The Radiobiology of Hyperthermia.

Prof Pedro C Lara

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Grupo de Trabajo en Radiobiologia
Grupo Hipertermia SEOR

Rafael Guerrero, Pedro C Lara, Félix Navarro, Barbara Salas

Agenda

- The pioneers
- Hyperhermia kills cells
- Hyperthermia resistance mechanism
- Hyperthermia induces immune response
- Hyperthemia cooperates with RT,CHT,IT
- Hyperthermia modifies tumot alfa/beta ratio

Pioneers

< Previous Article Volume 355, No. 9210, p1119–1125, 1 April 2000 Next Article >

Articles

Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial

Jacoba van der Zee, MD, Prof Dionisio González, González MD, Gerard C van Rhoon, PhD, Jan DP van Dijk, PhD, Wim LJ van Putten, MSc, Augustinus AM Hart, MSc, for the Dutch Deep Hyperthermia Group

DOI: http://dx.doi.org/10.1016/S0140-6736(00)02059-6

Dionisio González-González

"*Un Gy + Hipertermia es como si dieras 2 Gy*"

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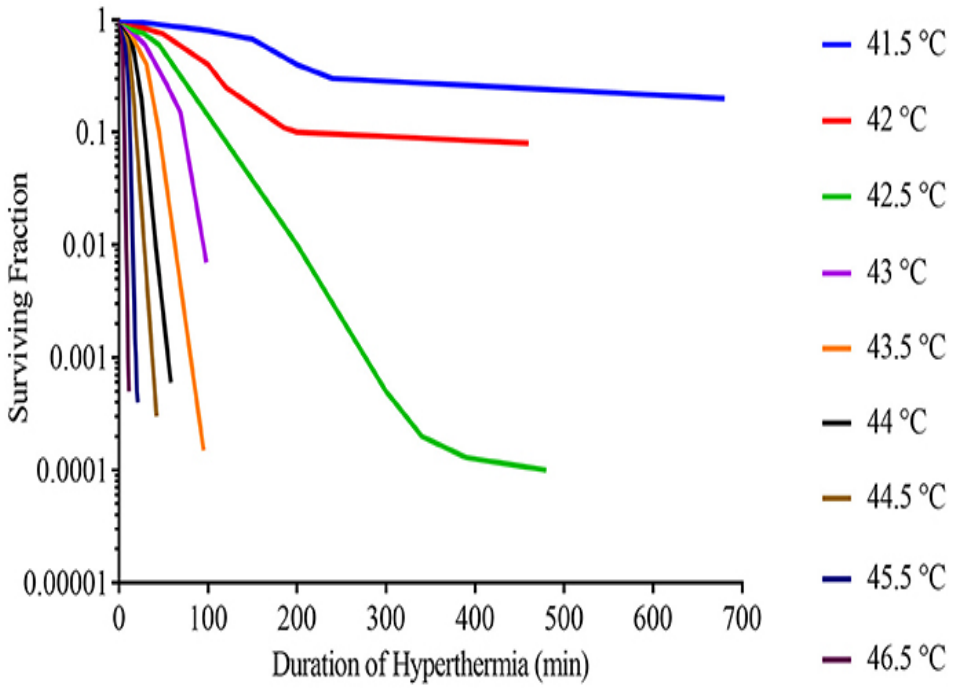
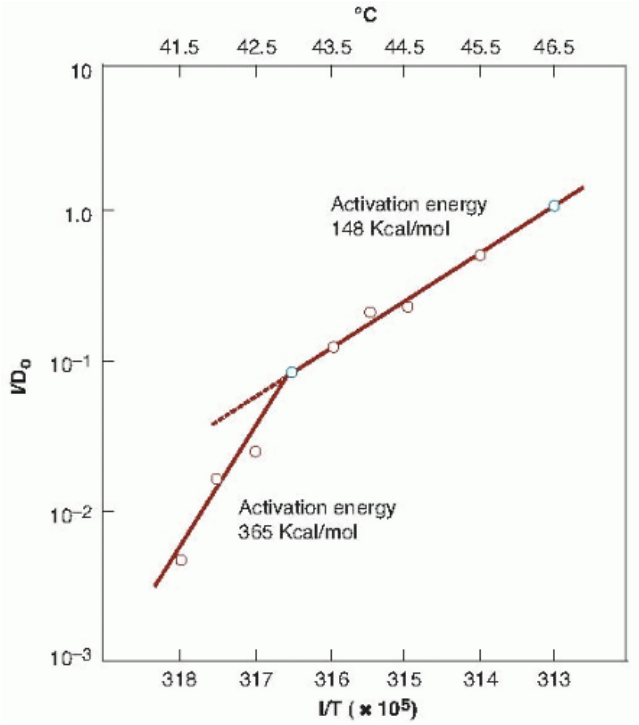
Direct effect of Hyperthermia





The activation energy for heat cytotoxicity is similar to that for protein denaturation (130-170 kcal/mol)

Increase cell death in hypoxic, low ph low energy microenviroment,

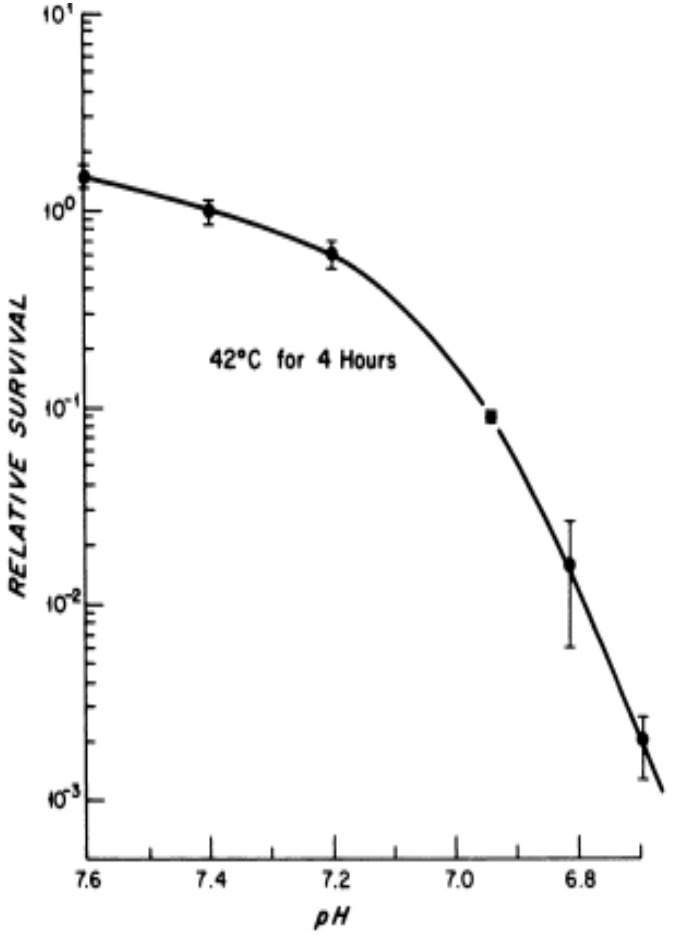
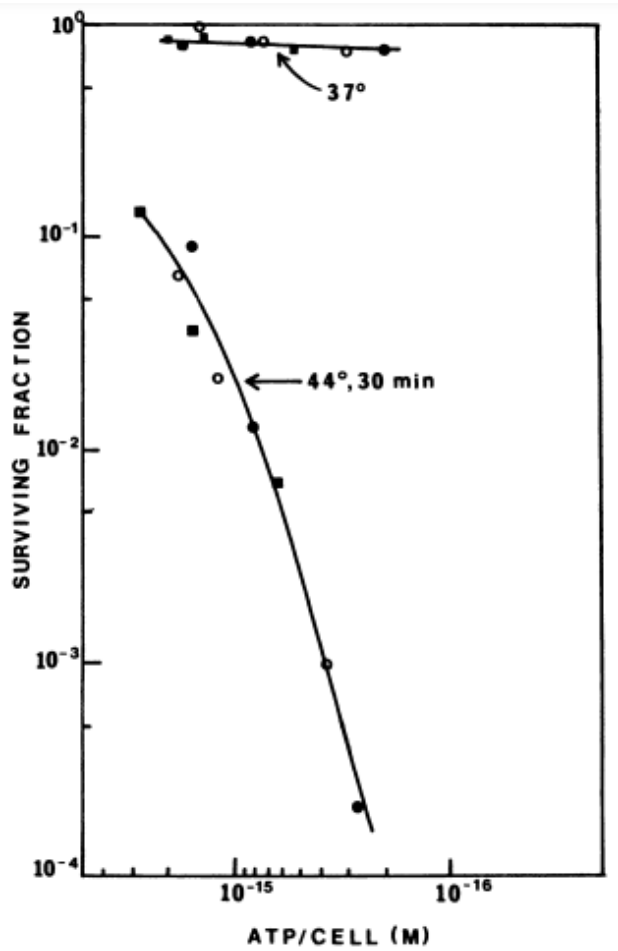
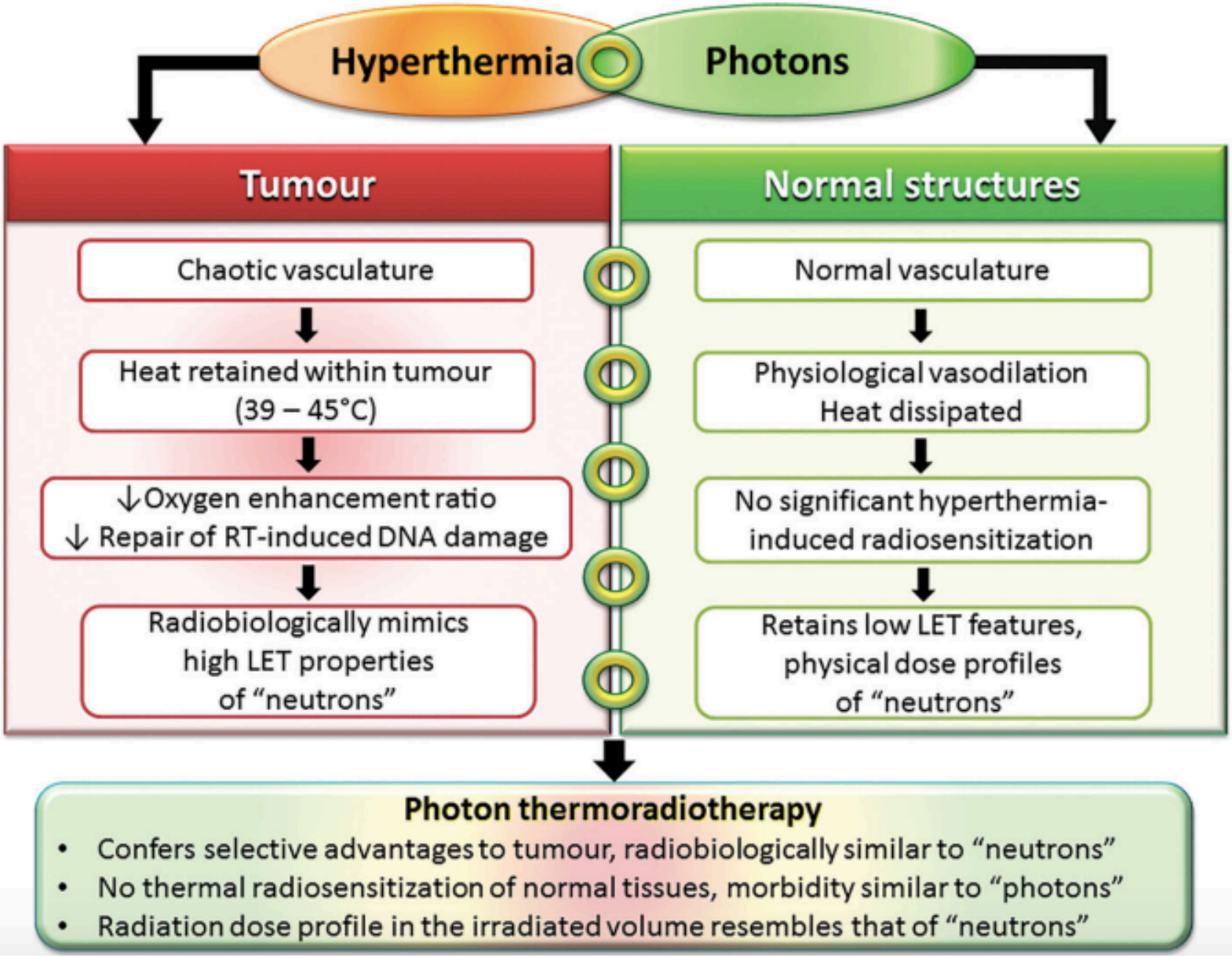
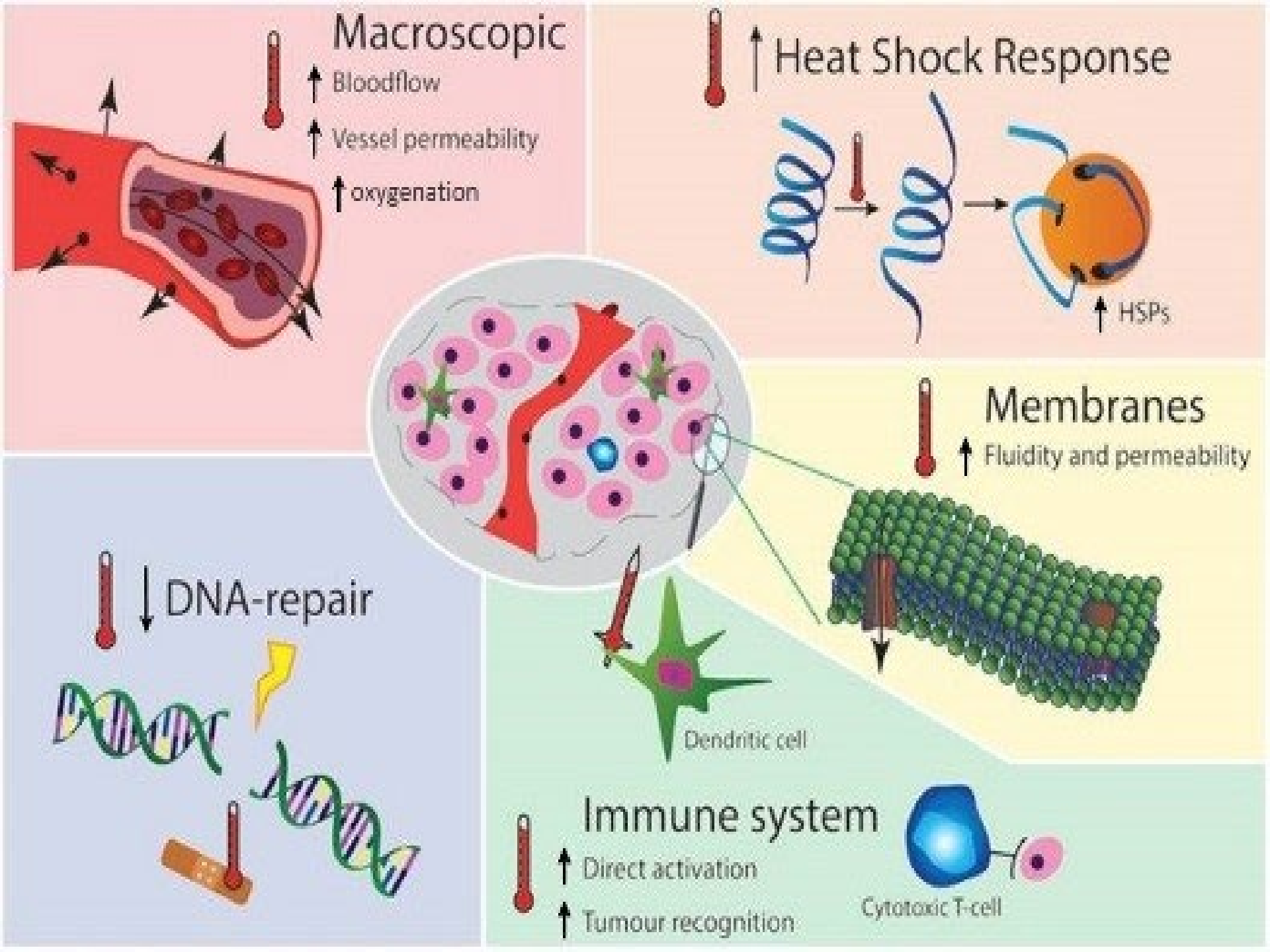
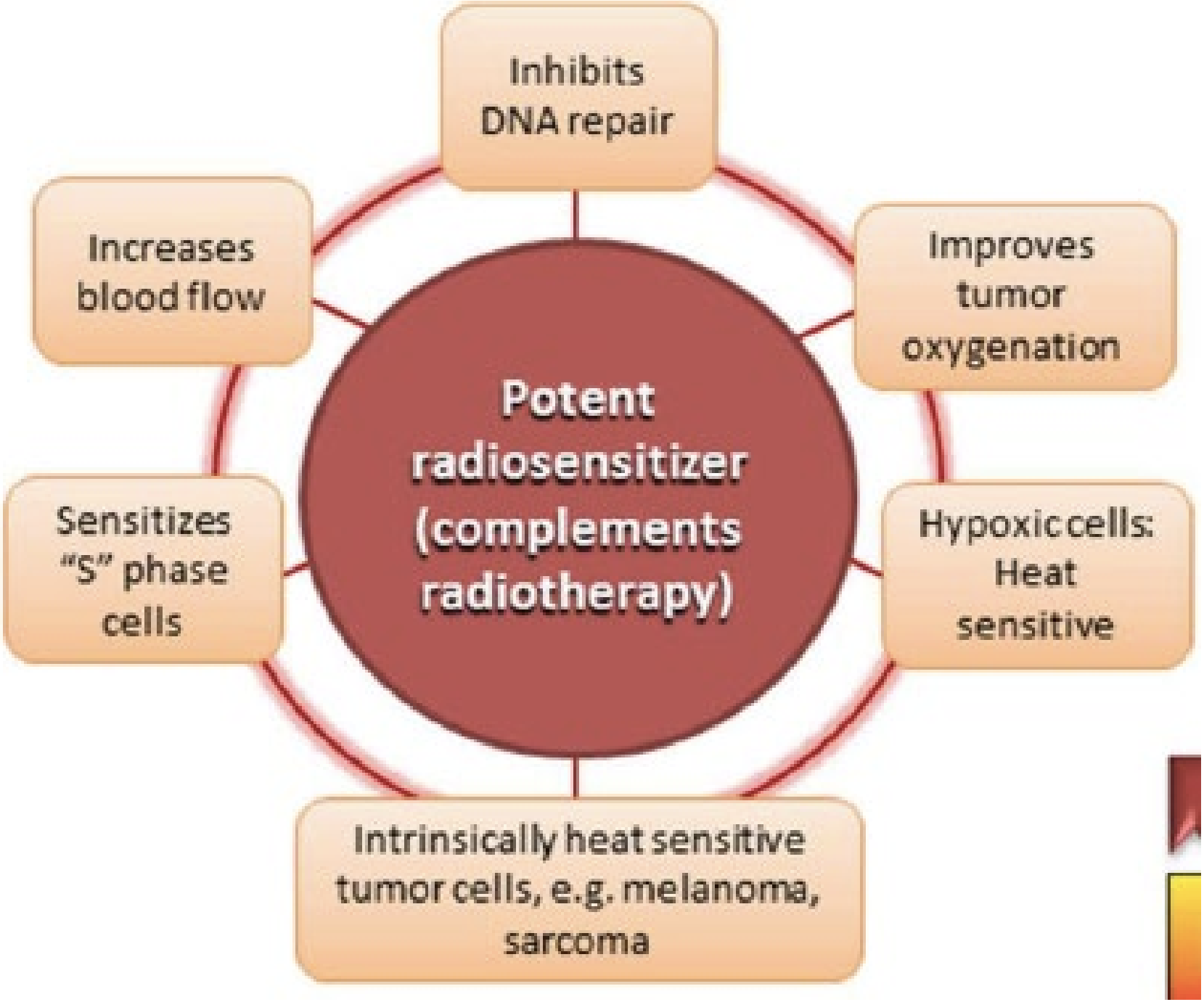


