systemic



RT induces higher surface expression of HSP70.

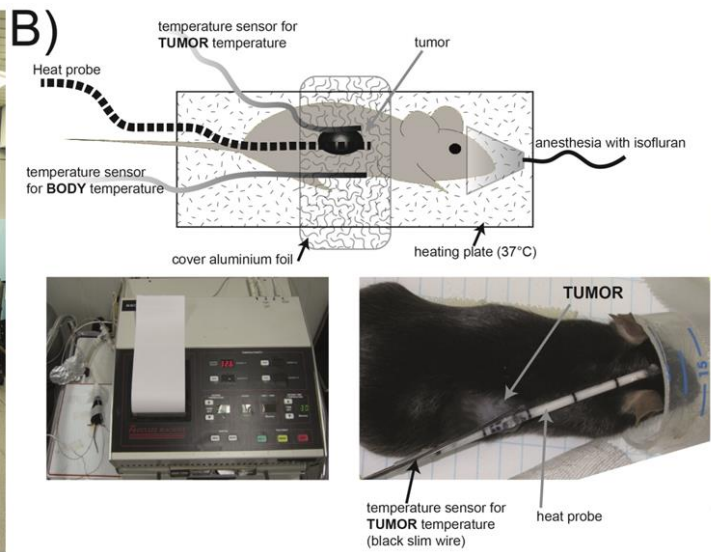
HT induces release of HSP70.

HCT15 colorectal tumor cells; 72 hours after treatment;
HT: 41.5° C for 1h; time interval between treatments: 4 hours

HT: 41.5° C



In vivo effects of RT and HT - applications resembling the human situation



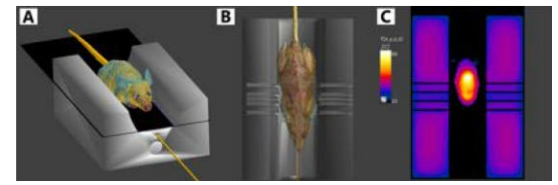
PATIENT: _____
 OPERATOR: _____
 SERIAL #1: _____

COLUMN 1: ELAPSED TIME
 COLUMN 2: DELIVERED TEMPERATURE
 COLUMN 3: CURRENT POWER LEVEL
 COLUMN 4: AVERAGE POWER LEVEL
 COLUMN 5: TEMPERATURE SENSOR # 1
 COLUMN 6: TEMPERATURE SENSOR # 2
 COLUMN 7: TEMPERATURE SENSOR # 3
 COLUMN 8: TEMPERATURE SENSOR # 4

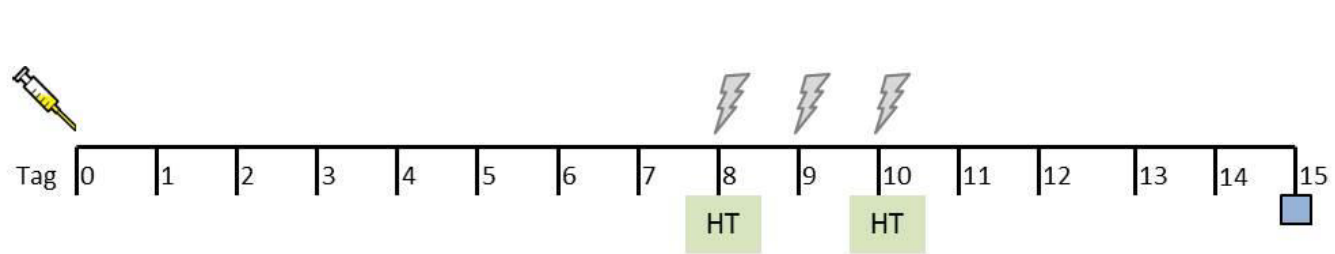
Time	Temp	Power	Avg Power	Sensor 1	Sensor 2	Sensor 3	Sensor 4
00:01	41.5	0.0	0.0	0.0	0.0	0.0	0.0
01:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
02:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
03:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
04:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
05:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
06:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
07:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
08:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
09:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
10:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
11:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
12:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
13:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
14:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
15:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
16:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
17:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
18:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
19:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
20:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
21:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
22:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
23:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
24:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
25:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
26:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
27:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
28:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
29:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
30:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
30:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0
30:00	41.5	0.0	0.0	0.0	0.0	0.0	0.0

