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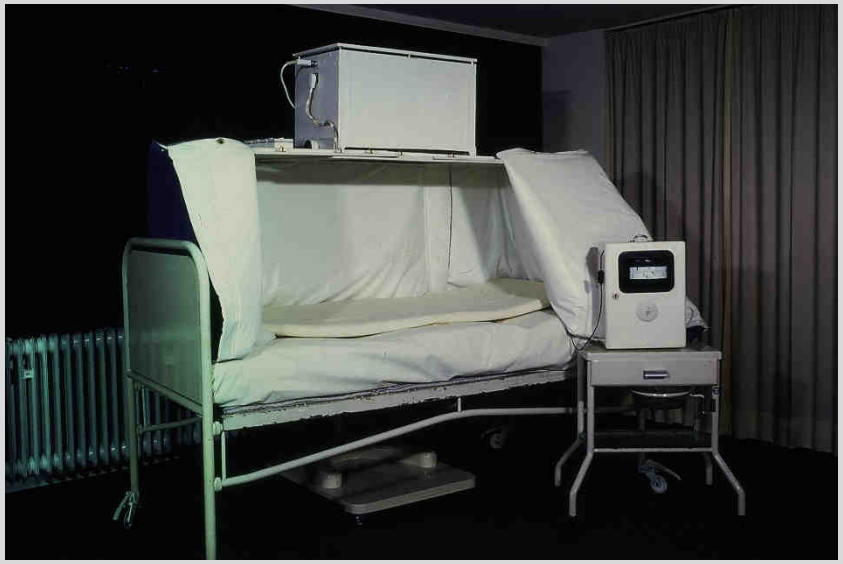
Water-filtered Infrared Fever-Range Whole-Body Hyperthermia (FR WBH) in Oncology and other indications

2015

Technology
and
Treatment Levels

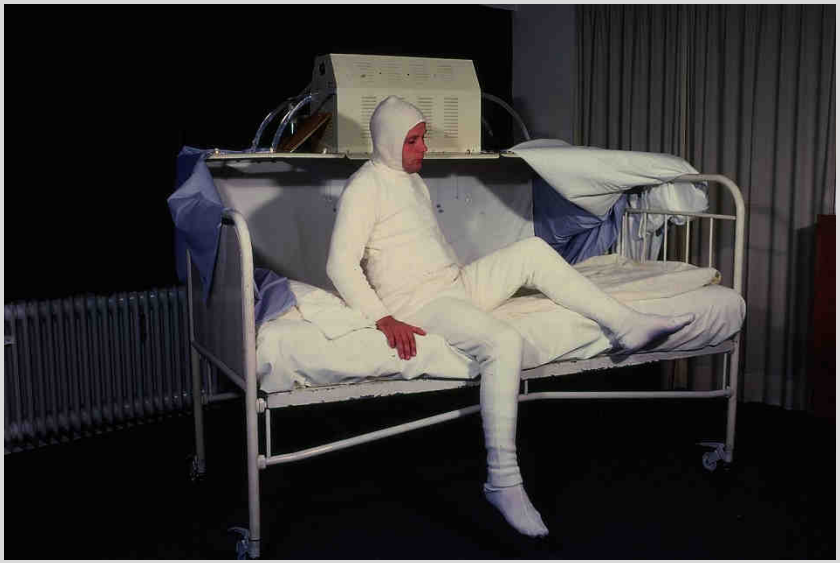
HISTORY



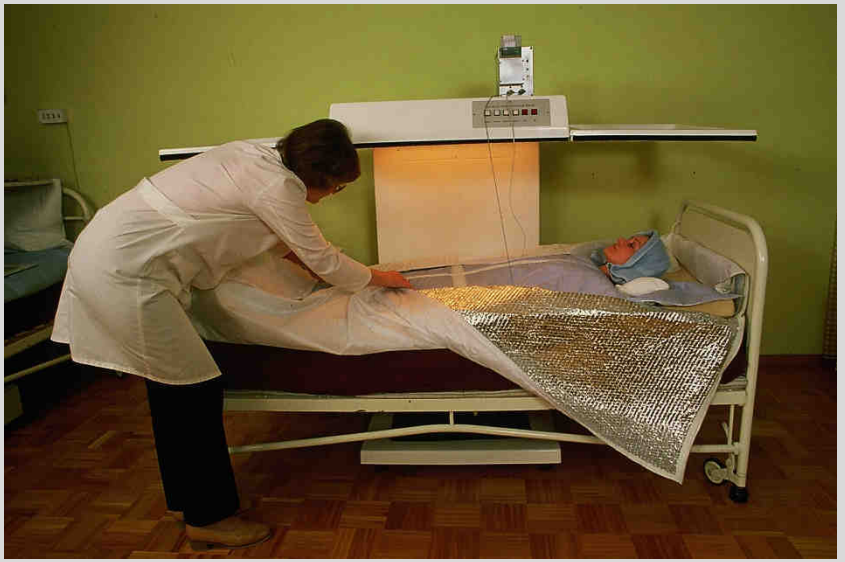
1961

Dr. med.
Martin Heckel

1926 - 2007



1965



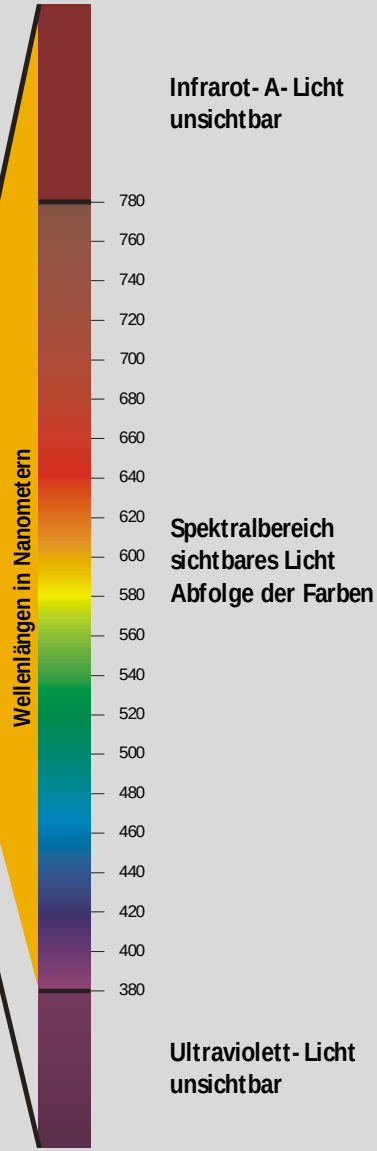
1982

Local Hyperthermia	
Technic	Target
Superficial hyperthermia • Infrared (water-filtered) • Microwaves	Skin tumor Superficial lesions (e.g. breast wall recurrence)
Loco-regional deep hyperthermia • Capacitive field (“Electro-Hyperthermia”) • Microwaves antenna	Local tumor control, mostly in combination with radio- or chemotherapy
Intraperitoneal hyperthermic perfusion with chemotherapy	• e.g. dissiminated ovarian cancer, bladder cancer
Interstitial hyperthermia • Invasive implantation of antenna • Magnetic liquids	• Direct destruction of local limited tumors

locoregional hyperthermia	whole-body hyperthermia by wIRA
Deep-seated tumor tissue is heated directly	Deep-seated tumor tissue is not heated directly
Blood flow is the cooler	Blood flow is the heater

Wellness	Medical use
Water, steam, IR-C	IR-A
Classical Sauna, IR-Sauna Steam room	Hyperthermia device
Short term application without considerable increase of core temperature	Long term application with considerable and controlled elevation of core temperature
Training of thermoregulatory reaction	Artificial fever temperatures

Bezeichnung	Wellenlänge	Oberbegriff
Mikro- u. Radiowellen	1 mm - 10^{4} m	elektrische Wellen
Infrarot-C	3000 nm-1 mm	optische Strahlung
Infrarot-B	1400-3000 nm	
Infrarot-A	**760-1400 nm**	**Spektrum PhotoDyn 501**
sichtbares Licht	**380-760 nm**	
Ultraviolett A, B, C	100-380 nm	
Grenzstrahlung Röntgen-Strahlen	1-100 nm 10^{-13} - 10^{-9} m	Röntgen- Strahlung
Gammastrahlung Kosmische Strahlung	10^{-16} - 10^{-13} m	natürliche und künstliche atomare Strahlung