Chart 3. Influence of pH on the thermal sensitivity of Chinese hamster ovary cells (13). *Bars*, SD.

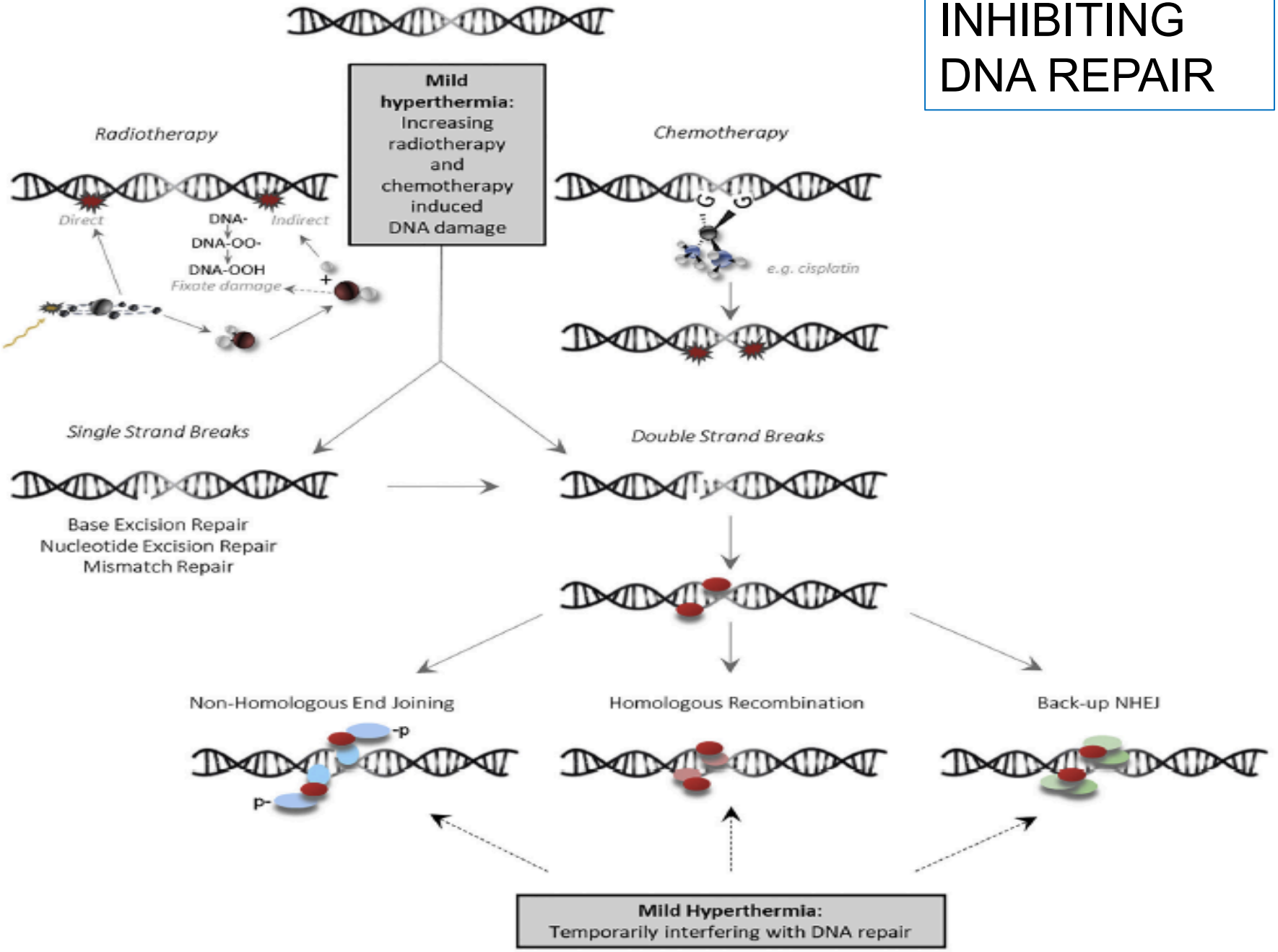



Hyperthermia
Photons
Tumour
Normal structures
Chaotic vasculature
Heat retained within tumour (39 – 45°C)
↓Oxygen enhancement ratio
↓ Repair of RT-induced DNA damage
Radiobiologically mimics high LET properties of "neutrons"
Normal vasculature
Physiological vasodilation
Heat dissipated
No significant hyperthermia-induced radiosensitization
Retains low LET features, physical dose profiles of "neutrons"
Photon thermoradiotherapy
• Confers selective advantages to tumour, radiobiologically similar to "neutrons"
• No thermal radiosensitization of normal tissues, morbidity similar to "photons"
• Radiation dose profile in the irradiated volume resembles that of "neutrons"

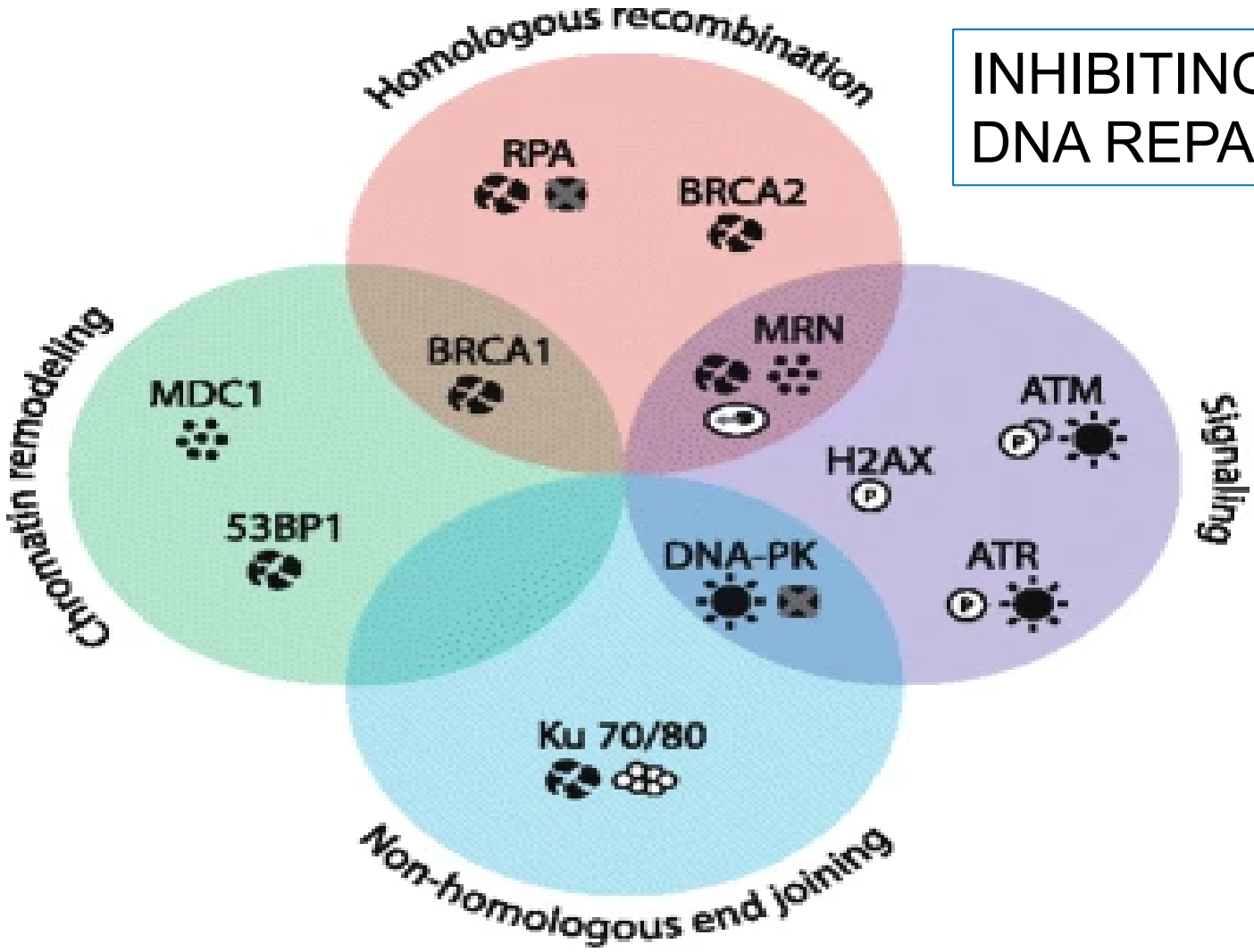

Macroscopic
Bloodflow
Vessel permeability
oxygenation
Heat Shock Response
HSPs
Membranes
Fluidity and permeability
DNA-repair
Dendritic cell
Immune system
Direct activation
Tumour recognition
Cytotoxic T-cell


Inhibits DNA repair
Improves tumor oxygenation
Hypoxic cells: Heat sensitive
Intrinsically heat sensitive tumor cells, e.g. melanoma, sarcoma
Sensitizes "S" phase cells
Increases blood flow
Potent radiosensitizer (complements radiotherapy)