TREATMENT COMPLETE

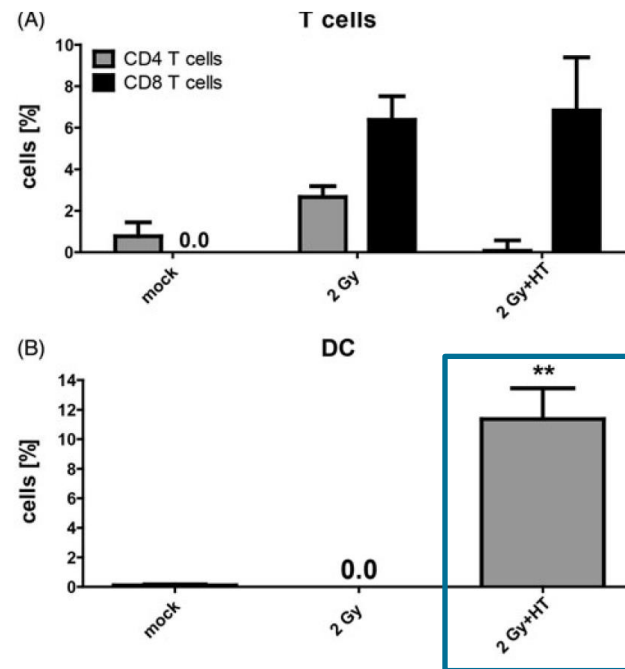
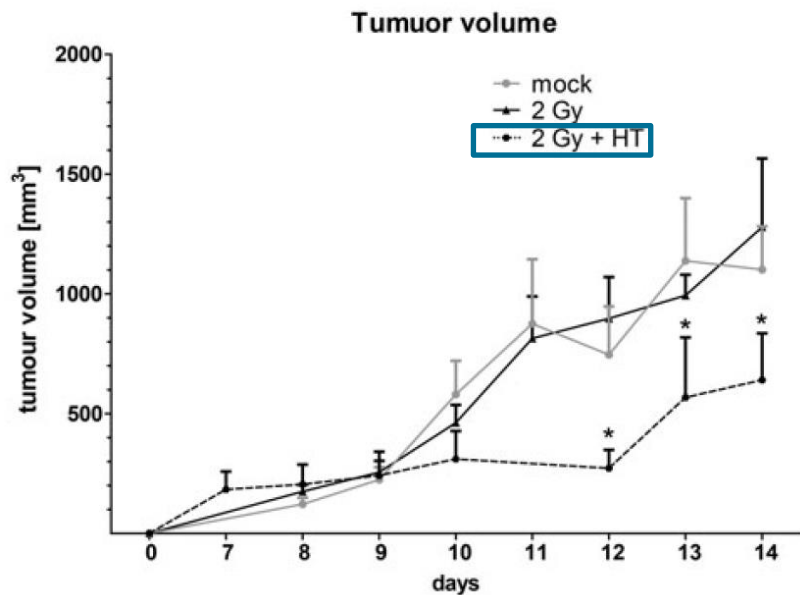
EXPOSURE TIME: 30 MINUTES
 time at 41.5°C