Infrarot-A-Licht unsichtbar

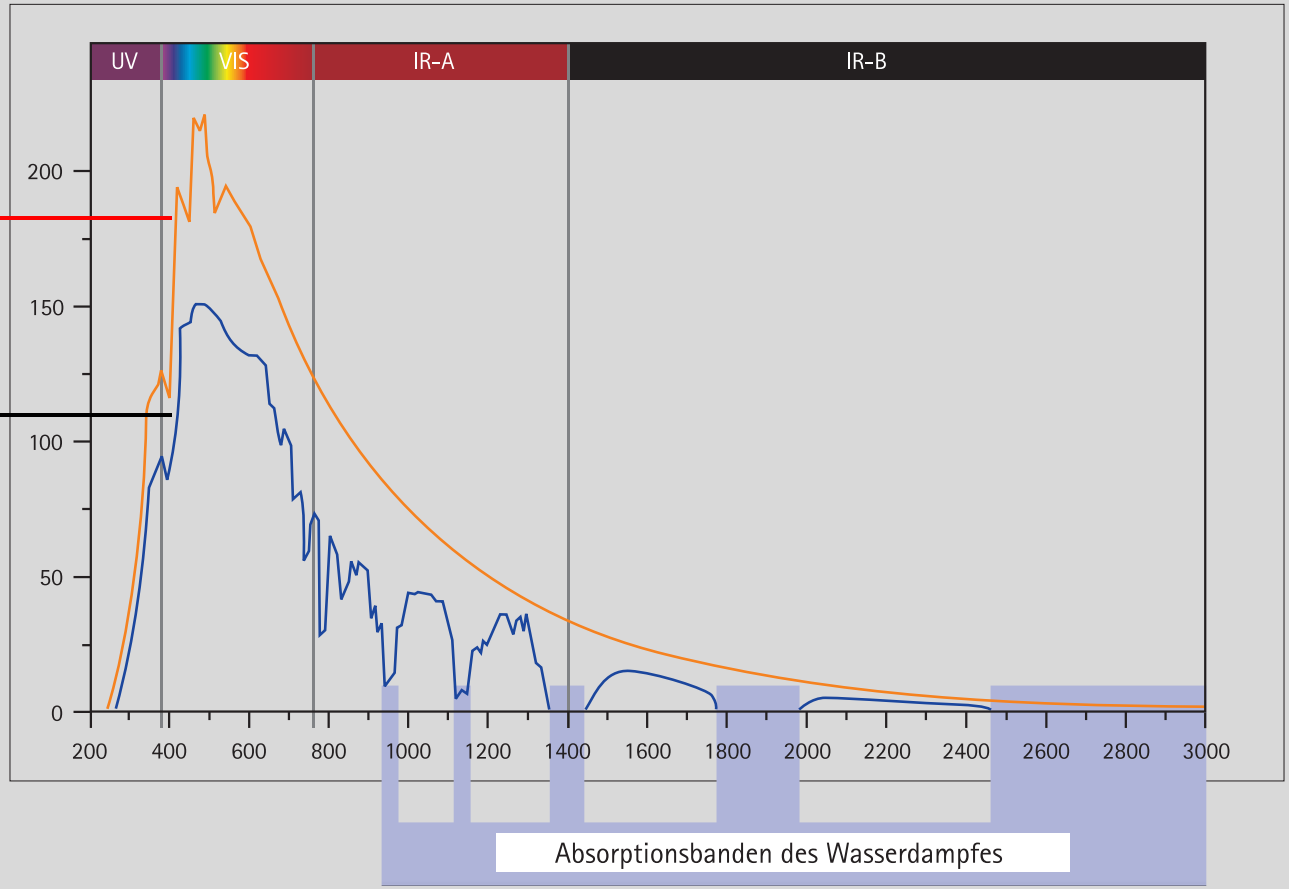
Spektralbereich sichtbares Licht Abfolge der Farben

Ultraviolett-Licht unsichtbar

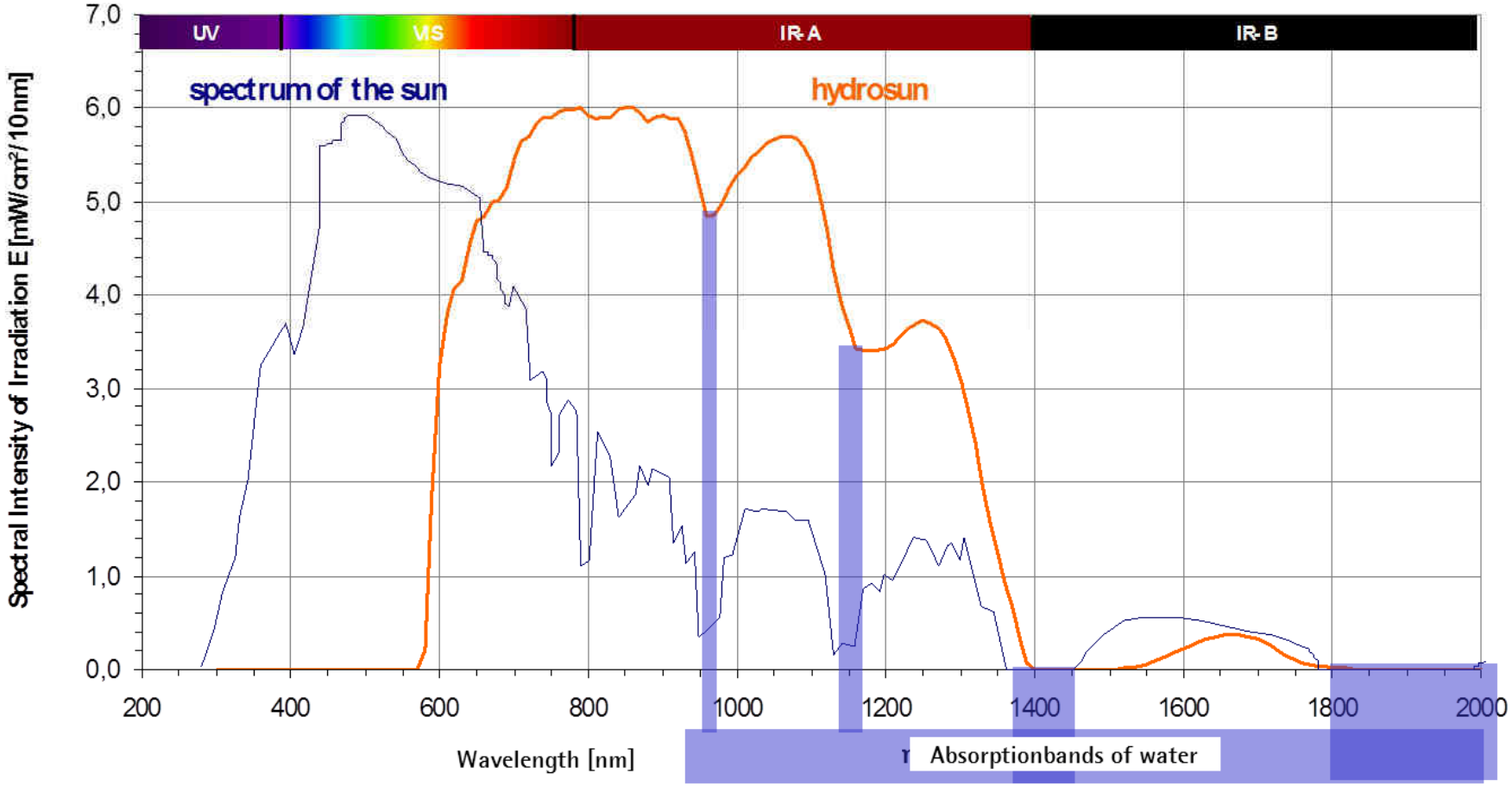
Visible light and IR-A, no UV !