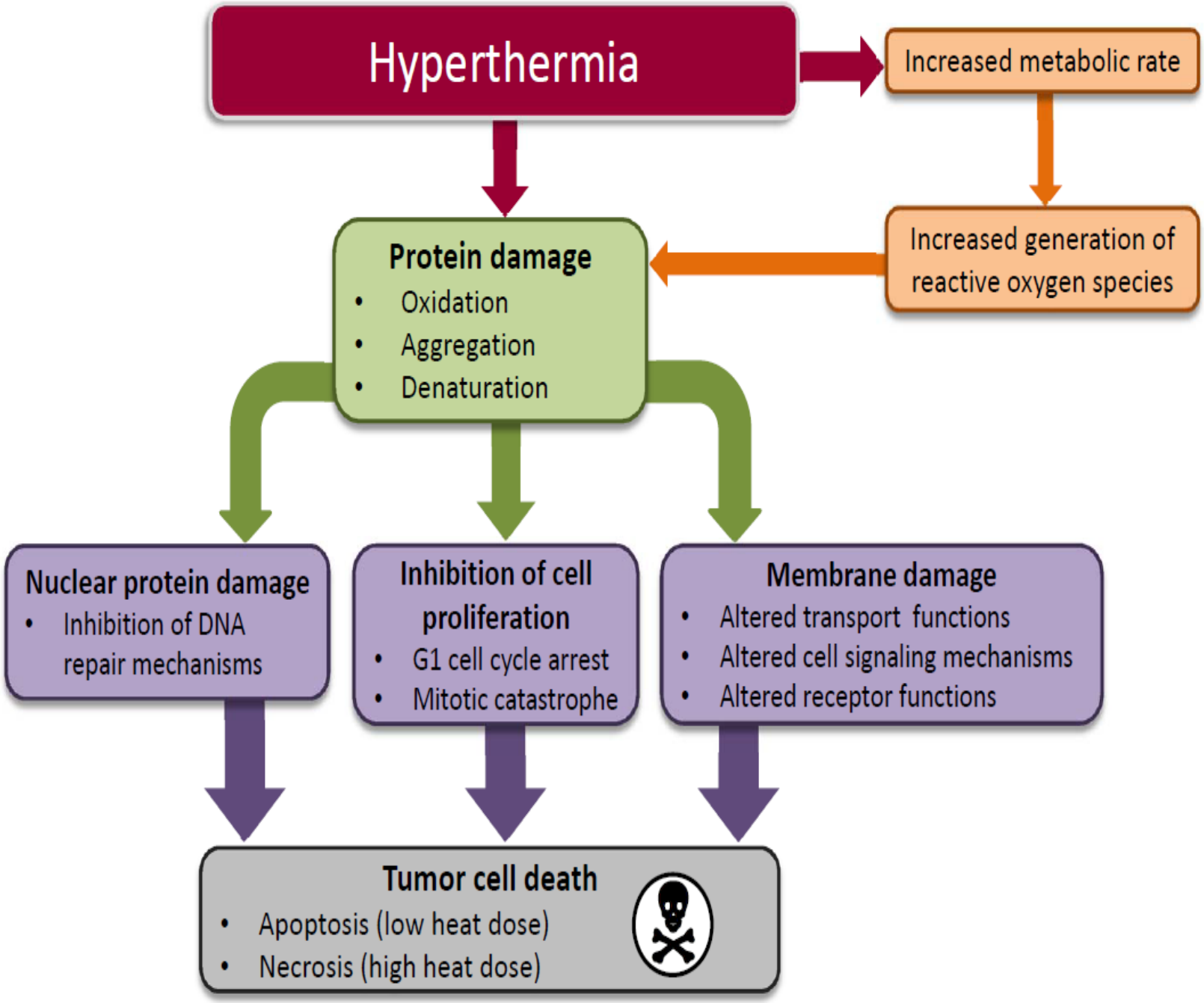
INHIBITING DNA REPAIR



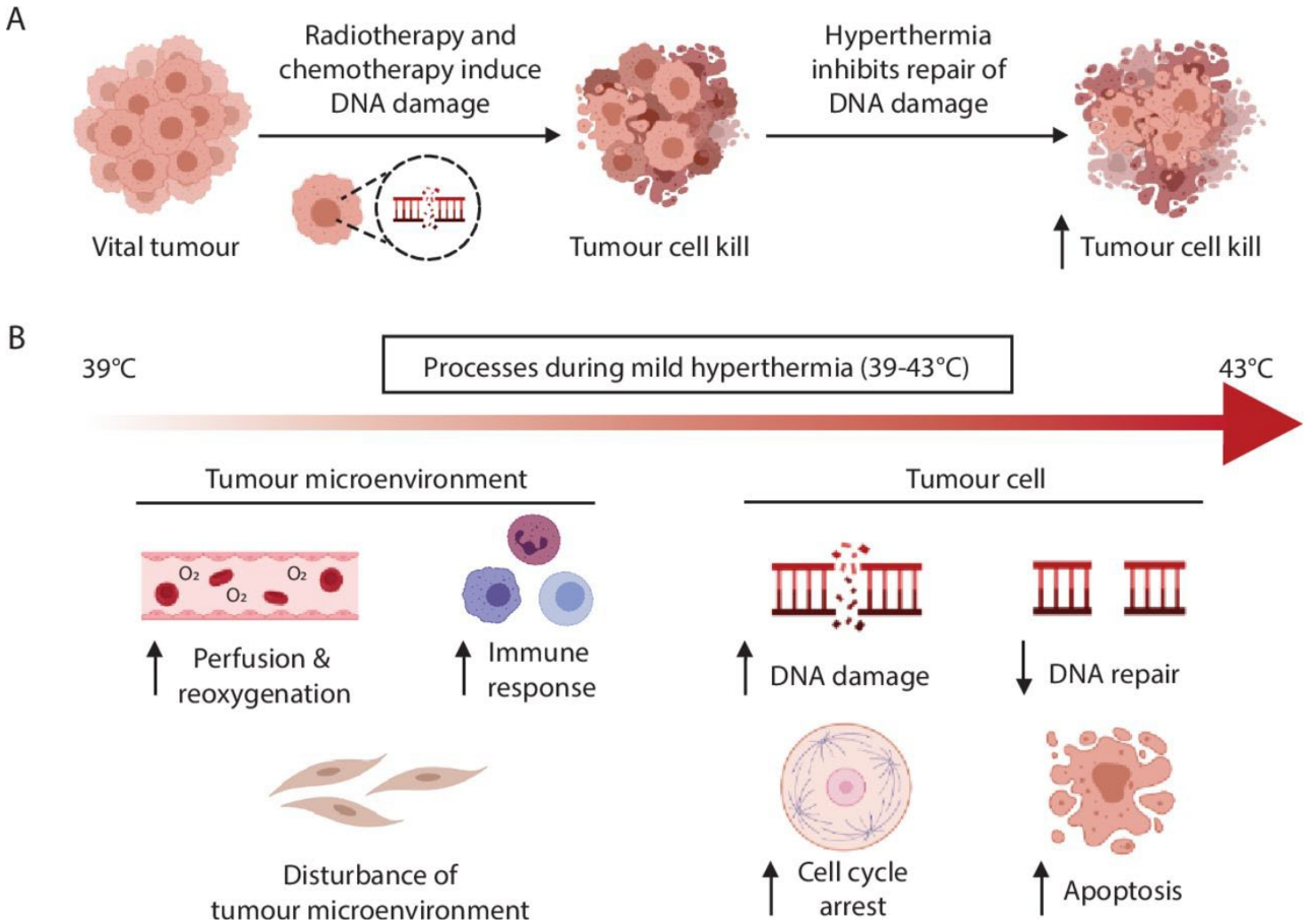
INHIBITING DNA REPAIR



- Degradation/depletion
- Aggregation
- Formation of IRIF-like foci
- Phosphorylation
- Autophosphorylation
- Inactivation/ inhibition of activity
- Activation/ increased activity
- Delocalization from the nucleus


Hyperthermia
Increased metabolic rate
Increased generation of reactive oxygen species
Protein damage
• Oxidation
• Aggregation
• Denaturation
Nuclear protein damage
• Inhibition of DNA repair mechanisms
Inhibition of cell proliferation
• G1 cell cycle arrest
• Mitotic catastrophe
Membrane damage
• Altered transport functions
• Altered cell signaling mechanisms
• Altered receptor functions
Tumor cell death
• Apoptosis (low heat dose)
• Necrosis (high heat dose)

Schematic overview of the enhanced effectiveness of radiotherapy or chemotherapy with hyperthermia.



Marloes IJff et al. Int J Gynecol Cancer 2022;ijgc-2021-002473

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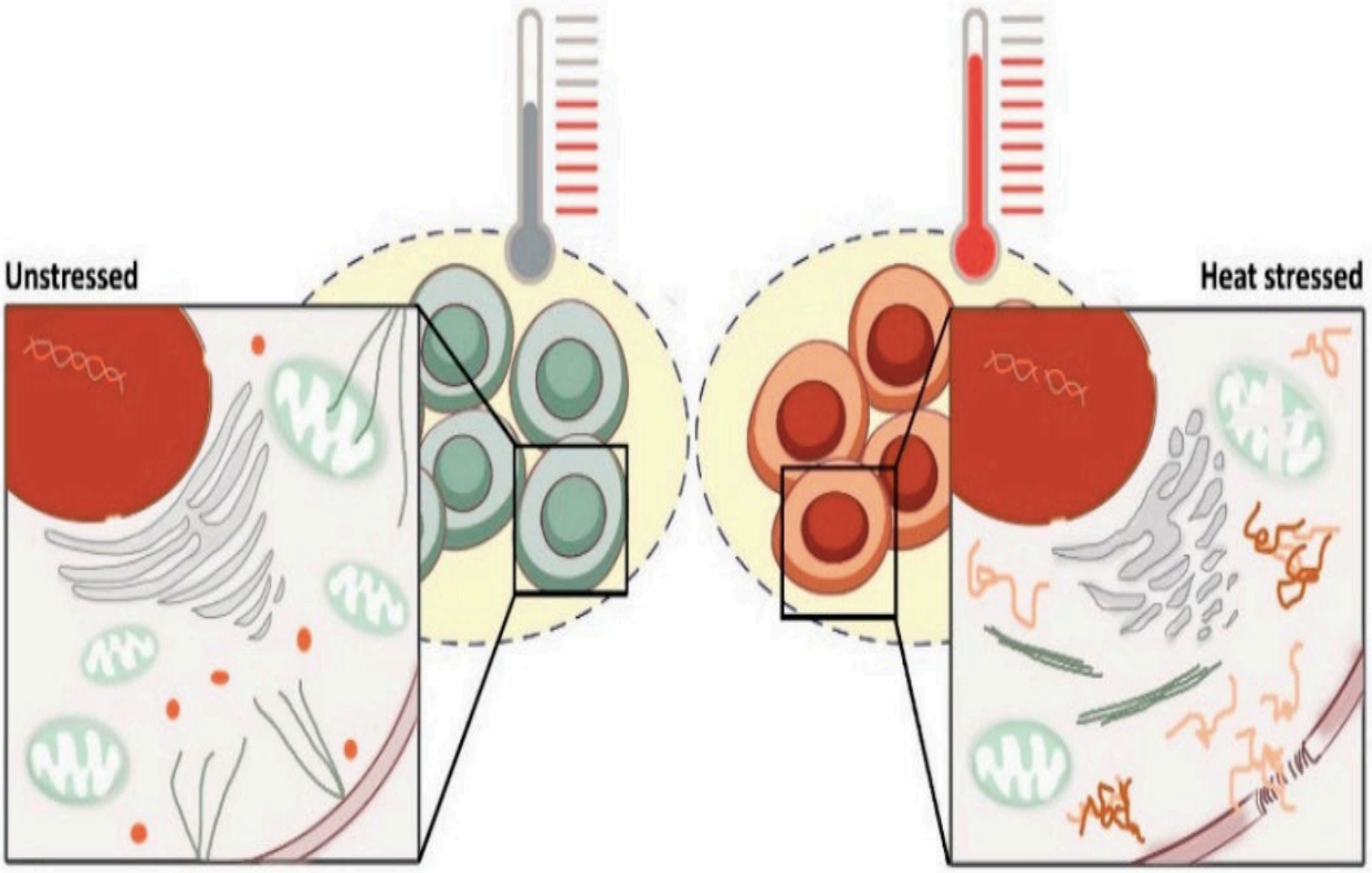
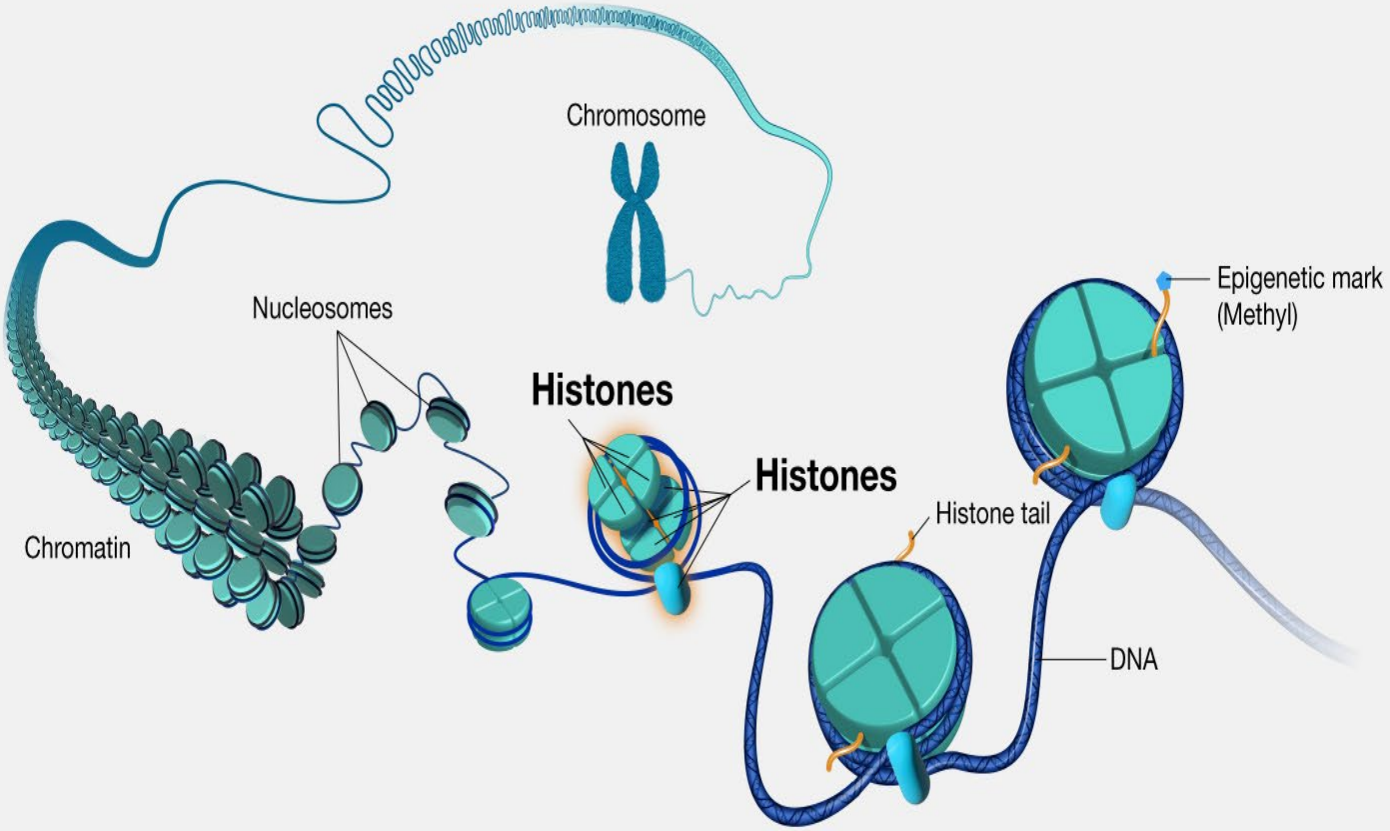
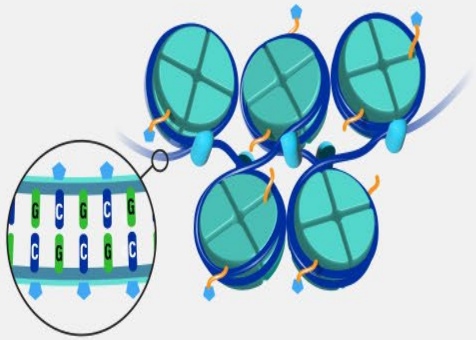
Cellular response to Hyperthermia

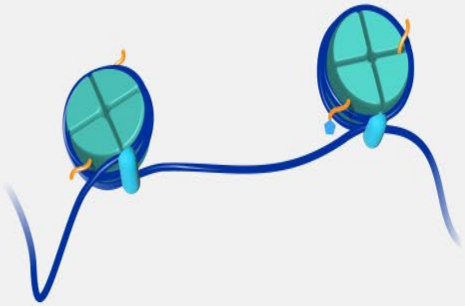




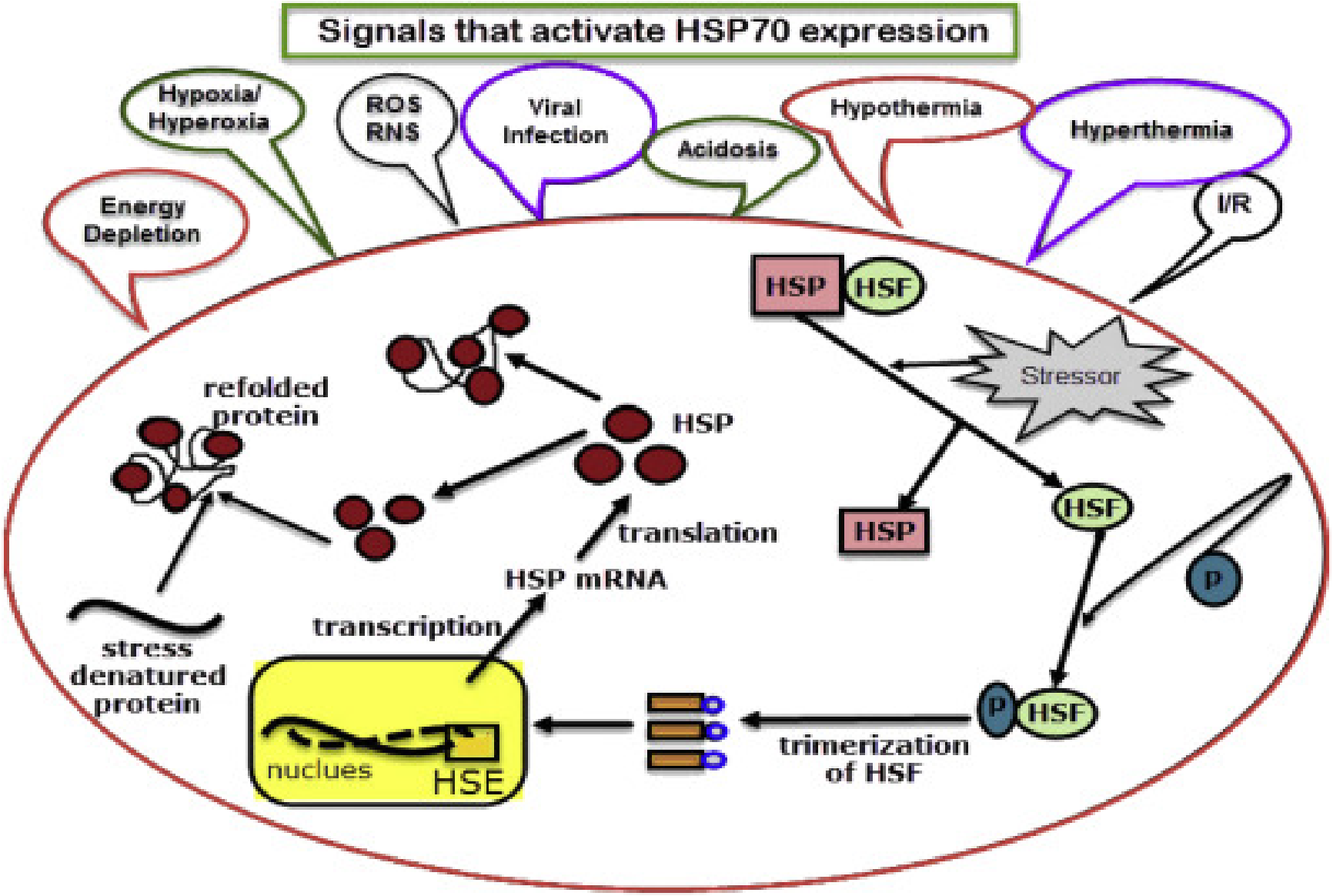
Closed chromatin (heterochromatin) is densely packed, and transcription cannot occur.