Master thesis
 Benjamin Kahler,
 09/2022



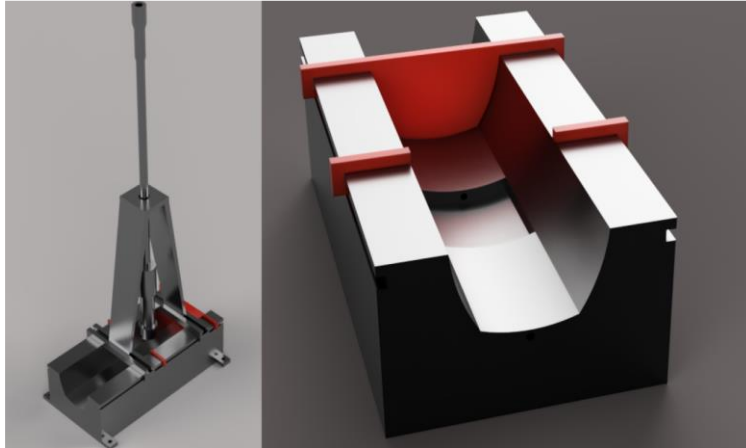
Increased tumor growth retardation and increased infiltration of dendritic cells when HT is added to RT



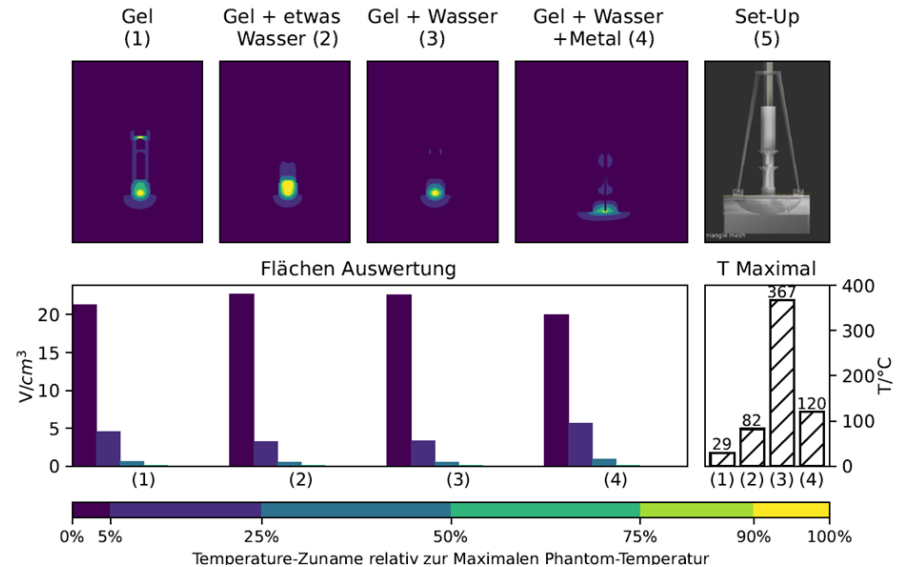
HT: 41.5° C



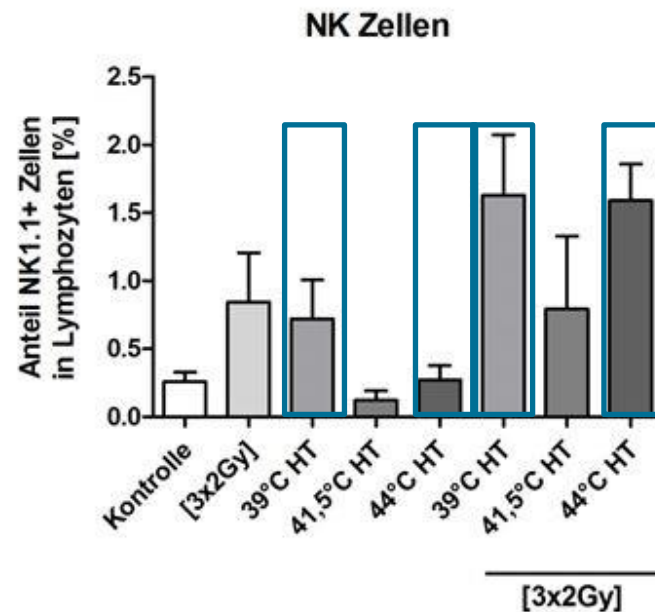
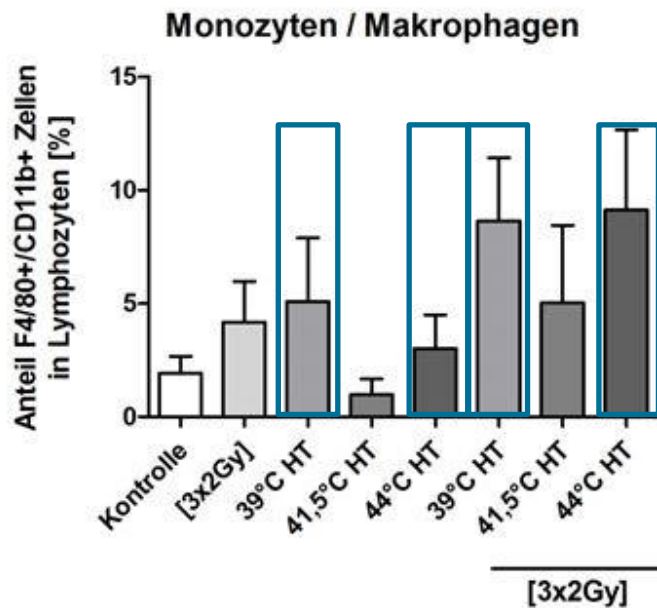
Advanced applicator development for preclinical *in vivo* analyses