Sun radiation outside of the atmosphere

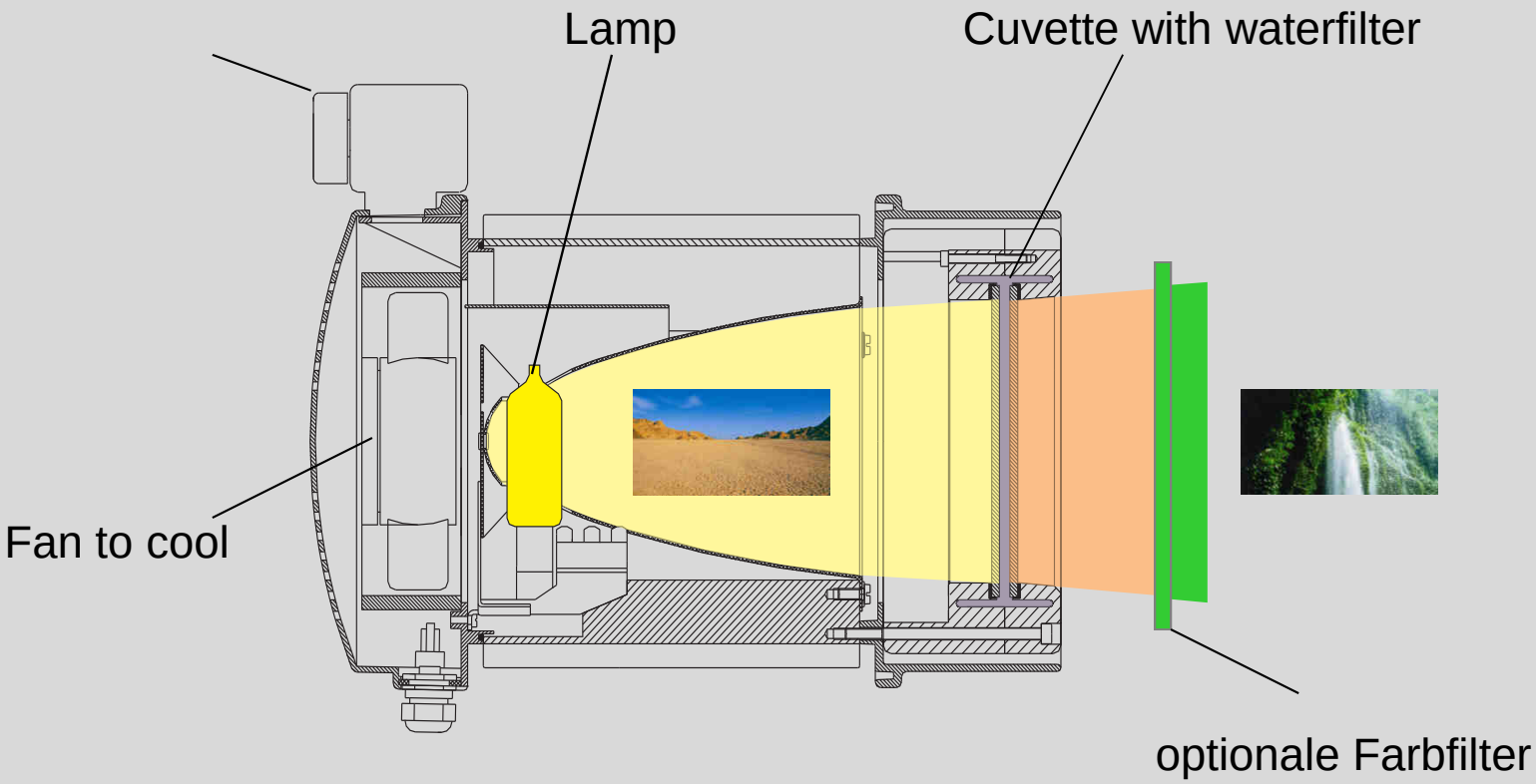
Sun radiation filtered by humid atmosphere



The Absorptionbands of water and hydrosun®

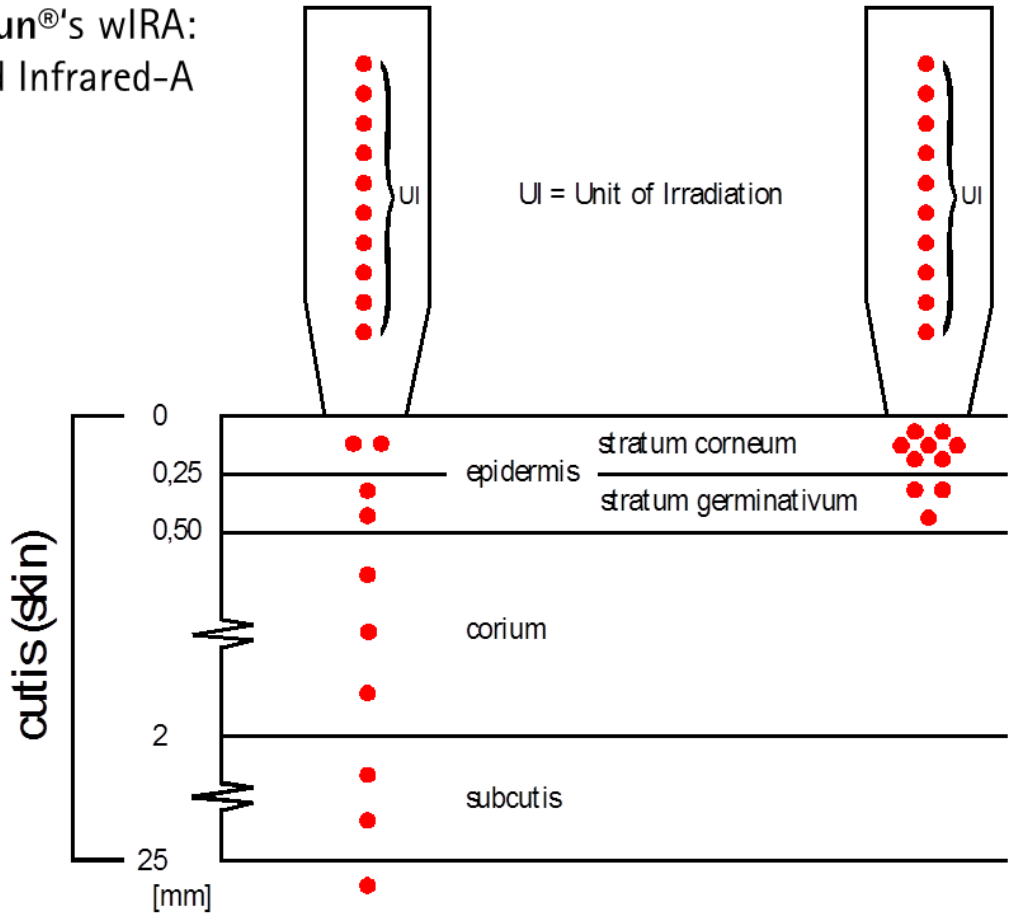


The technics of wIRA-radiation:



Depth of Penetration of Infrared Radiation

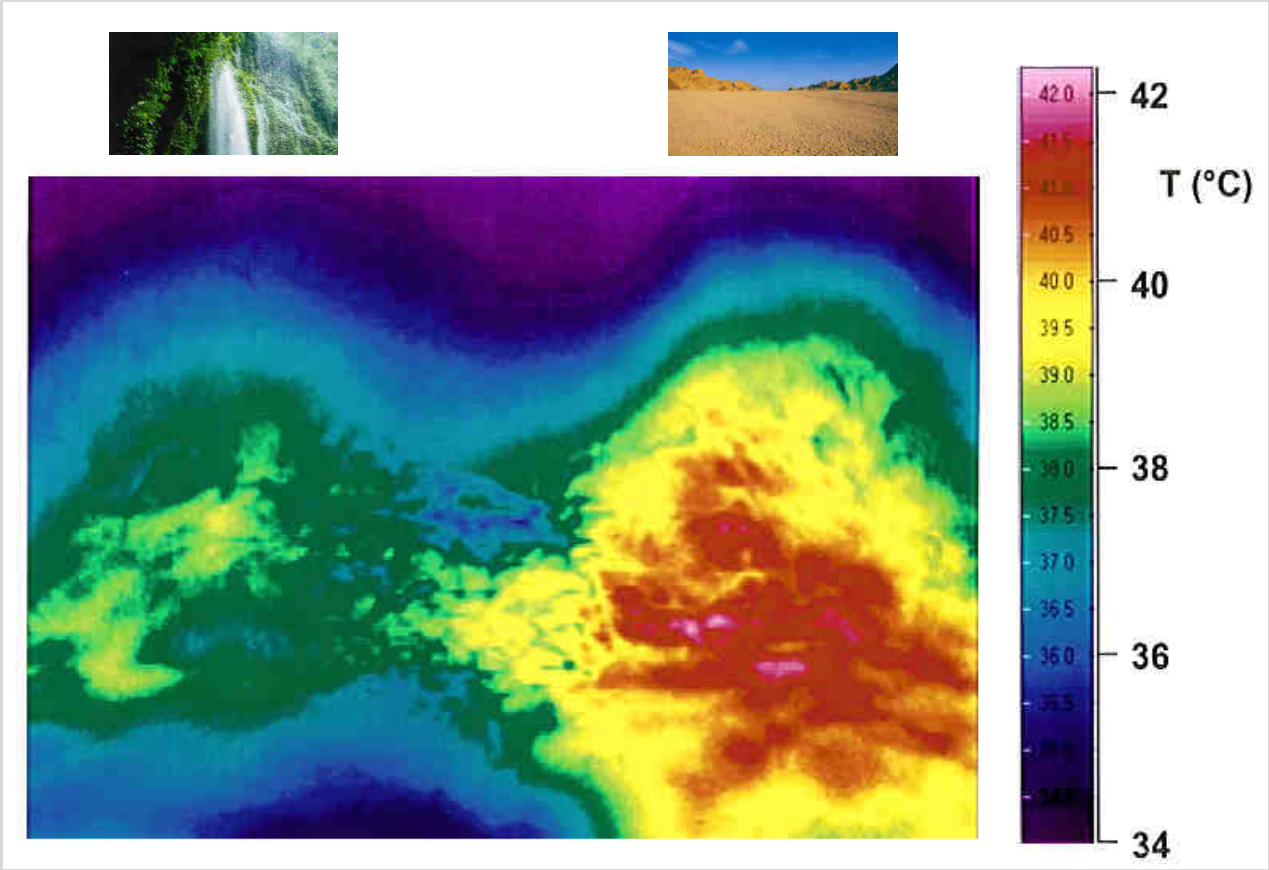
hydro**sun**®'s wIRA:
filtered Infrared-A