Open chromatin (euchromatin) is loosely packed, and transcription can occur.





Thermotolerance



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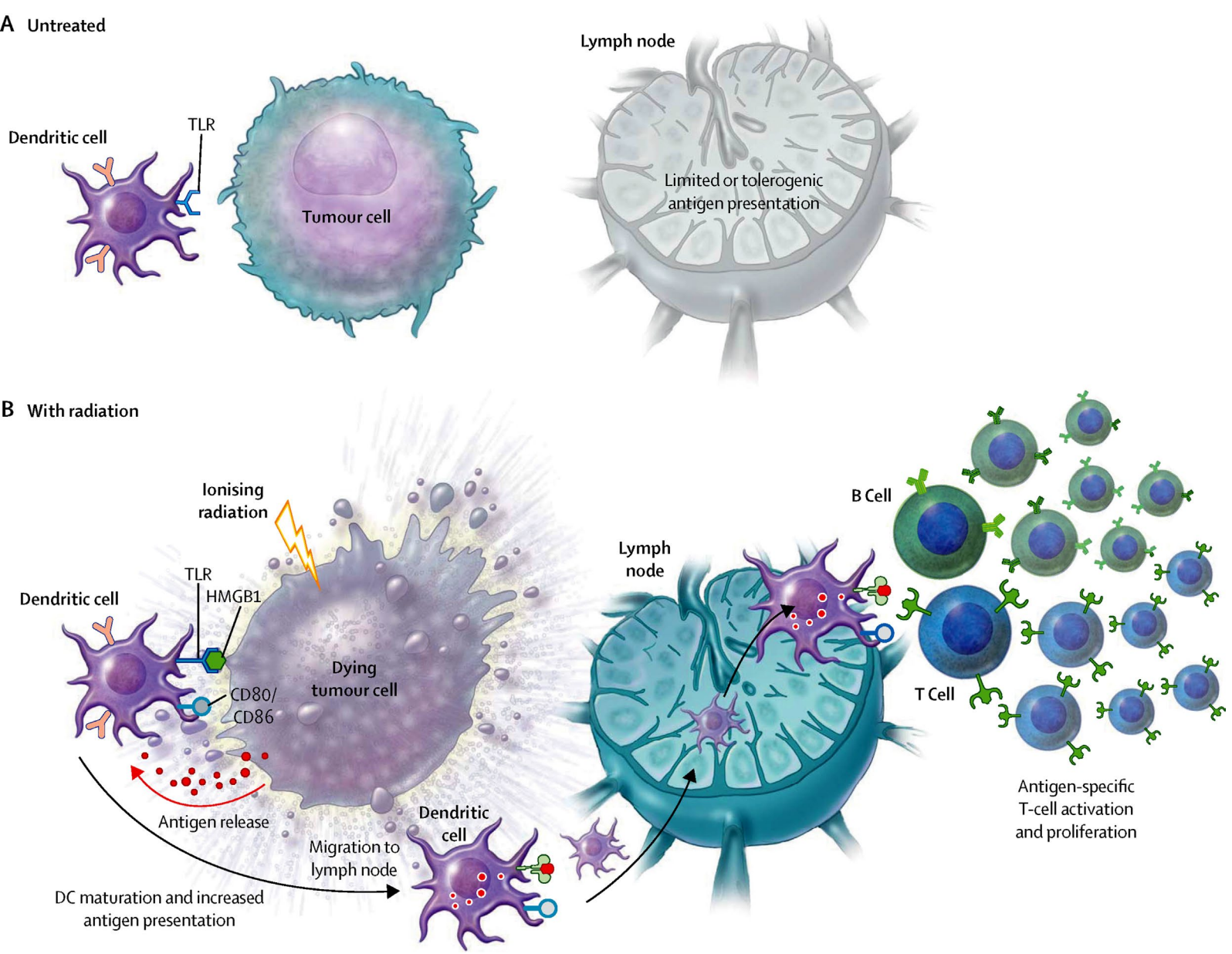
Immune mediated effects of Hyperthermia

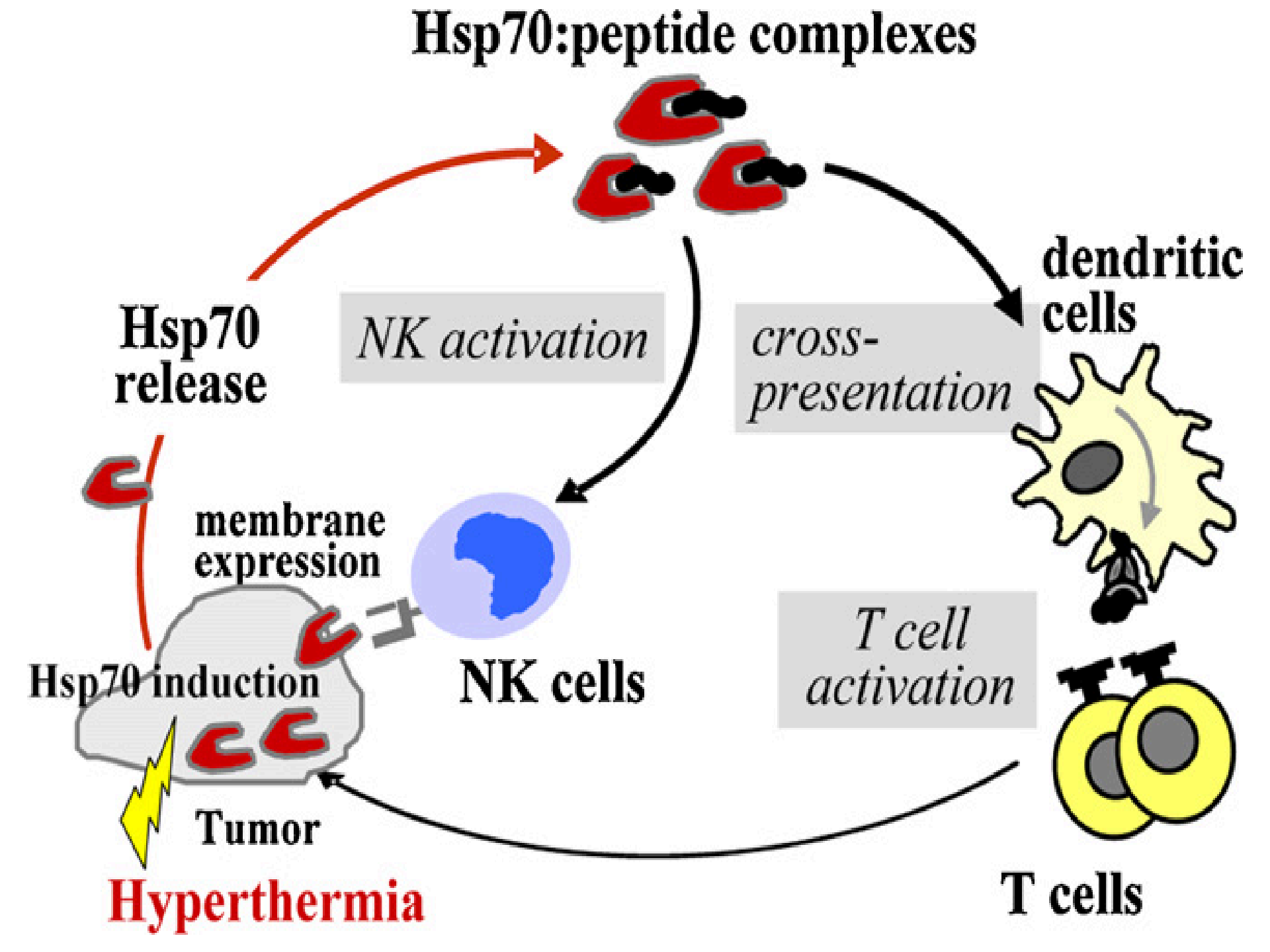
1) Enhanced immogenicity and HSP expresión

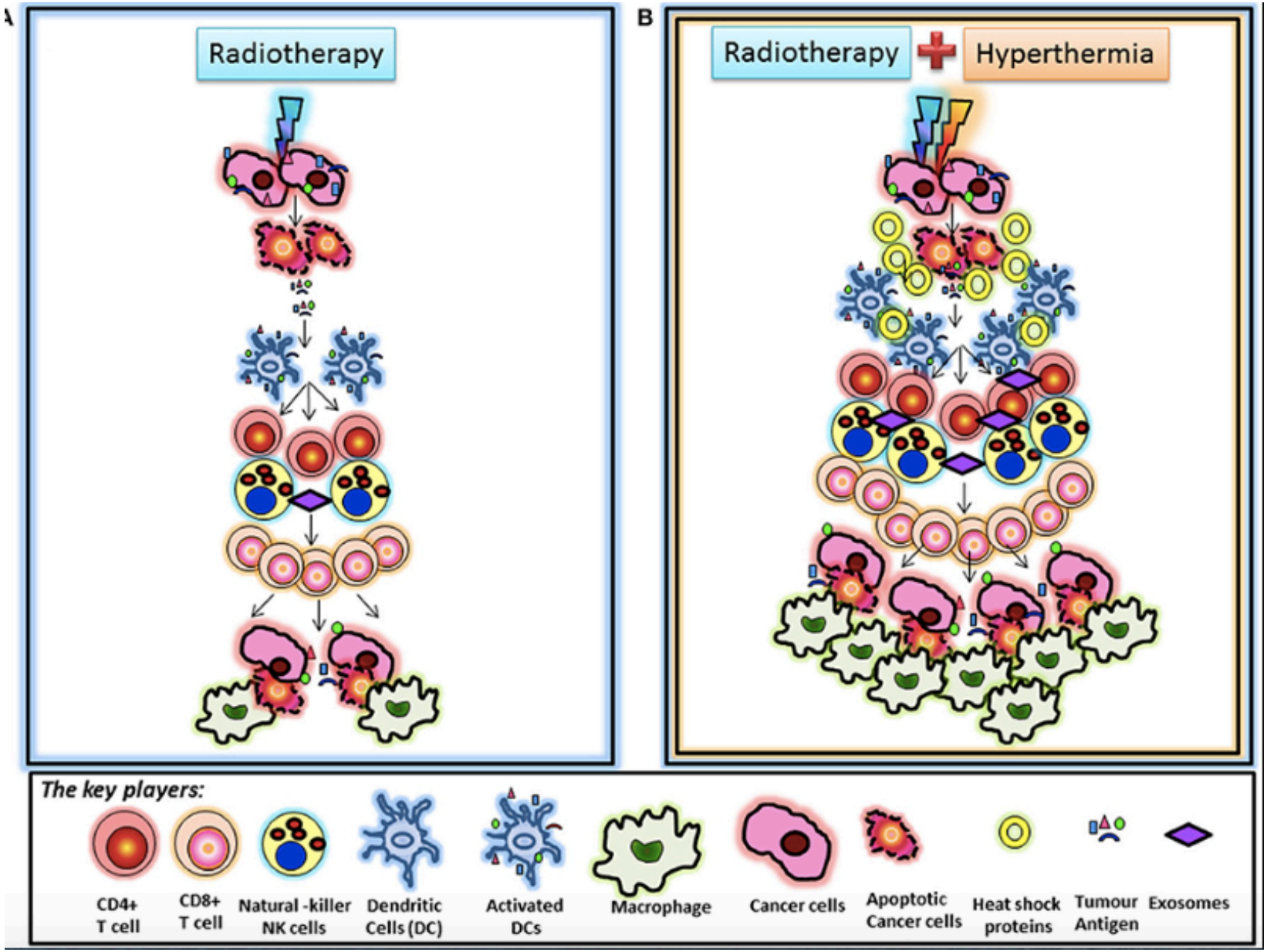
2) Thermally enhanced immune effector cells activation and function

3) Thermally enhanced vascular perfusión and delivery of trafficking of immune efefector celss to tumors



Sharabi AB, Lim M, DeWeese TL, Drake CG. Lancet Oncol. 2015 Oct;16(13):e498-509.


Hsp70:peptide complexes
Hsp70 release
NK activation
cross-presentation
dendritic cells
membrane expression
Hsp70 induction
NK cells
T cell activation
Tumor
Hyperthermia
T cells


A
Radiotherapy
B
Radiotherapy
Hyperthermia
The key players:
CD4+ T cell
CD8+ T cell
Natural -killer NK cells
Dendritic Cells (DC)
Activated DCs
Macrophage
Cancer cells
Apoptotic Cancer cells
Heat shock proteins
Tumour Antigen
Exosomes

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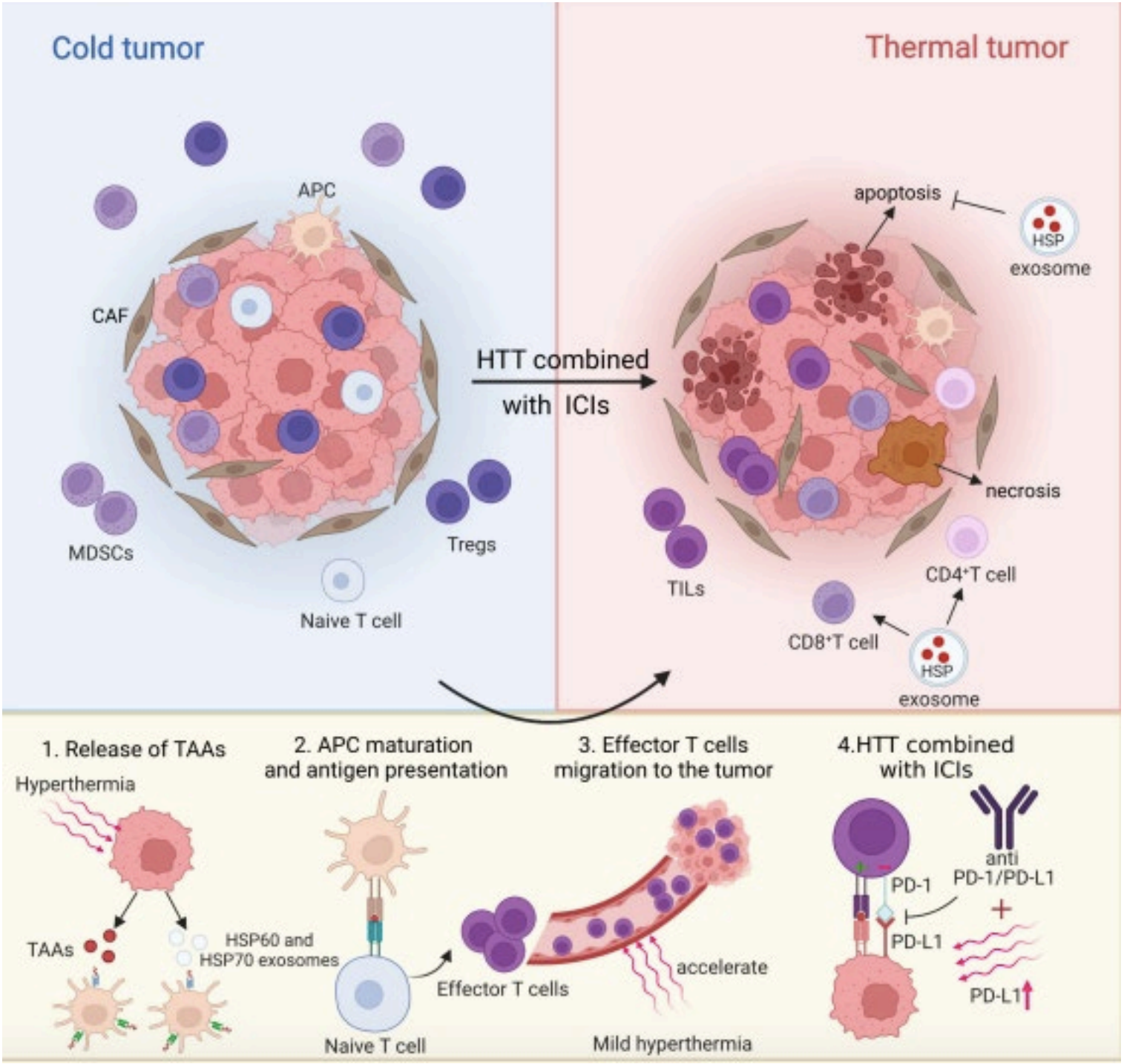
Hyperthermia combined with immune checkpoint inhibitor therapy in the treatment of primary and metastatic tumors