Erwärmungs-Vorhersage für verschiedenen Applikator Gebrauch



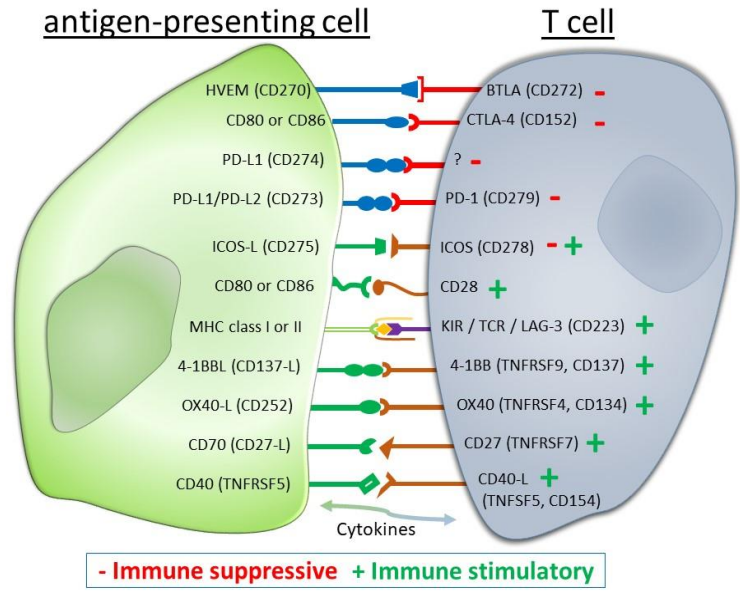
HT and RT foster infiltration of innate immune cells into B16 melanoma



- Homogenous or heterogenous temperature distribution immunological more beneficial?
- Comparable to immune effects of spatial fractionated RT (SFRT)?



Immune checkpoint molecules control T cell responses and show a high dynamic of expression