Infrared-B and -C
essential part of
conventional
infrared lamps

Temperatur distribution on the skin

wIRA conventional



hot ⇒ pain

warm ⇒ agreeable

body core temperature

Nach P. Vaupel, J. Rzeznik, E. Stofft: Wassergefilterte Infrarot-A-Strahlung versus konventionelle Infrarotstrahlung...; Physikalische Medizin, Heft 3, Juni 1995, S. 77-81

	mild WBH		fever-range WBH		extreme WBH
target temperature core temp, T(rectal)	**< 38,5 °C** x)		**38,5 °C - 40,5 °C** x)		**> 40,5 °C** x)
					intermediate | extrem
Duration of application inside the indicated temperature range	short	long	short	long	<41,5<
	< 30 min	> 30 min	< 4 h	> 4 h	> 1 h
Patient's stress	sweating, no thermoregulatory stress	sweating, no thermoregulatory stress	thermoregulatory stress, personal assistance, weak sedation if necessary	thermoregulatory stress, sedation necessary	deep intravenous or general anesthesia
Monitoring and supervision	without assistance, home use possible	assistance by a nurse parameter (minimum): T(axillary,sublingual,tymp.)	assistance by a nurse supervision by a doctor parameter (minimum): T(rectal), T(axill,subl,tymp) pulse rate	assistance by a nurse supervision by a doctor parameter (minimum): T(rectal), blood pressure ECG, pulse oximetry	intensive care supervision by a doctor
Indications (selected)	relaxation, wellness	rehabilitation, physiotherapy, orthopedics	chronic inflammation, rheumatology, dermatology, environmental medicine, oncology	oncology	oncology