Ximing Yang[1], Miaozhi Gao[1], Runshi Xu[1], Yangyang Tao[1], Wang Luo[1], Binya Wang[1], Wenliang Zhong[1,2], Lan He[3,4] and Yingchun He[1,2,3]*


Cold tumor
Thermal tumor
APC
CAF
MDSCs
Tregs
Naive T cell
HTT combined
with ICIs
apoptosis
HSP
exosome
necrosis
TILs
CD4⁺T cell
CD8⁺T cell
HSP
exosome
1. Release of TAAs
Hyperthermia
TAAs
HSP60 and
HSP70 exosomes
2. APC maturation
and antigen presentation
Naive T cell
3. Effector T cells
migration to the tumor
Effector T cells
accelerate
Mild hyperthermia
4.HTT combined
with ICIs
anti
PD-1/PD-L1
PD-1
PD-L1
PD-L1

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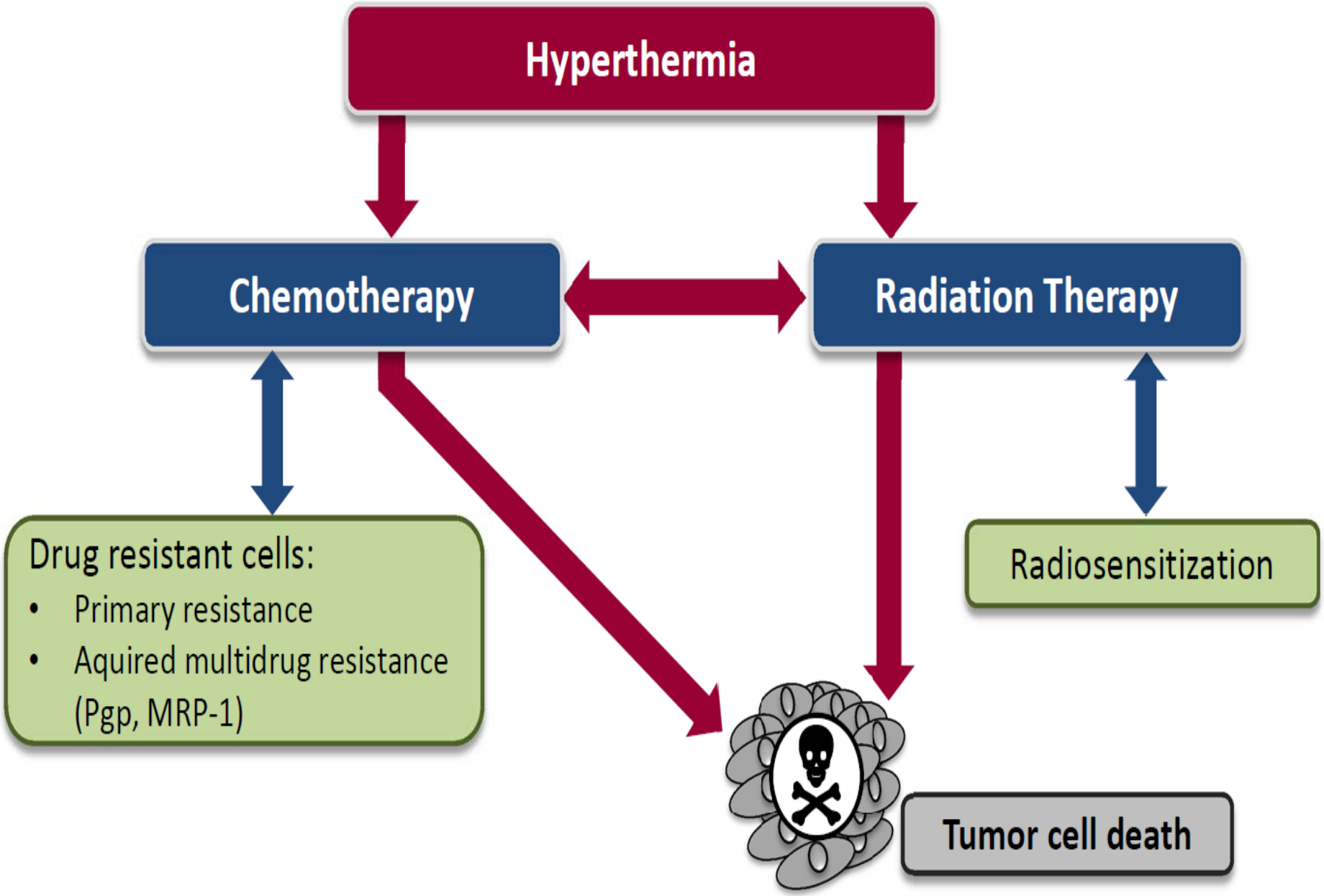
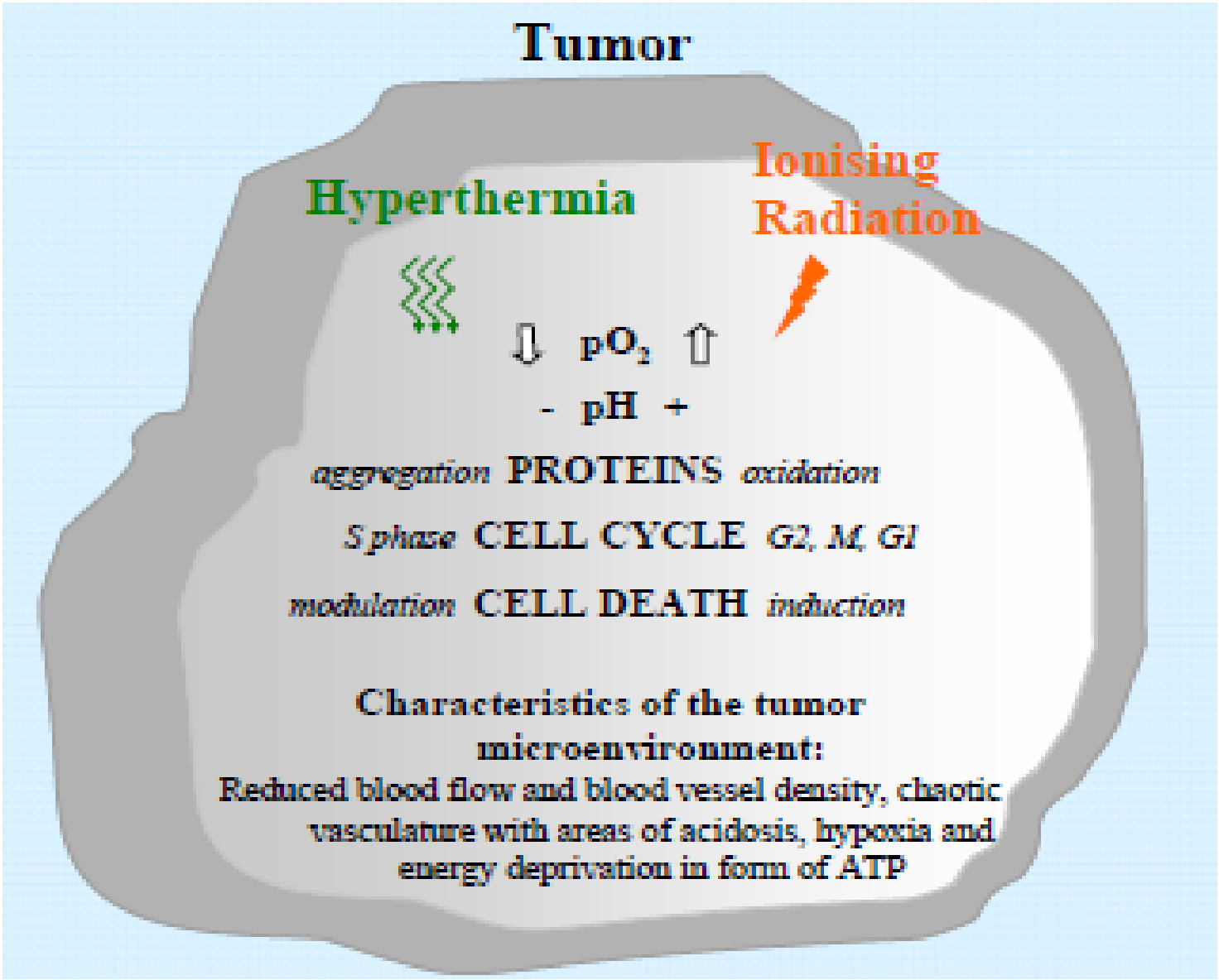

Hyperthermia
Chemotherapy
Radiation Therapy
Drug resistant cells:
• Primary resistance
• Aquired multidrug resistance (Pgp, MRP-1)
Radiosensitization
Tumor cell death

Synergistic effect of HT+RT



frontiers in Oncology

REVIEW
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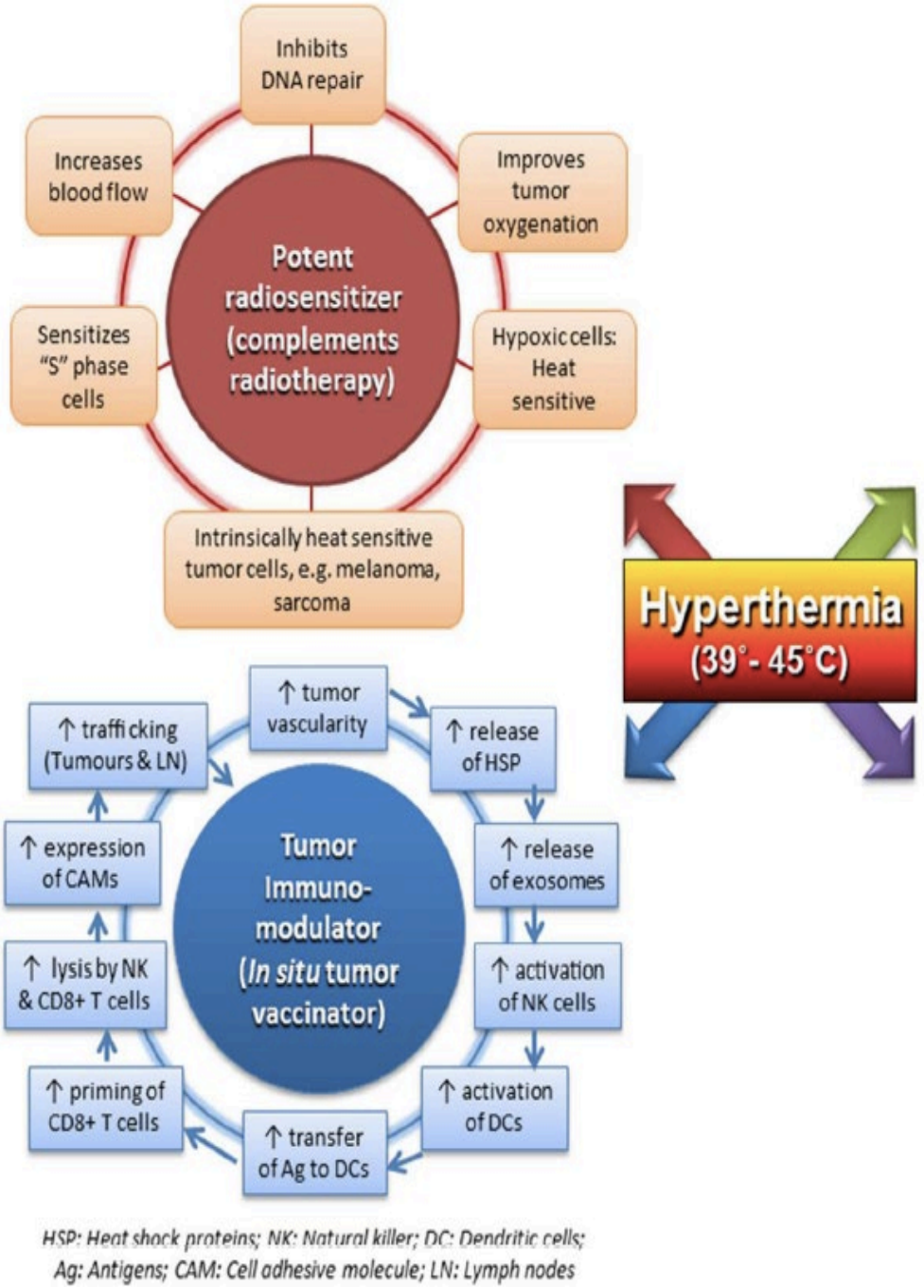
Integrating Loco-Regional Hyperthermia Into the Current Oncology Practice: SWOT and TOWS Analyses

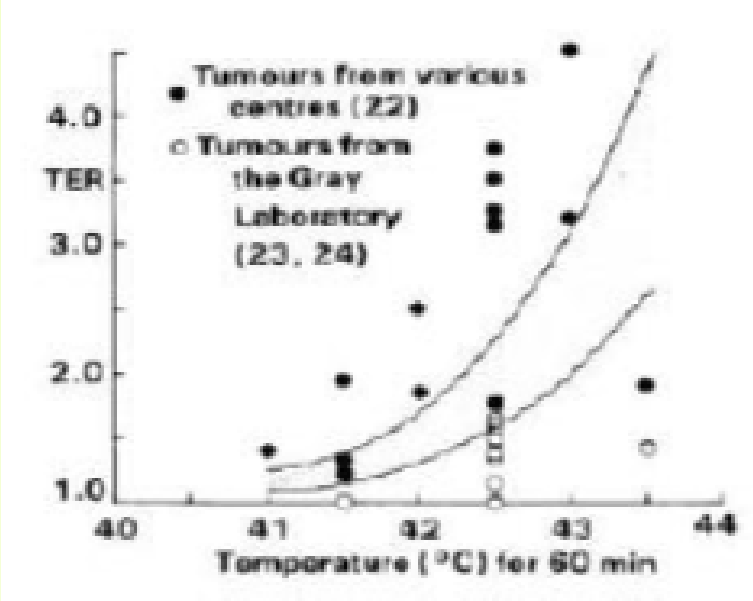
Niloy R. Datta[1], H. Petra Kok[2], Hans Crezee[2], Udo S. Gaipl[3] and Stephan Bodis[1]*

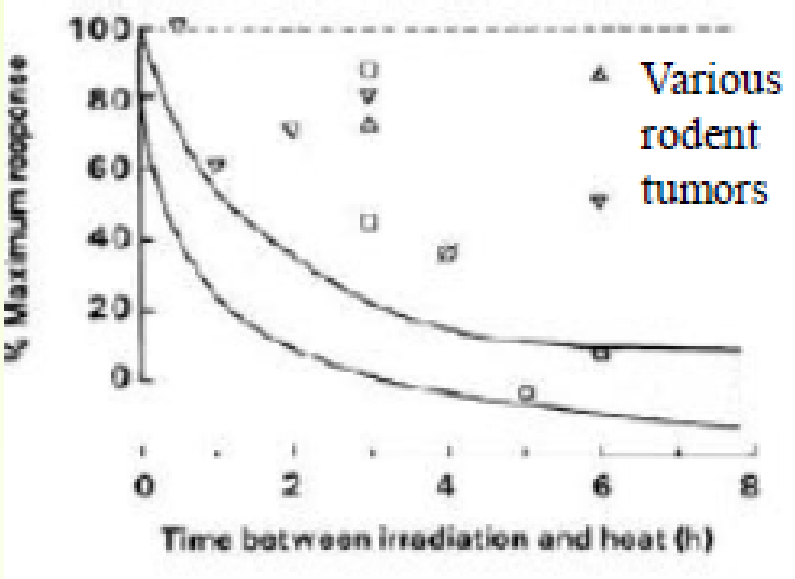
[1] Centre for Radiation Oncology KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland, [2] Department of Radiation Oncology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, [3] Department of Radiation Oncology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany