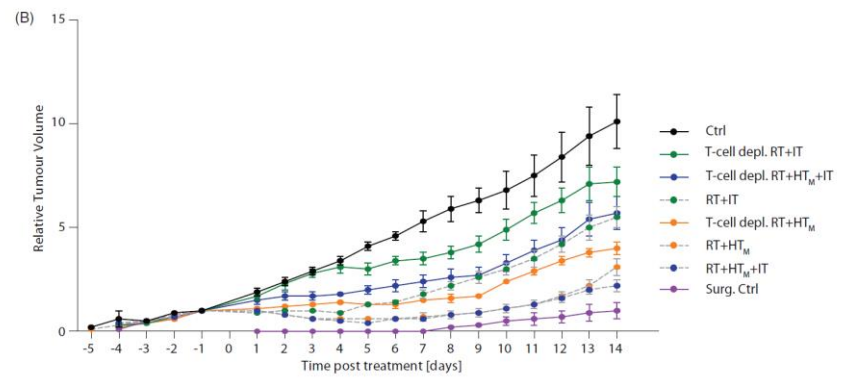
MCF-7

		d3			d5				
39 °C	CH	hypo	1.53	1.55	3.22**	1.27	2.03*	2.84**	
		normo	1.87	2.44*	2.62**	0.72	1.50	2.81	
	MH	hypo	1.62	1.24	1.39	1.69	1.92**	1.98**	
		normo	1.24	1.08	1.53	1.58	1.56	1.72*	
	41 °C	CH	hypo	1.80	1.27**	2.65**	1.71	1.79*	1.55
			normo	1.13	3.71**	2.68**	1.17	1.17	1.55
MH		hypo	1.22	1.27	1.39	1.89*	2.19**	1.59	
		normo	1.22	1.58	1.38	2.09**	2.49**	1.47	
44 °C		CH	hypo	2.08**	2.88**	4.53***	1.65	3.96**	2.06*
			normo	1.67	2.22*	3.42***	1.63	3.87***	2.49*
	MH	hypo	1.54	1.95	2.68*	1.08	1.04	1.71	
		normo	1.75	2.21	3.36**	1.46	1.24	1.91*	
			PD-L1	PD-L2	HVEM	PD-L1	PD-L2	HVEM	

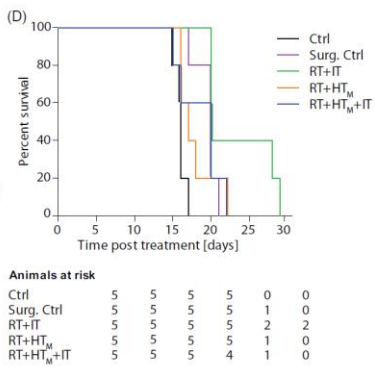
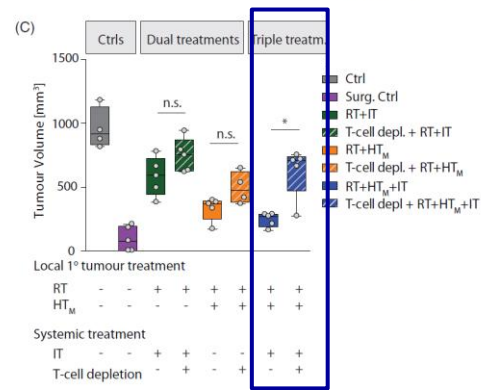




Preclinical hints that combination of RT and HT with ICI immune therapy induces anti-tumor immunity



HT: locally 43° C
 RT: 3x8Gy
 IT: anti-PD-L1/anti-CTLA-4



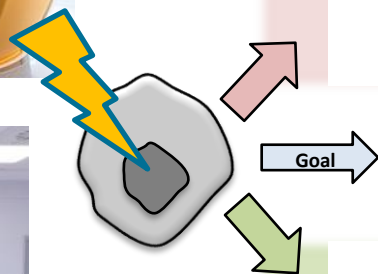
→ Anti-tumor response induced by triple treatment is dependent on T cells



Immune activation and immune suppression by radiotherapy



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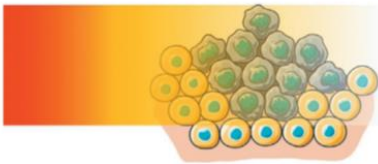
Local tumor control
Tumor cell killing



Temporal and spatial modulation of the RT dose impacts on the immune system

FLASH-RT

Time modulation of the dose



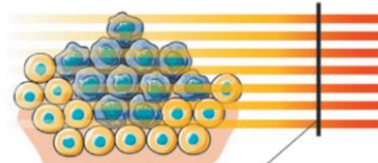
$\Delta t < 200$ ms

$\dot{D} \geq 40$ Gy/s (Ultra-High Dose Rate)