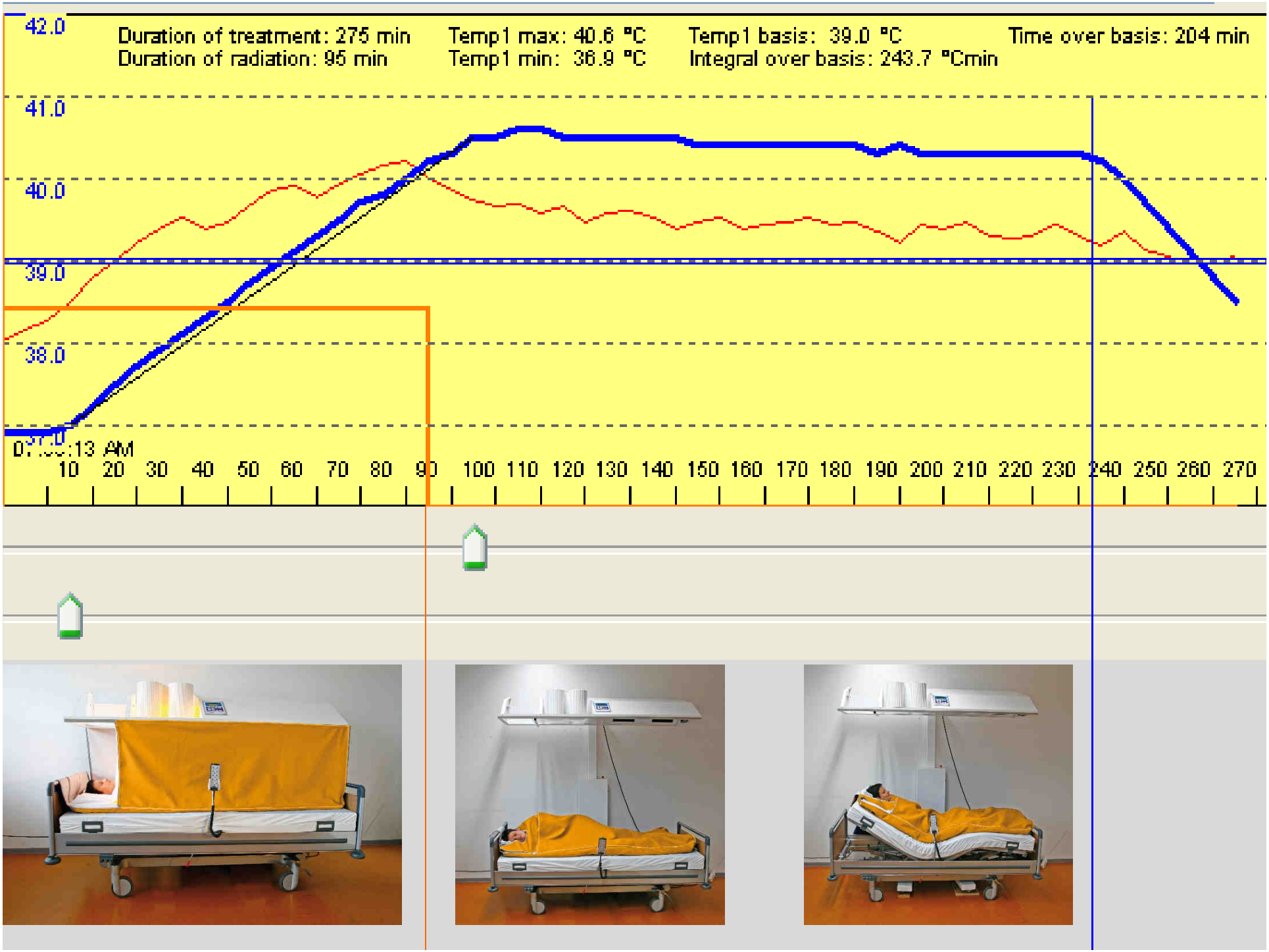
Beginning stress

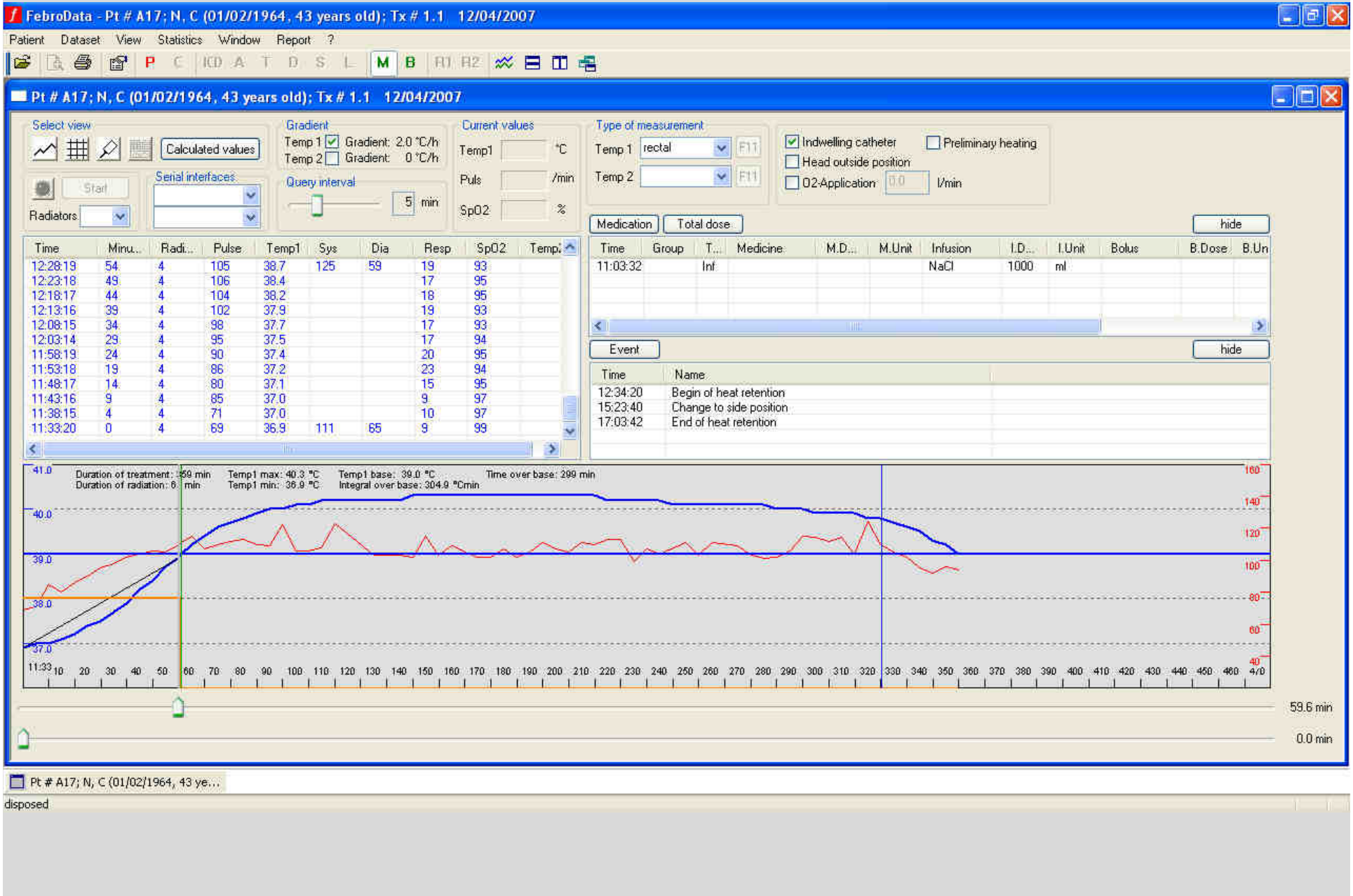
Beginning sedation

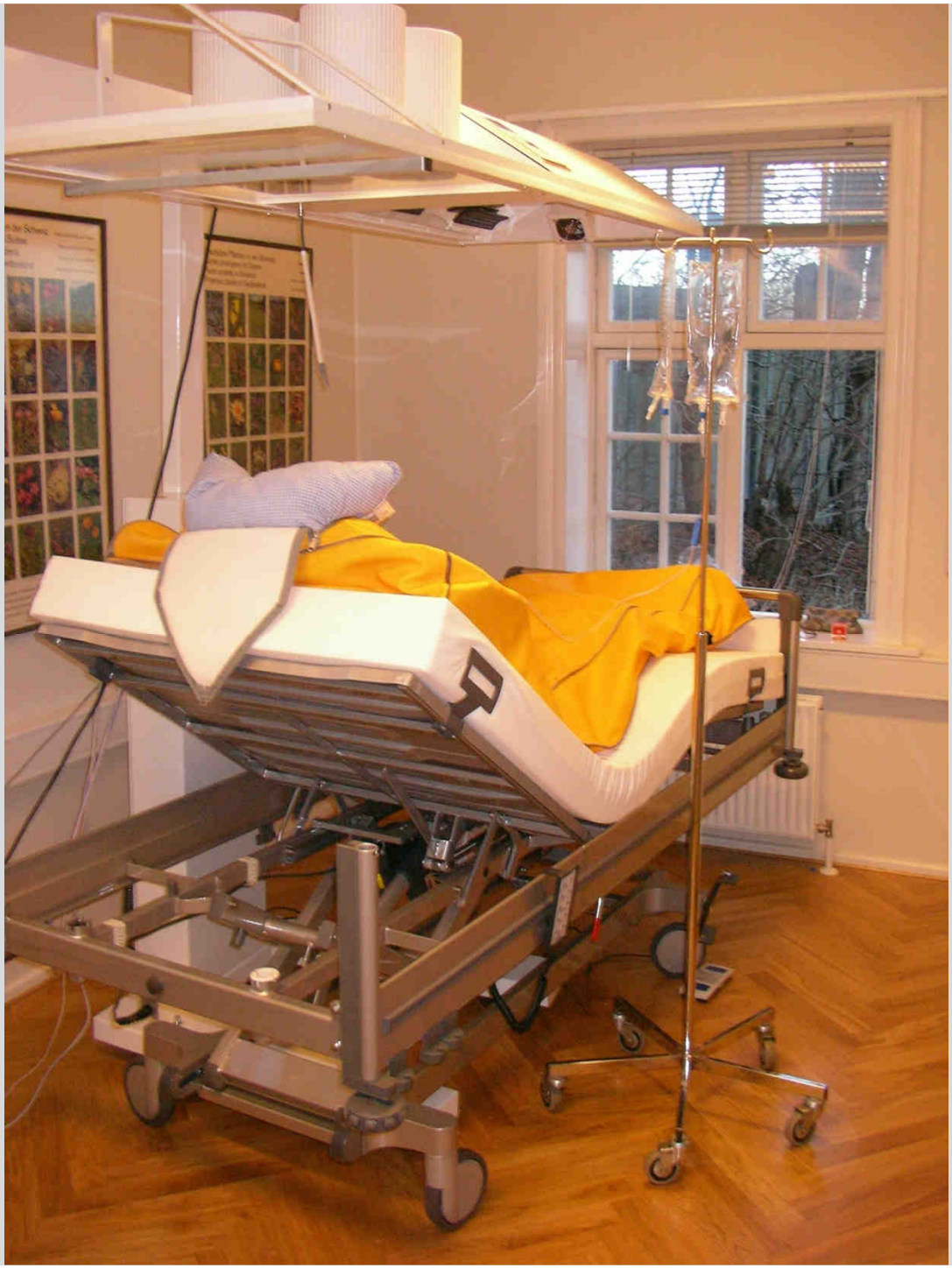
at home

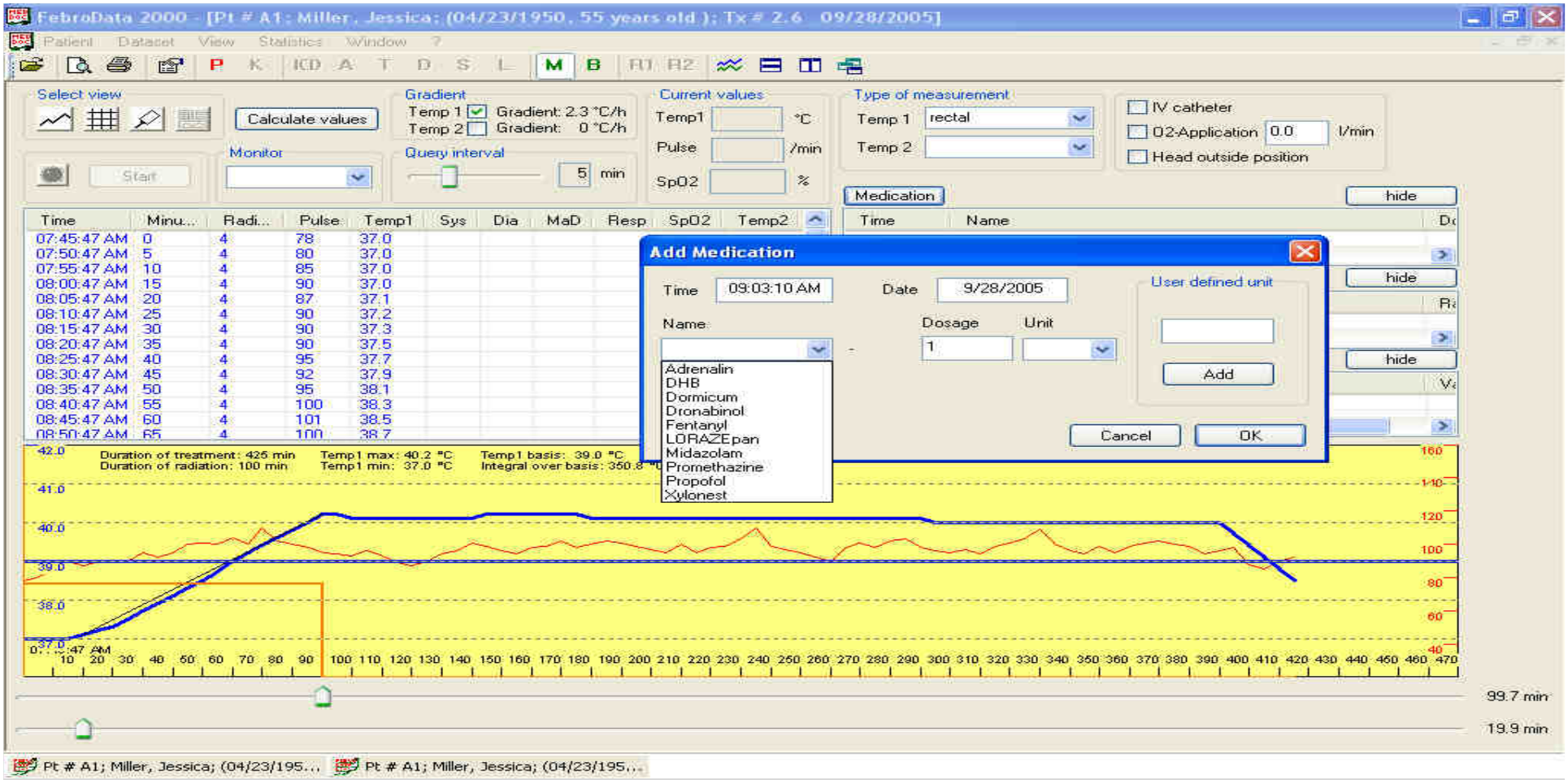
at ICU

big differences in individual patients


Duration of treatment: 275 min
Duration of radiation: 95 min
Temp1 max: 40.6 °C
Temp1 min: 36.9 °C
Temp1 basis: 39.0 °C
Integral over basis: 243.7 °Cmin
Time over basis: 204 min
42.0
41.0
40.0
39.0
38.0
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270