HSP: Heat shock proteins; NK: Natural killer; DC: Dendritic cells; Ag: Antigens; CAM: Cell adhesive molecule; LN: Lymph nodes

Thermal Enhancement Ratio





- TER for tumors (points) and normal tissues (range indicated by two curves)
- TER also depends on temperature, time at that temperate, and time interval between irradiation and heat
- In clinical evaluations TERs of only 1.15 to 1.5 were observed

Thermal Enhancement Ratio

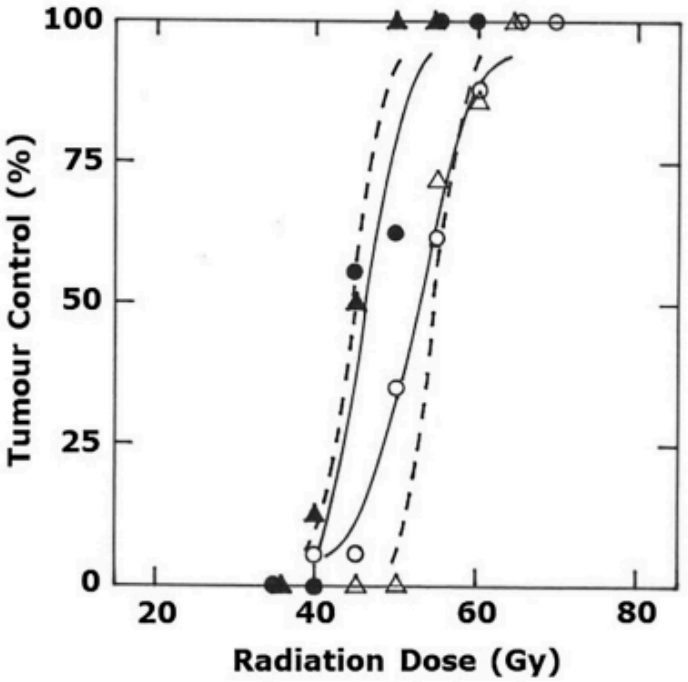
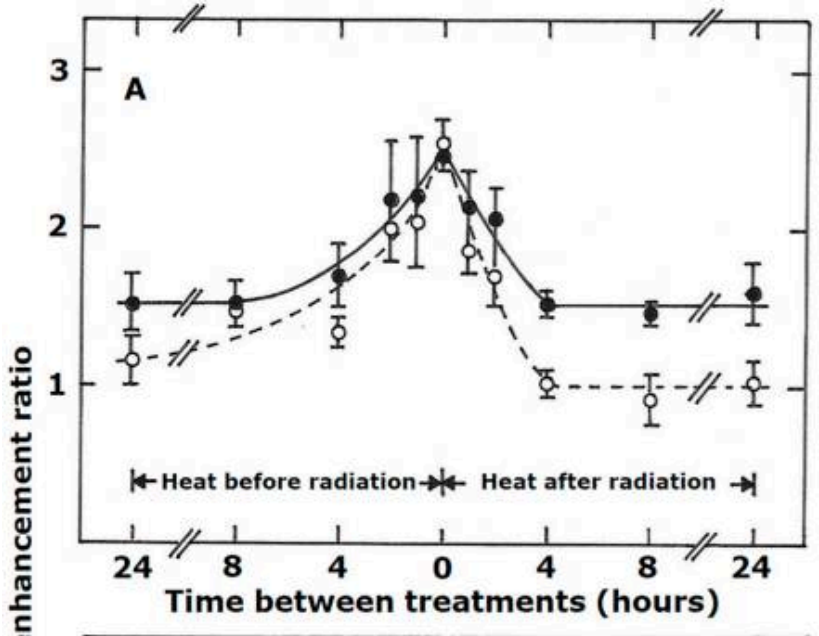
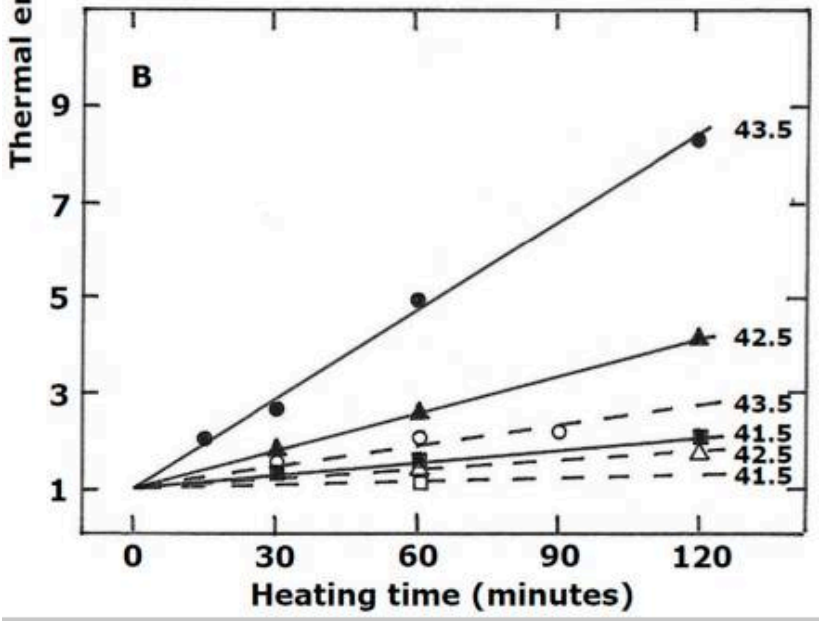


Figure 1. Radiation dose-response curves for C3H mammary carcinomas treated with either radiation alone (○, Δ) or radiation followed one hour later by heating at 41.5 °C for 60 min (●, ▲). The radiation treatment was administered using either an experimental Philips X-ray tube (○, ●) or a clinical Varian Clinac iX Linear Accelerator (Δ, ▲). Results show percentage of animals with local tumor control at 90 days after treating and are based on a minimum of 7 mice/group. Lines through the data were fitted following logit analysis.





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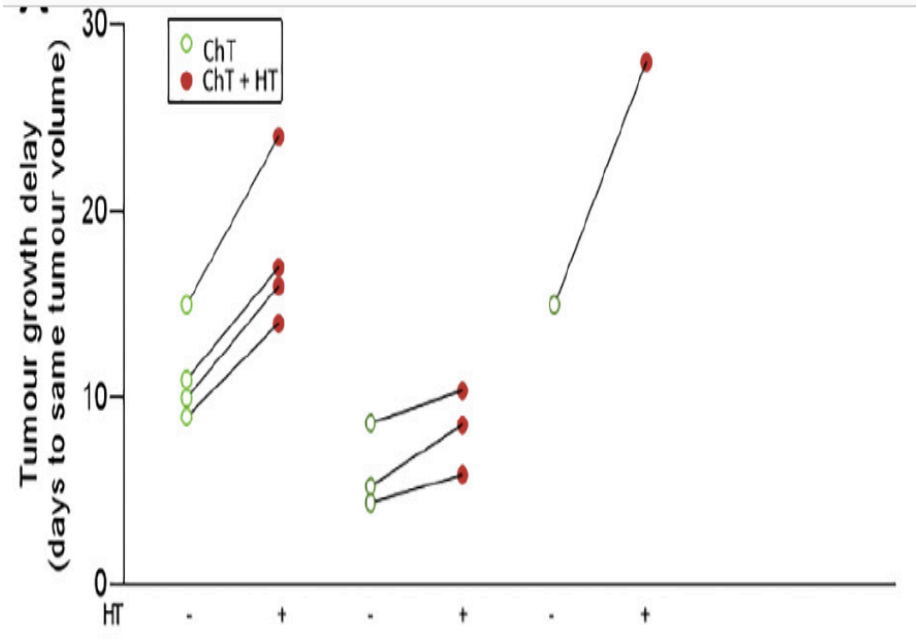
Advanced Drug Delivery Reviews

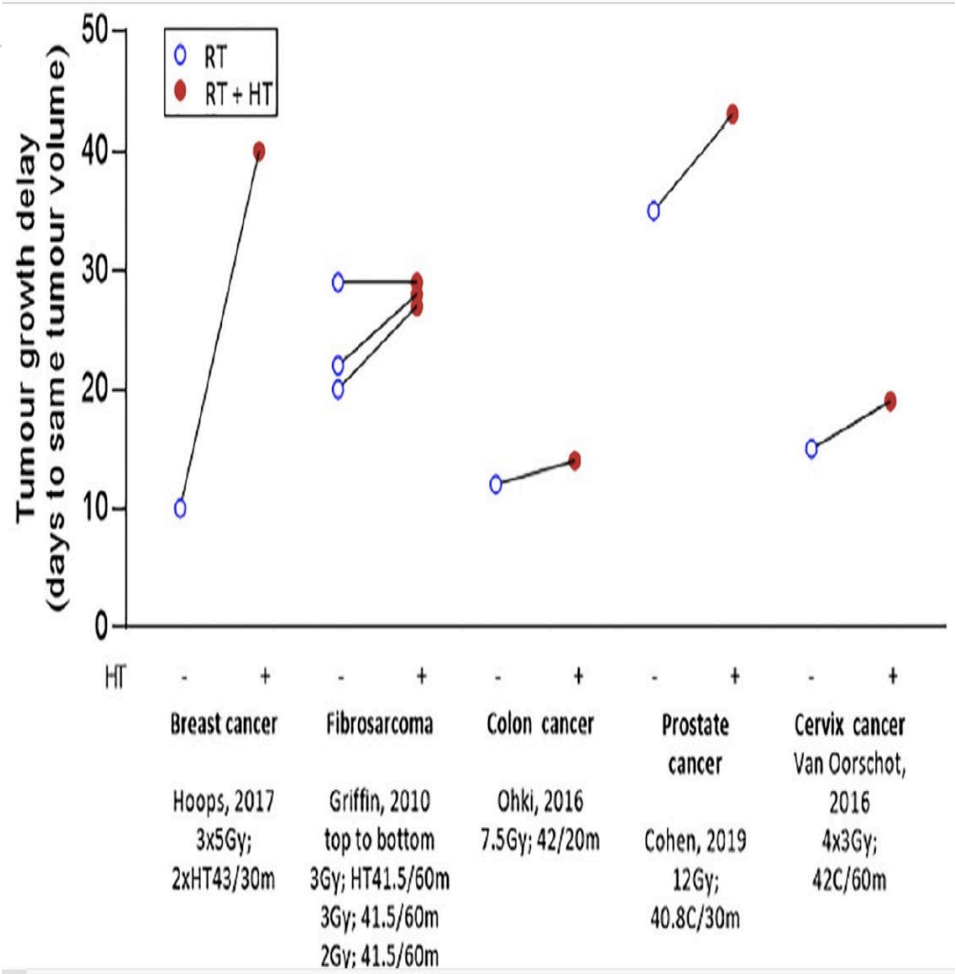
journal homepage: www.elsevier.com/locate/addr

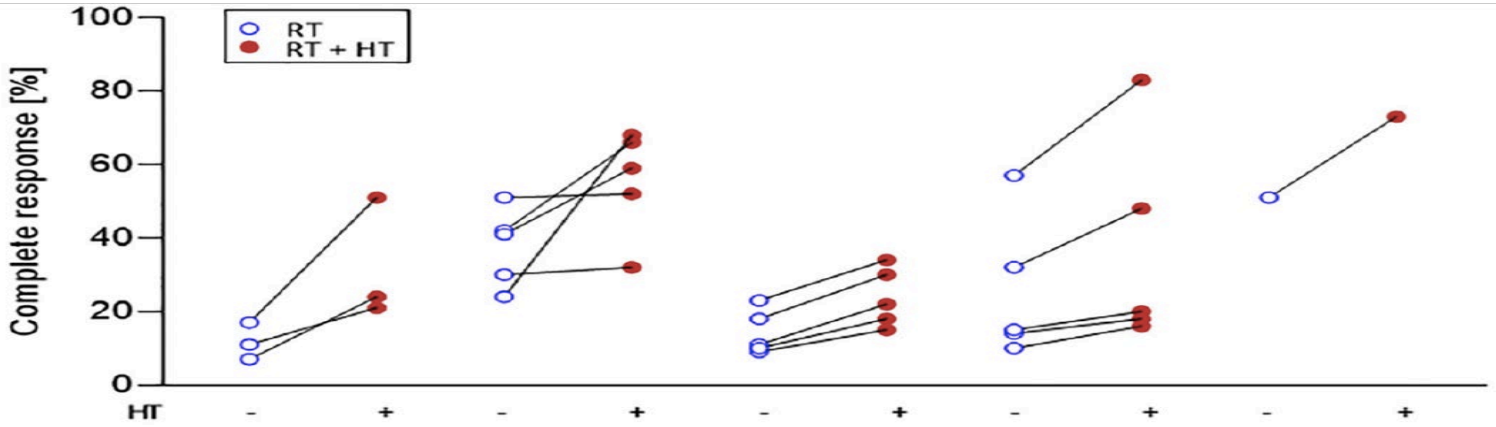
Molecular and biological rationale of hyperthermia as radio- and chemosensitizer

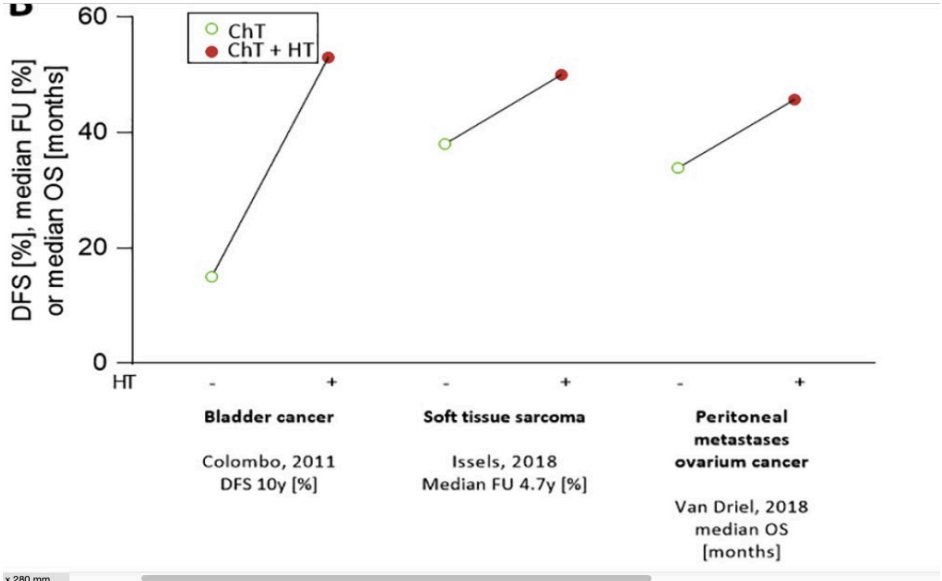
A.L. Oei [a,b,*], H.P. Kok [b], S.B. Oei [c], M.R. Horsman [d], L.J.A. Stalpers [a,b], N.A.P. Franken [a,b], J. Crezee [b]

RT/CHT+HT increases tumor growth delay






Complete response [%]
100
80
60
40
20
0
RT
RT + HT
HT
-
+
Recurrent breast cancer
Other superficial
Locally adv. head & neck cancer
Locally adv. cervical cancer
Bladder cancer
Wahl, 2008
Vernon, MRC, 1996
Vernon, ESHO, 1996
Perez, 1991
Jones 1996
Vernon, 1996
Kapp, 1990
Wen,2014.
Huilgol, 2010
Valdagni, 1994
Datta, 1990
Arcangeli, 1987
Van der Zee, 2002
Harima, 2001
Franckena, 2007
Chen, 1997
Datta, 1987
Van der Zee, 2000