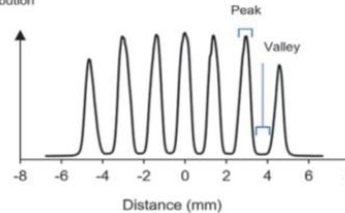
Homogeneous dose distribution

SFRT

Spatial modulation of the dose



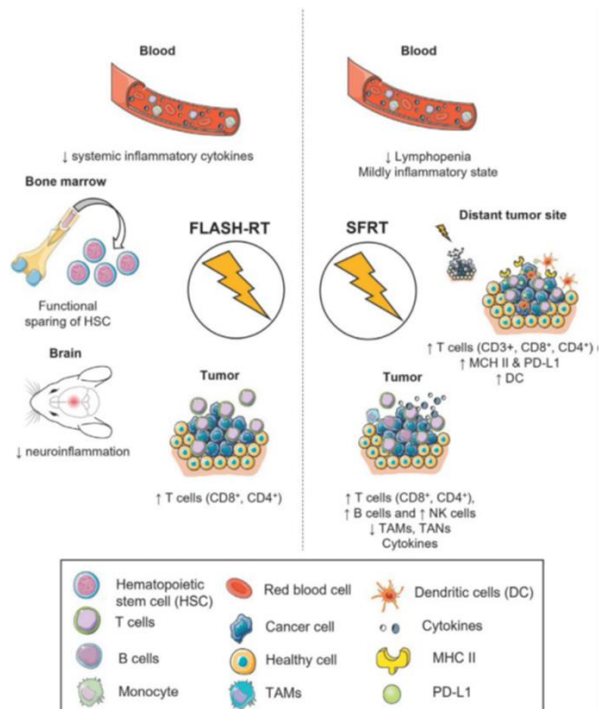
Lateral dose distribution



Healthy tissues sparing
Equivalent or superior tumor control



Temporal and spatial modulation of the RT dose impacts on the immune system



FLASH-RT

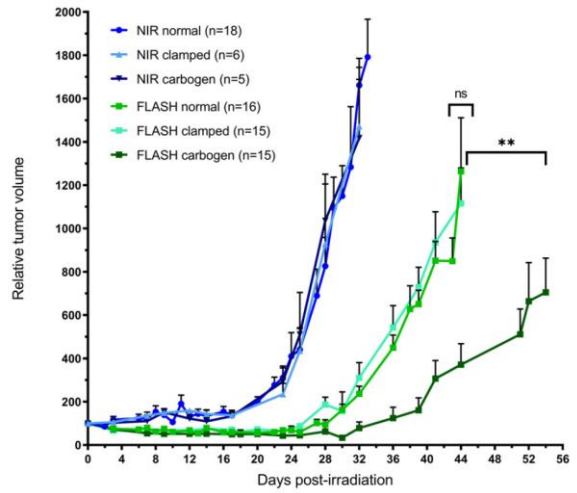
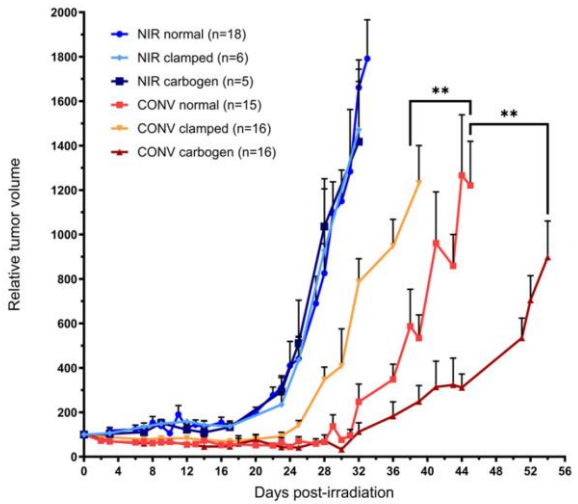
- By reducing the irradiated blood volume, immune cells circulating in the blood are spared (currently only considered *in silico*)
- Fewer secondary reactive oxygen radicals (ROS)
- Less lipid peroxidation (work on this is in print)

SFRT

- Dose peaks in the tumour release many antigens and trigger immunogenic cell death
- At the same time, immune cells and vessels are spared in the dose valleys