FebroData - Pt # A17; N, C (01/02/1964, 43 years old); Tx # 1.1 12/04/2007
Patient Dataset View Statistics Window Report ?
Pt # A17; N, C (01/02/1964, 43 years old); Tx # 1.1 12/04/2007
Select view
Calculated values
Start
Radiators
Serial interfaces
Gradient
Temp 1 Gradient: 2.0 °C/h
Temp 2 Gradient: 0 °C/h
Query interval
5 min
Current values
Temp1 °C
Puls /min
SpO2 %
Type of measurement
Temp 1 rectal
Temp 2
Indwelling catheter
Preliminary heating
Head outside position
O2-Application l/min
Medication
Total dose
hide
Time Group T... Medicine M.D... M.Unit Infusion I.D... I.Unit Bolus B.Dose B.Un
11:03:32 Inf NaCl 1000 ml
Event
hide
Time Name
12:34:20 Begin of heat retention
15:23:40 Change to side position
17:03:42 End of heat retention
Time Minu... Radi... Pulse Temp1 Sys Dia Resp SpO2 Temp
12:28:19 54 4 105 38.7 125 59 19 93
12:23:18 49 4 106 38.4 19 95
12:18:17 44 4 104 38.2 18 95
12:13:16 39 4 102 37.9 19 93
12:08:15 34 4 98 37.7 17 93
12:03:14 29 4 95 37.5 17 94
11:58:19 24 4 90 37.4 20 95
11:53:18 19 4 86 37.2 23 94
11:48:17 14 4 80 37.1 15 95
11:43:16 9 4 85 37.0 9 97
11:38:15 4 4 71 37.0 10 97
11:33:20 0 4 69 36.9 111 65 9 99
Duration of treatment: 59 min
Duration of radiation: 6 min
Temp1 max: 40.3 °C
Temp1 min: 36.9 °C
Temp1 base: 39.0 °C
Integral over base: 304.9 °Cmin
Time over base: 299 min
41.0
40.0
39.0
38.0
37.0
160
140
120
100
80
60
40
11:33
59.6 min
0.0 min
Pt # A17; N, C (01/02/1964, 43 ye...
disposed





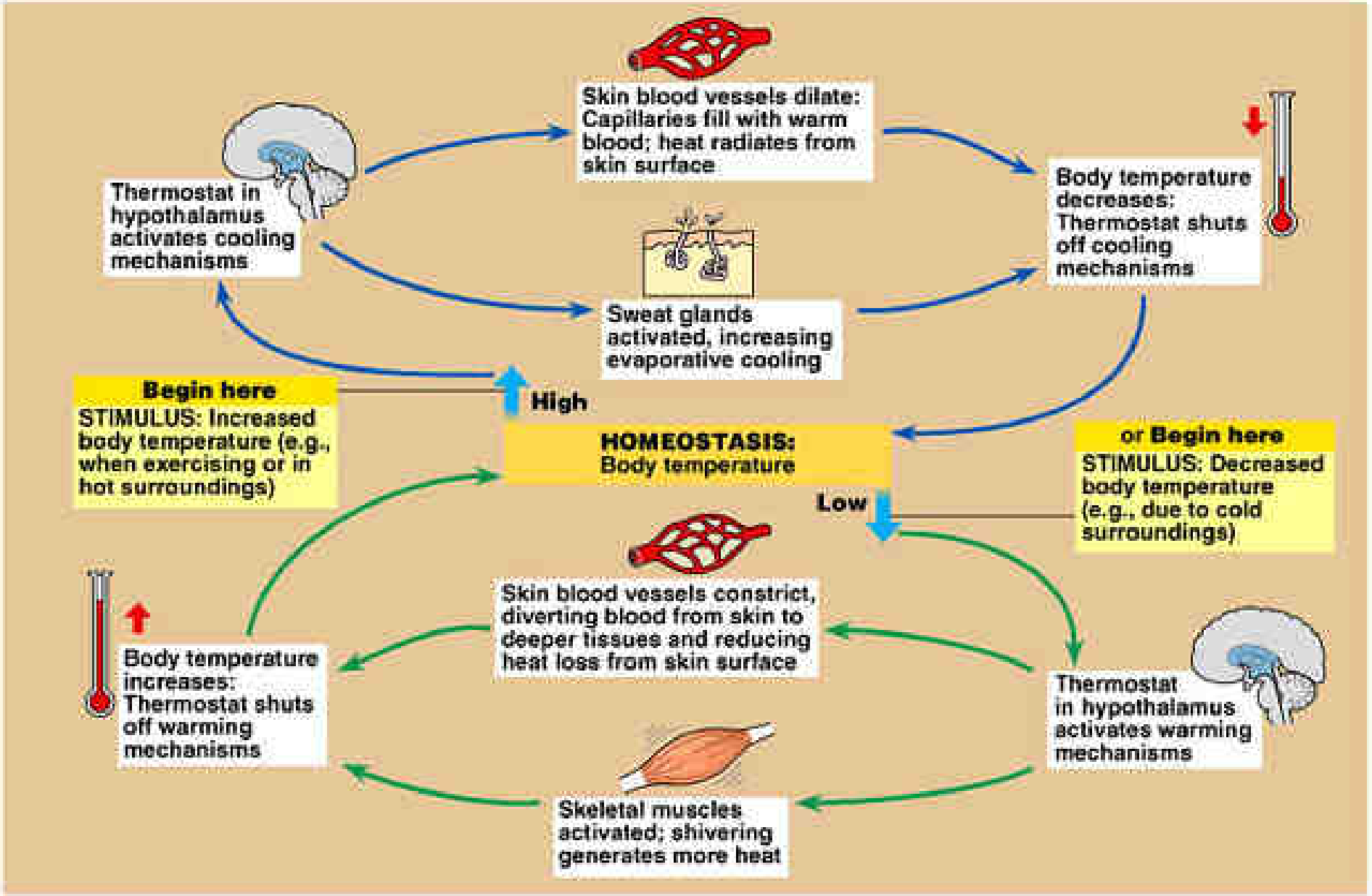
Good software documentation should be applied to analyse and improve treatments

Basic research of FR WBH

FR WBH:
no thermal cell killing effect !

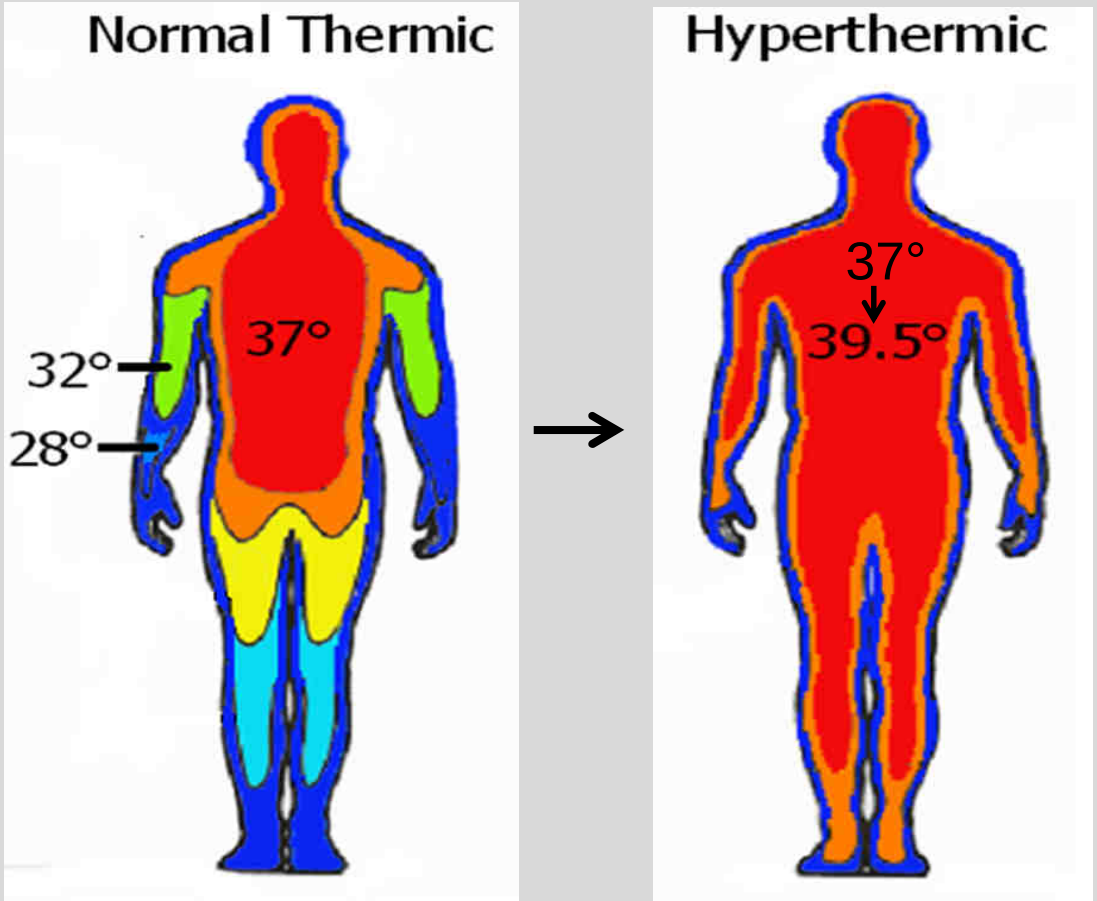
but at least 2 overlapping mechanisms
which can aid in cancer therapy:

Blood flow changes
Immunological changes



Range of “normothermic” temperatures in the body

These gradients are *actively* maintained by thermoregulatory control mechanisms.