DFS [%], median FU [%] or median OS [months]
60
40
20
0
ChT
ChT + HT
HT
-
+
Bladder cancer
Colombo, 2011
DFS 10y [%]
Soft tissue sarcoma
Issels, 2018
Median FU 4.7y [%]
Peritoneal metastases ovarium cancer
Van Driel, 2018
median OS
[months]

Therapeutic Gain Factor

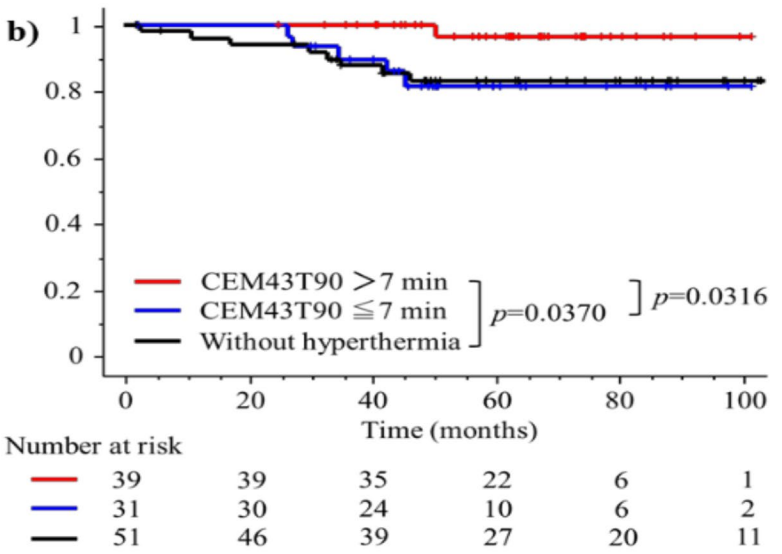
- The therapeutic gain factor can be defined as the ratio of the TER in the tumor to the TER in normal tissues

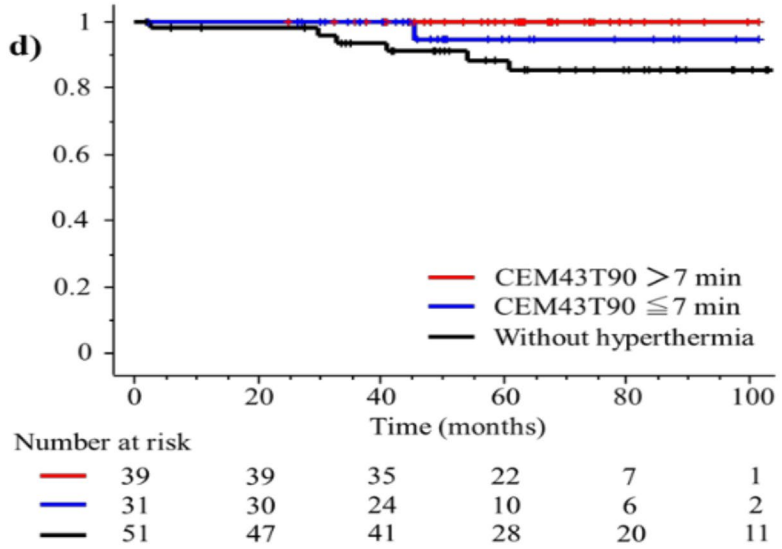
Author	Journal	Year	RCT/ cohort	Treatment arms	HT-related toxicity ≥grade 3
Harima	IJH	2001	RCT	RT vs. RHT	2/20 (10) at 3 years; not significant different from RT alone
Van der Zee	IJH	2002	RCT	RT vs. RHT	No significant difference between treatment groups.
Vasanathan	IJROBP	2005	RCT	RT vs. RHT	Acute tox grade 3: 1x blister 1/55 (2); Late tox grade 3: 2x bowel 2/55 (4)
Lutgens	RO	2016	RCT	CRT vs. RHT	No significant difference between treatment groups.
Harima	IJH	2016	RCT	CRT vs. RCHT	No hyperthermia related toxicity was observed
Minnaar	Plos One	2019	RCT	CRT vs. RCHT	No significant difference between treatment groups.
Wang	IJROBP	2020	RCT	CRT vs. RCHT	No significant difference between treatment groups.
Franckena	IJROBP	2009	Cohort		45/378 (12) at 5 years; No significant different from RT alone
Westermann	IJH	2012	Cohort		No significant difference between treatment groups.
Kroesen	OBGNAS	2019	Cohort		No significant difference between treatment groups.

Thermal dose

1) The heat-induced cytotoxicty of tumor cells is dependent on both temperature and time.

2) Cumulative equivalent minutes at 43º (CEM 43ºC)





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Radiotherapy and Oncology 138 (2019) 1–8

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Original Article

Hyperthermia with radiotherapy reduces tumour alpha/beta: Insights from trials of thermoradiotherapy vs radiotherapy alone

Niloy R. Datta [a,*], Stephan Bodis [a,b]

[a] Centre for Radiation Oncology KSA-KSB, Kantonsspital Aarau; and [b] Department of Radiation Oncology, University Hospital Zurich, Switzerland

Table 1
Summary of the randomized studies of RT vs HTRT, complete responders in each arm, corresponding BED of the RT schedule and the estimated α/β with HTRT for each study.

Author	Site	RT/HTRT		Hyperthermia				RT		HTRT		BED (RT) (Gy_{10})	$\%CR_{HTRT}/\%CR_{RT}$ (%)	BED_{HTRT} (Gy)	Estimated α/β for HTRT (Gy)
		Dose (Gy)	Dose/fr (Gy)	T (°C)	Time (mins)	Per week	Total sessions	Total	CR	Total	CR				
Wahl et al. [35]	RcBC	48.0	2.0	NA	NA	NA	NA	18	7	36	24	57.6	1.71	98.7	1.89
Vernon et al. (MRC) [36]	RcBC	28.8	3.6	43.0	60.0	1	3	59	17	90	51	39.2	1.97	77.0	2.15
Vernon et al. (ESHO) [36]	RcBC	32.0	4.0	43.0	60.0	2	8	29	11	27	21	44.8	2.05	91.9	2.14
Wen et al. [37]	LAHNC	70.0	2.0	44.4	60.0	2	6	49	23	49	34	84.0	1.48	124.2	2.58
Huilgol et al. [38]	LAHNC	70.0	2.0	42.3	30.0	1	7	26	11	28	22	84.0	1.86	156.0	1.63
Valdagni et al. [39]	LAHNC	68.0	2.0	42.5	30.0	2	12	22	9	18	15	81.6	2.04	165.0	1.38
Datta et al. [40]	LAHNC	64.0	2.0	42.5	50.0	2	12	32	10	33	18	76.8	1.75	134.1	1.83
Arcangeli et al. [41]	LAHNC	60.0	1.5	42.5	45.0	3	7	43	18	38	30	69.0	1.89	130.1	1.28
Harima et al. [42]	LACC	52.2	1.8	40.6	60.0	1	3	20	10	20	16	61.6	1.60	98.6	2.03
Franckena et al. [43]	LACC	48.3	2.0	42.0	60.0	1	5	56	32	58	48	58.0	1.45	83.9	2.71
Chen et al. [44]	LACC	40.0	2.0	42.0	45.0	2	8	30	14	30	18	48.0	1.29	61.7	3.68
Datta et al. [45]	LACC	60.0	2.0	42.5	45.0	2	12	26	15	27	20	72.0	1.28	92.4	3.70

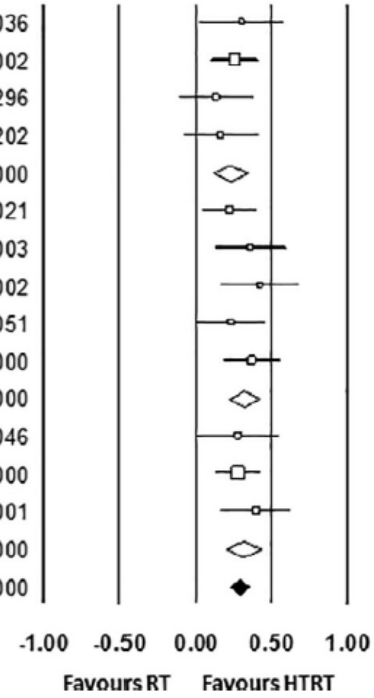
Abbreviations: RT: Radiotherapy; HTRT: Thermoradiotherapy; T: Temperature; RcBC: Recurrent breast cancer; LAHNC: Locally advanced head and neck cancer; LACC: Locally advanced cancer cervix; BED: Biologically effective dose; RcBC: Recurrent breast cancer; LAHNC: Locally advanced head and neck cancer; LACC: Locally advanced cancer cervix; $\%CR_{HTRT}$: % complete response with HTRT; $\%CR_{RT}$: % complete response with RT.
BED_{HTRT} and α/β_{HTRT} are estimated as described in text.
*Average dose to RT group: 68 Gy whilst to HTRT 67.5 Gy.
+Only patients with neck nodes were considered, treated with 1.5 Gy–2 Gy per fraction, 3 fractions/day.
For all LACC studies, only external RT doses were considered.

12 trials totalling 864 patients were included in this analysis. 454 patients received HTRT whilst 410 were treated with RT.

Risk difference for "Complete Response at end of RT (HTRT vs RT)"

Group by Subgroup within study	Study name	Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cervix (IIB-IVA)	Harima et al (35)	0.300	0.143	0.021	0.019	0.581	2.095	0.036
Cervix (IIB-IVA)	Franckena et al (36)	0.256	0.083	0.007	0.094	0.418	3.099	0.002
Cervix (IIB-IVA)	Chen et al (37)	0.133	0.128	0.016	-0.117	0.384	1.044	0.296
Cervix (IIB-IVA)	Datta et al (38)	0.164	0.128	0.017	-0.088	0.416	1.275	0.202
Cervix (IIB-IVA)		0.221	0.056	0.003	0.111	0.332	3.944	0.000
Head neck (III / IV)	Wen et al (30)	0.224	0.097	0.009	0.034	0.415	2.313	0.021
Head neck (III / IV)	Huilgol et al (31)	0.363	0.124	0.015	0.119	0.606	2.922	0.003
Head neck (III / IV)	Valdagni et al (32)	0.424	0.137	0.019	0.156	0.692	3.102	0.002
Head neck (III / IV)	Datta et al (33)	0.233	0.119	0.014	-0.001	0.467	1.953	0.051
Head neck (III / IV)	Arcangeli et al (34)	0.371	0.100	0.010	0.175	0.567	3.702	0.000
Head neck (III / IV)		0.313	0.050	0.003	0.214	0.411	6.213	0.000
Recurrent breast	Wahl et al (28)	0.278	0.139	0.019	0.005	0.551	1.996	0.046
Recurrent breast	Vernon et al (MRC) (29)	0.279	0.079	0.006	0.124	0.433	3.536	0.000
Recurrent breast	Vernon et al (ESHO) (29)	0.398	0.120	0.015	0.162	0.635	3.307	0.001
Recurrent breast		0.308	0.060	0.004	0.191	0.425	5.164	0.000
Overall		0.282	0.032	0.001	0.220	0.344	8.894	0.000

Test for heterogeneity, $I^2 = 0.00$, p:ns
Subgroup analysis: Q = 1.721, df = 2, p: ns



Complete Response was achieved in 43.1% (177/410) with RT compared to 69.8% (317/454) with HTRT (RD: 0.28, 95% CI 0.22–0.34, $p < 0.001$).

OR and RR were both in favour of HTRT (OR: 3.33, 95% CI 2.48–4.46, $p < 0.001$; RR: 1.61, 95% CI 1.43–1.82, $p < 0.001$).

Table 1
Summary of the randomized studies of RT vs HTRT, complete responders in each arm, corresponding BED of the RT schedule and the estimated α/β with HTRT for each study.

Author	Site	RT/HTRT		Hyperthermia				RT		HTRT		BED (RT) (Gy_{10})	$\%CR_{HTRT}/\%CR_{RT}$ (%)	BED_{HTRT} (Gy)	Estimated α/β for HTRT (Gy)
		Dose (Gy)	Dose/fr (Gy)	*T* (°C)	Time (mins)	Per week	Total sessions	Total	CR	Total	CR				
Wahl et al. [35]	RcBC	48.0	2.0	NA	NA	NA	NA	18	7	36	24	57.6	1.71	98.7	1.89
Vernon et al. (MRC) [36]	RcBC	28.8	3.6	43.0	60.0	1	3	59	17	90	51	39.2	1.97	77.0	2.15
Vernon et al. (ESHO) [36]	RcBC	32.0	4.0	43.0	60.0	2	8	29	11	27	21	44.8	2.05	91.9	2.14
Wen et al. [37]	LAHNC	70.0	2.0	44.4	60.0	2	6	49	23	49	34	84.0	1.48	124.2	2.58
Huilgol et al. [38]	LAHNC	70.0	2.0	42.3	30.0	1	7	26	11	28	22	84.0	1.86	156.0	1.63
Valdagni et al. [39]	LAHNC	68.0	2.0	42.5	30.0	2	12	22	9	18	15	81.6	2.04	165.0	1.38
Datta et al. [40]	LAHNC	64.0	2.0	42.5	50.0	2	12	32	10	33	18	76.8	1.75	134.1	1.83
Arcangeli et al. [41]	LAHNC	60.0	1.5	42.5	45.0	3	7	43	18	38	30	69.0	1.89	130.1	1.28
Harima et al. [42]	LACC	52.2	1.8	40.6	60.0	1	3	20	10	20	16	61.6	1.60	98.6	2.03
Franckena et al. [43]	LACC	48.3	2.0	42.0	60.0	1	5	56	32	58	48	58.0	1.45	83.9	2.71
Chen et al. [44]	LACC	40.0	2.0	42.0	45.0	2	8	30	14	30	18	48.0	1.29	61.7	3.68
Datta et al. [45]	LACC	60.0	2.0	42.5	45.0	2	12	26	15	27	20	72.0	1.28	92.4	3.70

Abbreviations: RT: Radiotherapy; HTRT: Thermoradiotherapy; T: Temperature; RcBC: Recurrent breast cancer; LAHNC: Locally advanced head and neck cancer; LACC: Locally advanced cancer cervix; BED: Biologically effective dose; RcBC: Recurrent breast cancer; LAHNC: Locally advanced head and neck cancer; LACC: Locally advanced cancer cervix; $\%CR_{HTRT}$: % complete response with HTRT; $\%CR_{RT}$: % complete response with RT.
BED_{HTRT} and α/β_{HTRT} are estimated as described in text.
*Average dose to RT group: 68 Gy whilst to HTRT 67.5 Gy.
+Only patients with neck nodes were considered, treated with 1.5 Gy–2 Gy per fraction, 3 fractions/day.
For all LACC studies, only external RT doses were considered.

LOCALLY RECURRENT BREAST CANCER

Table 1
Summary of the randomized studies of RT vs HTRT, complete responders in each arm, corresponding BED of the RT schedule and the estimated α/β with HTRT for each study.

Author	Site	RT/HTRT		Hyperthermia				RT		HTRT		BED (RT) (Gy_{10})	$\%CR_{HTRT}/\%CR_{RT}$ (%)	BED_{HTRT} (Gy)	Estimated α/β for HTRT (Gy)
		Dose (Gy)	Dose/fr (Gy)	T (°C)	Time (mins)	Per week	Total sessions	Total	CR	Total	CR				
Wahl et al. [35]	RcBC	48.0	2.0	NA	NA	NA	NA	18	7	36	24	57.6	1.71	98.7	1.89
Vernon et al. (MRC) [36]	RcBC	28.8	3.6	43.0	60.0	1	3	59	17	90	51	39.2	1.97	77.0	2.15
Vernon et al. (ESHO) [36]	RcBC	32.0	4.0	43.0	60.0	2	8	29	11	27	21	44.8	2.05	91.9	2.14

HT increase BED by a factor of 2

LOCALLY ADVANCED HEAD&NECK CANCER

Table 1

Summary of the randomized studies of RT vs HTRT, complete responders in each arm, corresponding BED of the RT schedule and the estimated α/β with HTRT for each study.