FLASH-RT works in hypoxic tumor regions

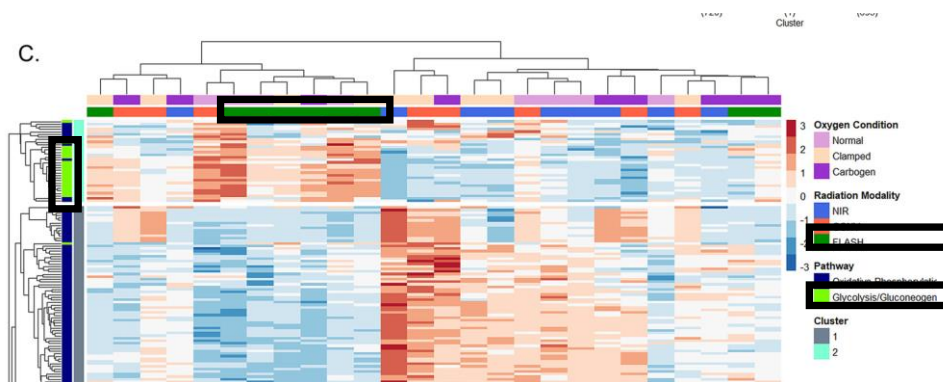
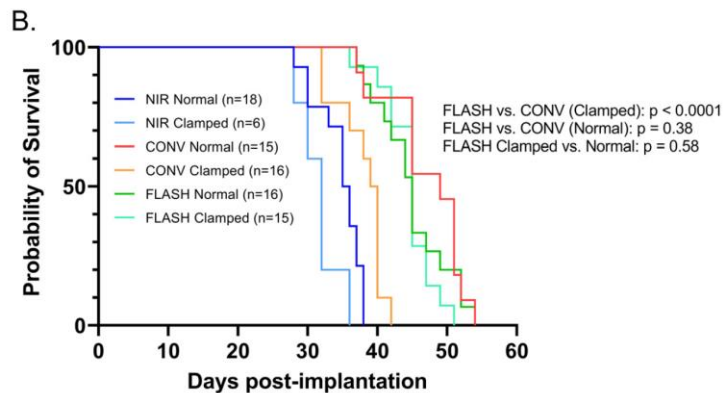


Carbogen breathing: pO₂ ↑

Clamped: pO₂ ↓



FLASH-RT works in hypoxic tumor regions and fosters glycolysis



RNAseq → many DEGs: cell cycle, ribosomal translation and **metabolic switch to glycolysis**

Conclusions



- Hyperthermia promotes immune cell infiltration
- FLASH-RT reduces radiation exposure of circulation immune cells
- Hyperthermia affects the innate and adaptive immune systems
- FLASH-RT reduces activation of TGF- β in the tissue
- Hyperthermia modulates oxygen content of tumor tissue
- FLASH-RT works in hypoxic regions
- Focused hyperthermia has few site effects on normal tissue
- FLASH-RT spares normal tissue (less ROS)

→ **From the immunological point of view hyperthermia and FLASH-RT go together well**





Thanks to our cooperation partners



Prof. Gerard van Rhoon

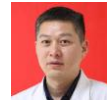


Dr. Hans Crezee

AlphaTAU



Prof. Yona Keisari



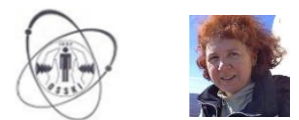
Prof. Hu Ma



Prof. Eric Deutsch



Dr. Roger Sun



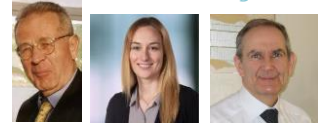
Prof. Katalin Lumniczky



Prof. Claudia Fournier



Dr. Raymond Pommet



Dr. Gerhard Sennewald
Dr. Maria Meindl
Dipl.-Ing. Martin Wadepohl



Prof. Kirsten Lauber



Prof. Diana Dudziak
Prof. Thomas Winkler
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Prof. Christoph Alexiou
PD Luis Munoz



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Dr. Serge Candeias



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Prof. Kerstin Borgmann



Dr. Sander Bekeschus



Dr. Jian-Guo Zhou



Thanks to my team and for your attention!



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