In the beginning of a WBH treatment the rectal temperature does not change for 15–30 min.

1. Heating of the shell

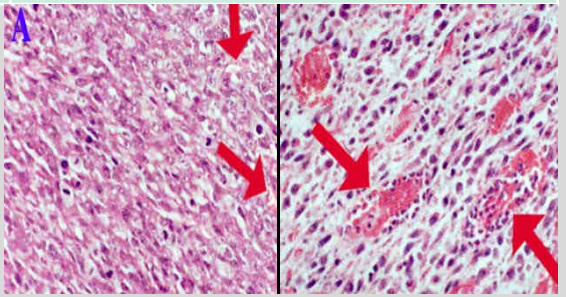
2. Elevation of the core temperature

Mountcastle, 1963

Hanson, 1984

	Healthy tissue	Tumor tissue
Before FR WBH	normal	reduced
During FR WBH	increased	increased
After FR WBH	normal	Increased (till 2 days after WBH !)

Maybe only in body periphery ?



Enlargement of tumor blood vessels after 8 hr of whole body hyperthermia (WBH). Colon 26 tumors from a mouse not treated shows normal blood vessels (arrows) and from a mouse treated with with 8 hr of WBH shoes enlarged blood vessels (arrows). Two week after WBH, tumors were removed…

Burd R. et al. J Cell Physiol 177:137-147 (1998)

Increased perfusion

- ⇨ increased oxygenation of tumor tissue
- ⇨ decreased Interstitial Fluid Pressure
- ⇨ increased efficacy of radiotherapy

Published OnlineFirst April 21, 2011; DOI:10.1158/0008-5472.CAN-10-4482

Molecular and Cellular Pathobiology

Cancer Research

Mild Elevation of Body Temperature Reduces Tumor Interstitial Fluid Pressure and Hypoxia and Enhances Efficacy of Radiotherapy in Murine Tumor Models

Arindam Sen[1], Maegan L. Capitano[1], Joseph A. Spernyak[2], John T. Schueckler[1], Seneca Thomas[1], Anurag K. Singh[3], Sharon S. Evans[1], Bonnie L. Hylander[1], and Elizabeth A. Repasky[1]

- ⇨ counteracting the immunosuppressive effect of hypoxia

Int. J. Hyperthermia, May 2010; 26(3): 232–246

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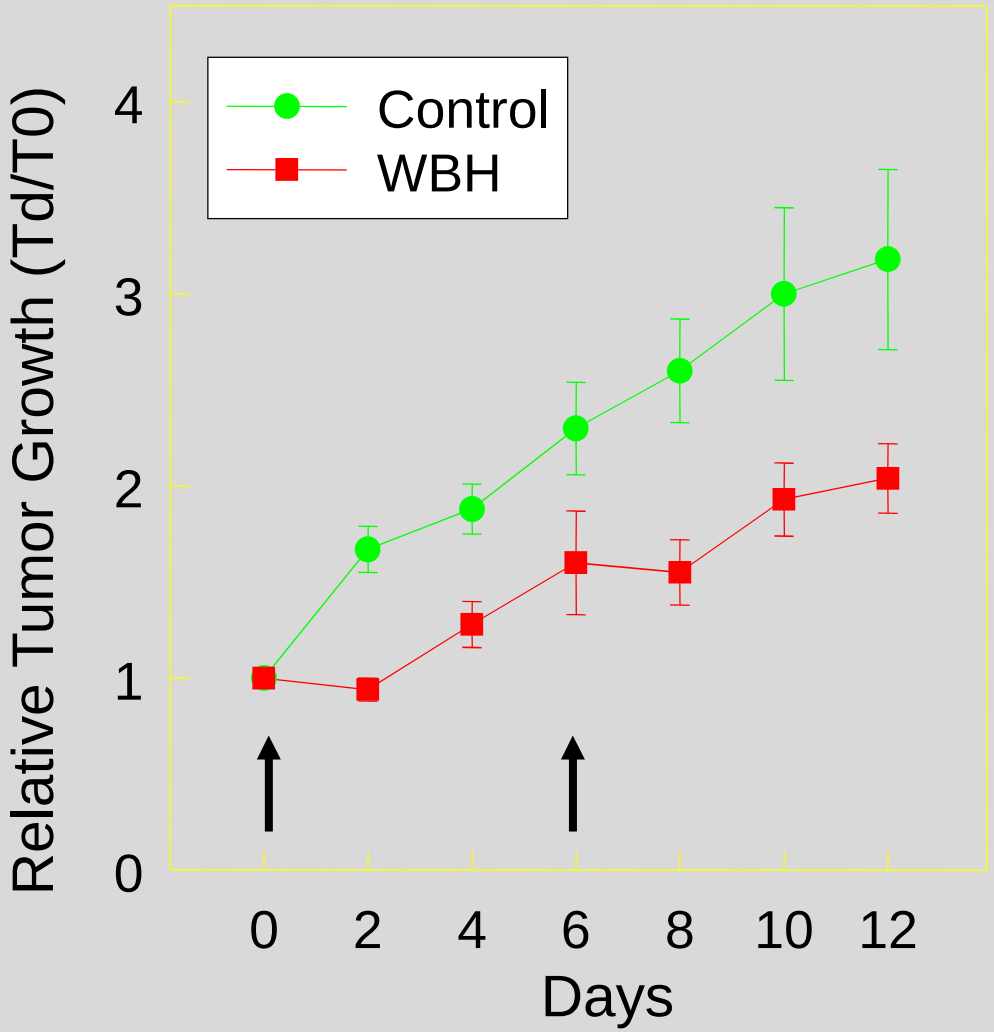
healthcare

Hypoxia-driven immunosuppression: A new reason to use thermal therapy in the treatment of cancer?

CHEN-TING LEE, THOMAS MACE, & ELIZABETH A. REPASKY

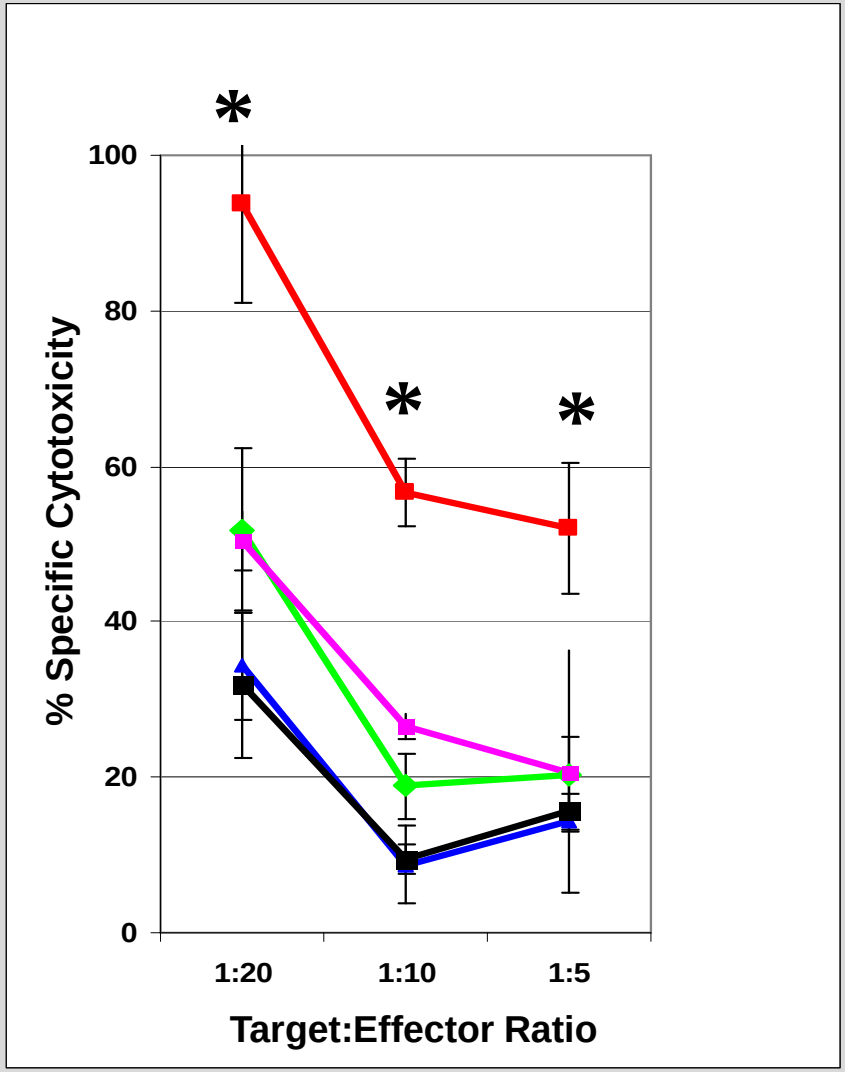
Department of Immunology, Roswell Park Cancer Institute, Buffalo, New York, USA