Author	Site	RT/HTRT		Hyperthermia				RT		HTRT		BED (RT) (Gy_{10})	$\%CR_{HTRT}/\%CR_{RT}$ (%)	BED_{HTRT} (Gy)	Estimated α/β for HTRT (Gy)
		Dose (Gy)	Dose/fr (Gy)	T (°C)	Time (mins)	Per week	Total sessions	Total	CR	Total	CR				
Wen et al. [37]	LAHNC	70.0	2.0	44.4	60.0	2	6	49	23	49	34	84.0	1.48	124.2	2.58
Huilgol et al. [38]	LAHNC	70.0	2.0	42.3	30.0	1	7	26	11	28	22	84.0	1.86	156.0	1.63
Valdagni et al. [39]	LAHNC	68.0	2.0	42.5	30.0	2	12	22	9	18	15	81.6	2.04	165.0	1.38
Datta et al. [40]	LAHNC	64.0	2.0	42.5	50.0	2	12	32	10	33	18	76.8	1.75	134.1	1.83
Arcangeli et al. [41]	LAHNC	60.0	1.5	42.5	45.0	3	7	43	18	38	30	69.0	1.89	130.1	1.28

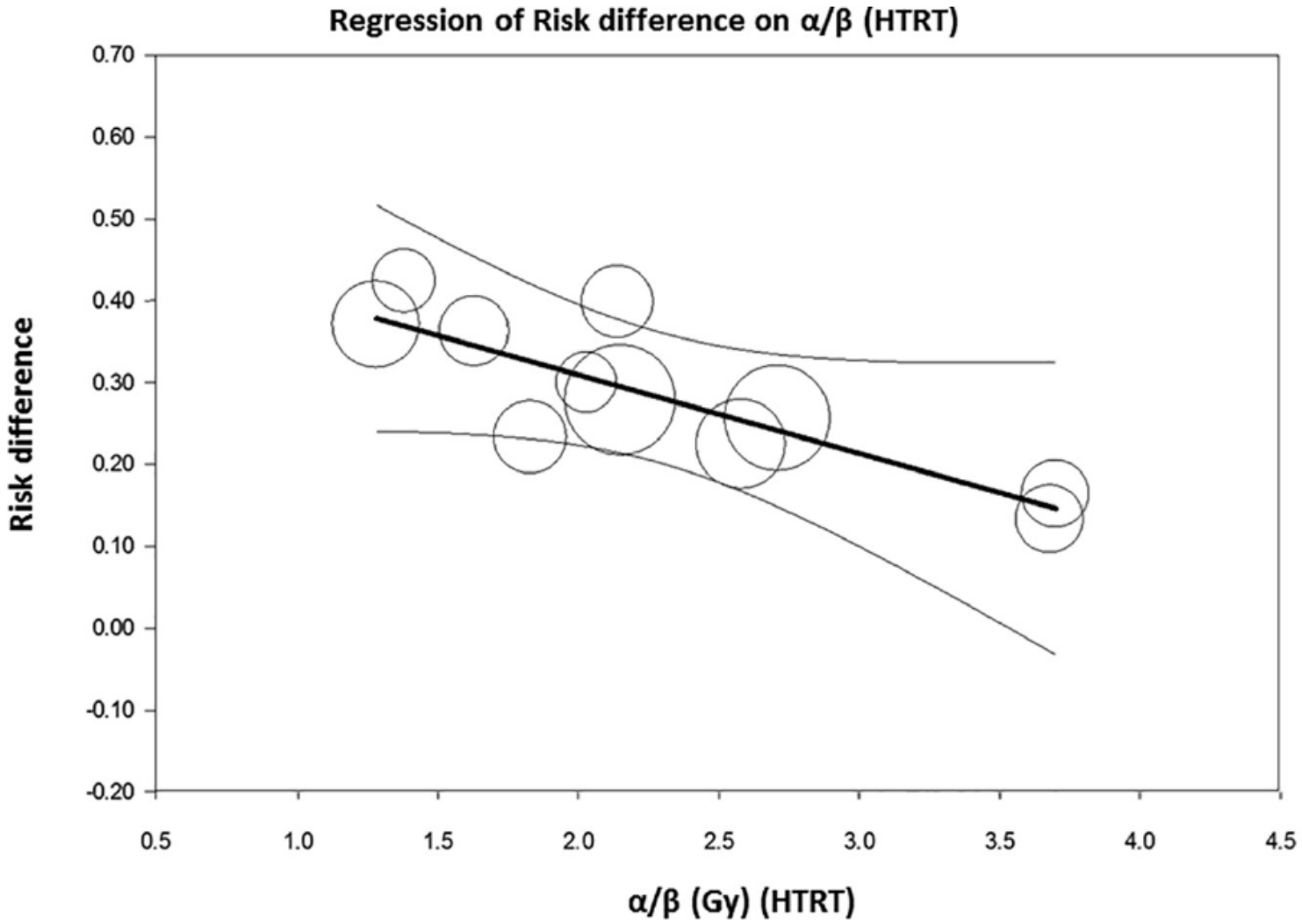
HT increase BED by a factor of 1.7

LOCALLY ADVANCED CERVICAL CANCER

Table 1
Summary of the randomized studies of RT vs HTRT, complete responders in each arm, corresponding BED of the RT schedule and the estimated α/β with HTRT for each study.

Author	Site	RT/HTRT		Hyperthermia				RT		HTRT		BED (RT) (Gy_{10})	$\%CR_{HTRT}/\%CR_{RT}$ (%)	BED_{HTRT} (Gy)	Estimated α/β for HTRT (Gy)
		Dose (Gy)	Dose/fr (Gy)	*T* (°C)	Time (mins)	Per week	Total sessions	Total	CR	Total	CR				
Harima et al. [42]	LACC	52.2	1.8	40.6	60.0	1	3	20	10	20	16	61.6	1.60	98.6	2.03
Franckena et al. [43]	LACC	48.3	2.0	42.0	60.0	1	5	56	32	58	48	58.0	1.45	83.9	2.71
Chen et al. [44]	LACC	40.0	2.0	42.0	45.0	2	8	30	14	30	18	48.0	1.29	61.7	3.68
Datta et al. [45]	LACC	60.0	2.0	42.5	45.0	2	12	26	15	27	20	72.0	1.28	92.4	3.70

HT increase BED by a factor of 1.5


Regression of Risk difference on α/β (HTRT)
Risk difference
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
-0.20
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
α/β (Gy) (HTRT)

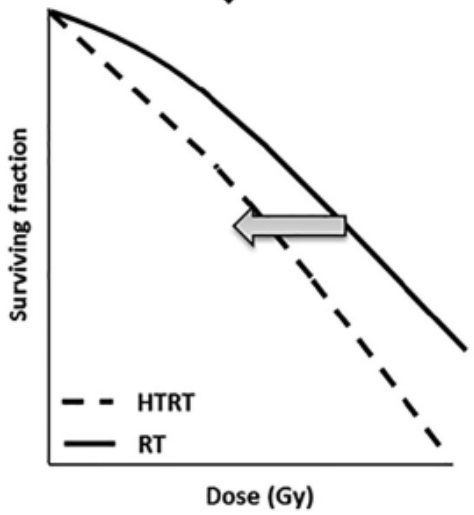
Hyperthermia (HT)(39 – 43°C)
Inhibits repair of radiation (RT) induced double strand DNA break

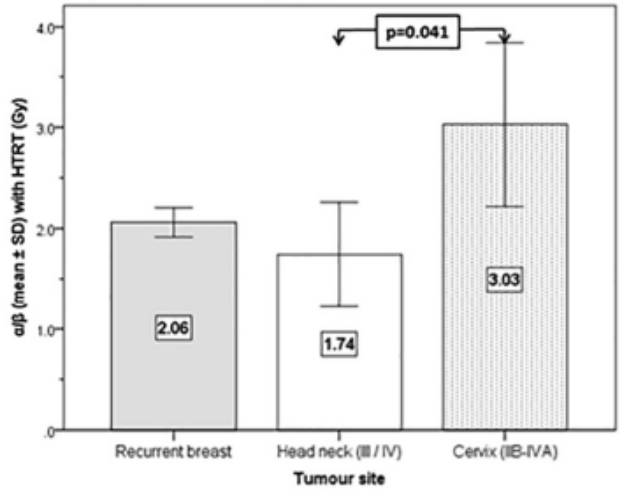
HT with RT increases the quadratic (β) component of α/β ratio

HT with RT reduces α/β ratio of cell survival curve compared to RT alone

Cell survival studies (HTRT vs RT): ↓ α/β ratio

Clinical trials (HTRT vs RT): ↓ α/β ratio





HT with RT induces reduction in tumour α/β and results in radiosensitization

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Does the combination of hyperthermia with low LET (linear energy transfer) radiation induce anti-tumor effects equivalent to those seen with high LET radiation alone?

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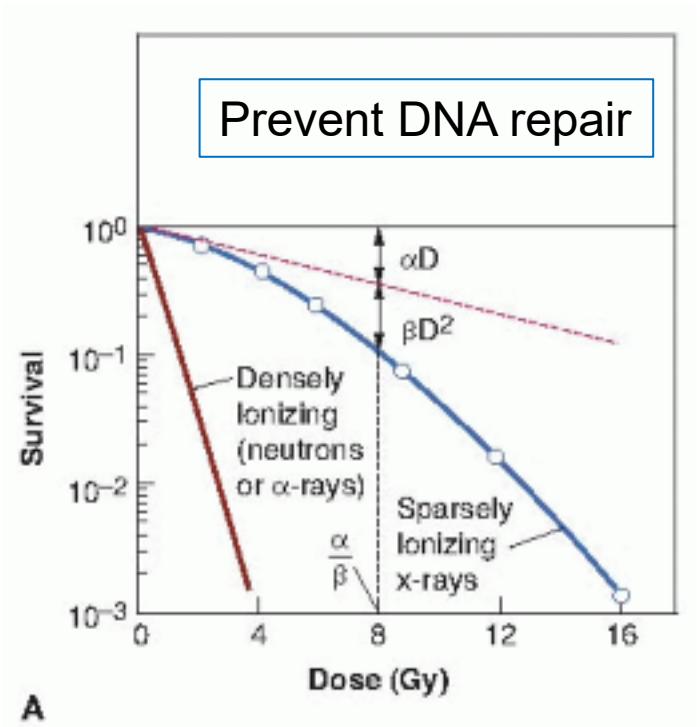
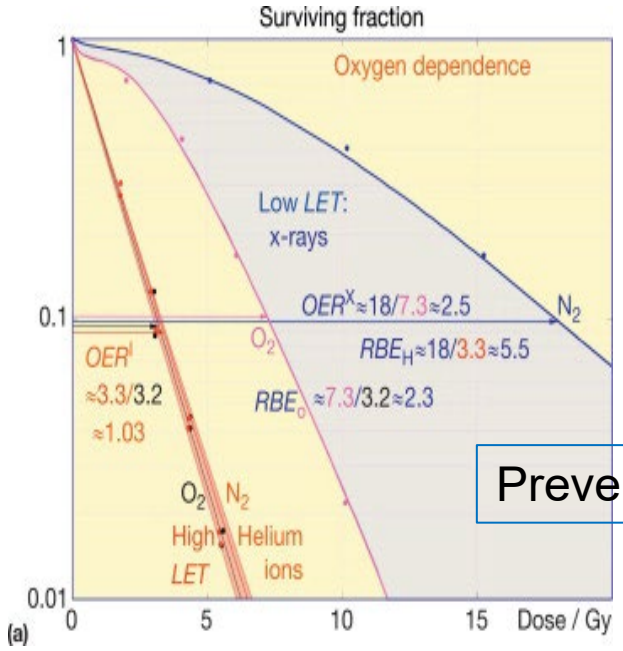
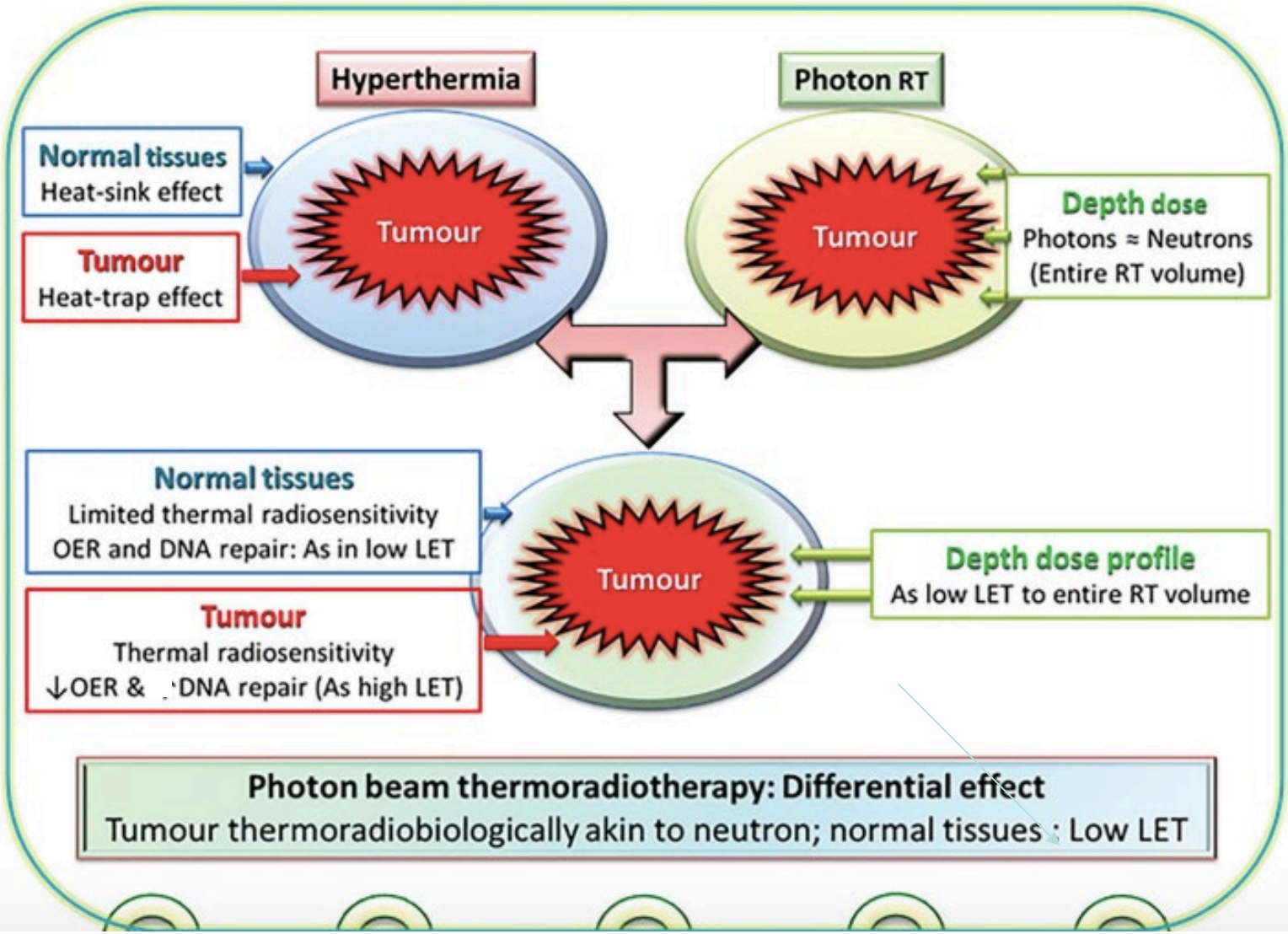




Prevent hypoxia


Hyperthermia
Photon RT
Normal tissues
Heat-sink effect
Tumour
Heat-trap effect
Tumour
Tumour
Depth dose
Photons ≈ Neutrons
(Entire RT volume)
Normal tissues
Limited thermal radiosensitivity
OER and DNA repair: As in low LET
Tumour
Thermal radiosensitivity
↓OER & DNA repair (As high LET)
Tumour
Depth dose profile
As low LET to entire RT volume
Photon beam thermoradiotherapy: Differential effect
Tumour thermoradiobiologically akin to neutron; normal tissues : Low LET

Summary

- Hyperthermia Kills cells over 43º
- Lower temperatures elicit Themotolerance
- Hyperthemia increases immune response
- Hyperthermia increase RT efficacy
- Hyperthermia reduces tumor alfa/beta ratio
- HT+RT may mimic High LET radiotherapy

Grupo de Trabajo en Radiobiologia
Grupo Hipertermia SEOR

Rafael Guerrero, Pedro C Lara, Félix Navarro, Barbara Salas