Modest control of tumor growth in SCID mice by FR WBH



Burd et al., J. Cell Physiol. 1998

Thermal enhancement of NK cytotoxicity is temperature dependent



Ostberg, Dayanc et al.,

J. Leuk. Biol; 2006

33°C

37°C

38°C

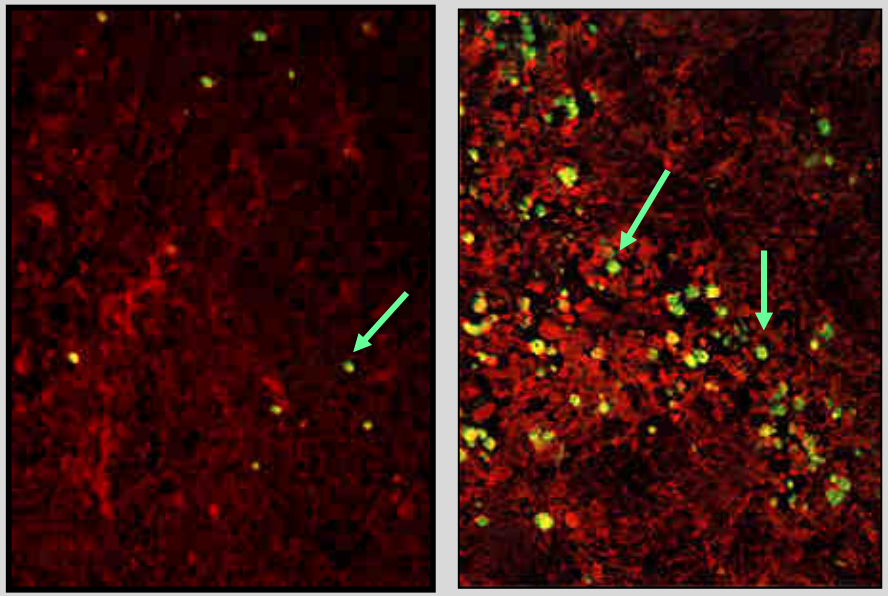
39.5°C

42°C

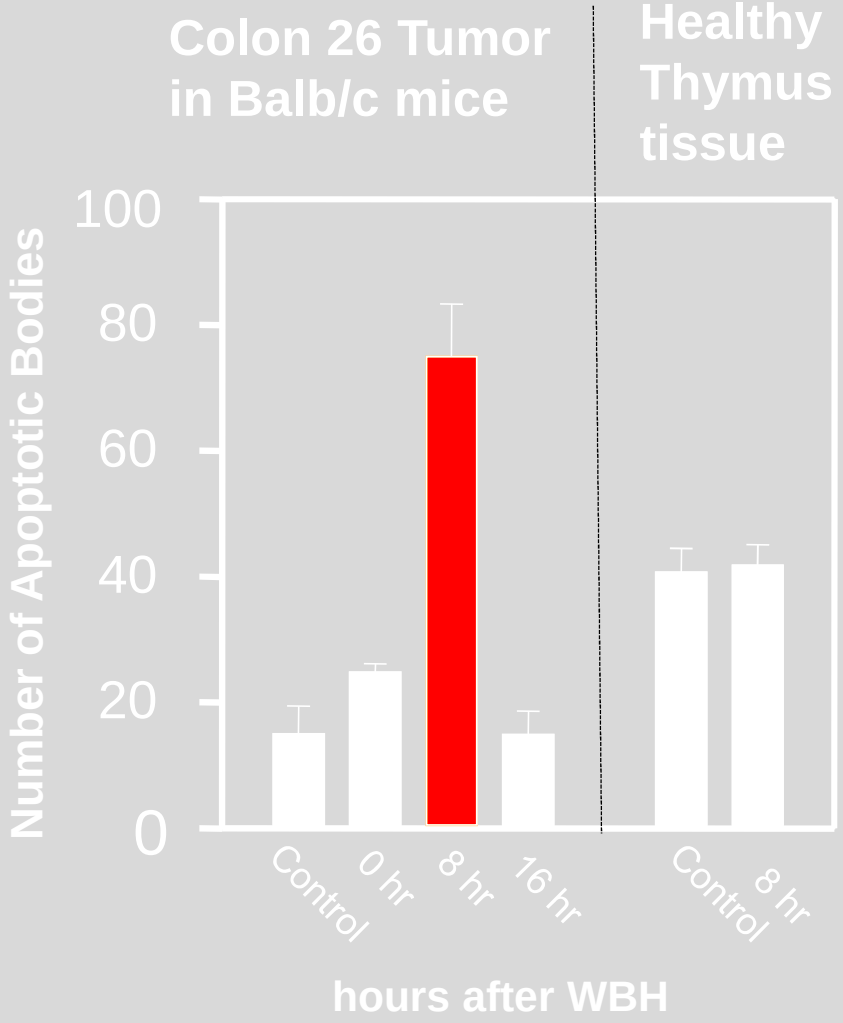
* , $p<0.05$

Mild, fever-range WBH results in increased apoptosis in tumor but not in normal tissues

Human breast tumor in SCID mice



Control 8 hrs post WBH

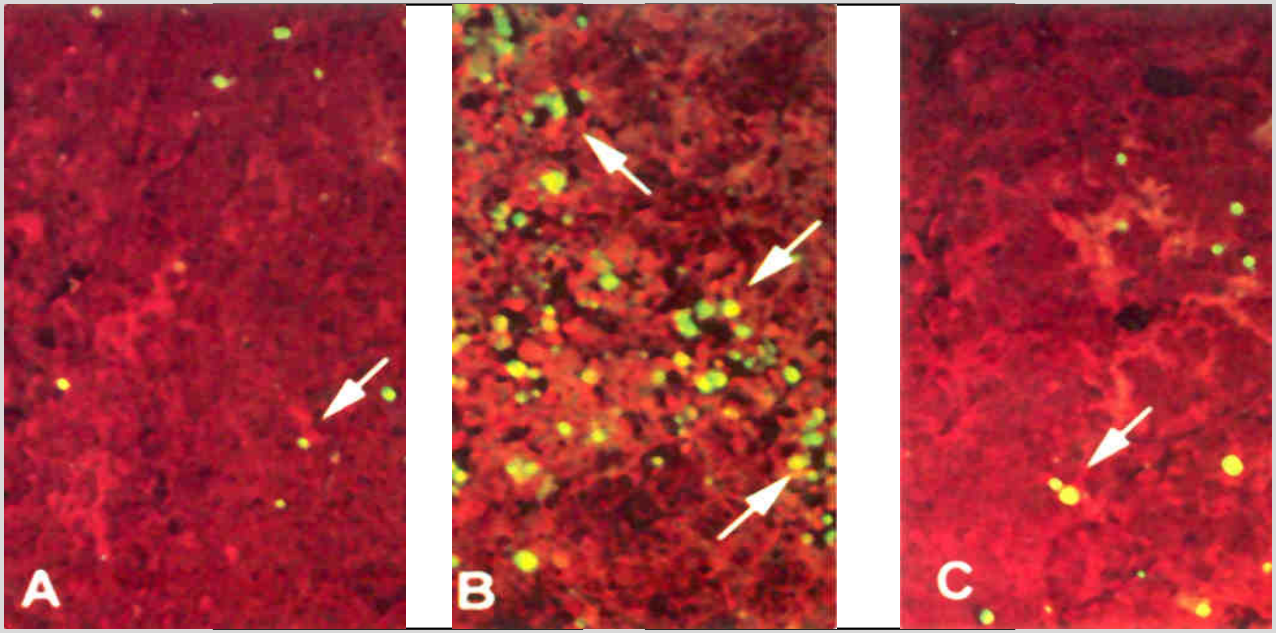


Burd, Repasky, 1998

Induction of apoptosis by WBH is NK cell mediated

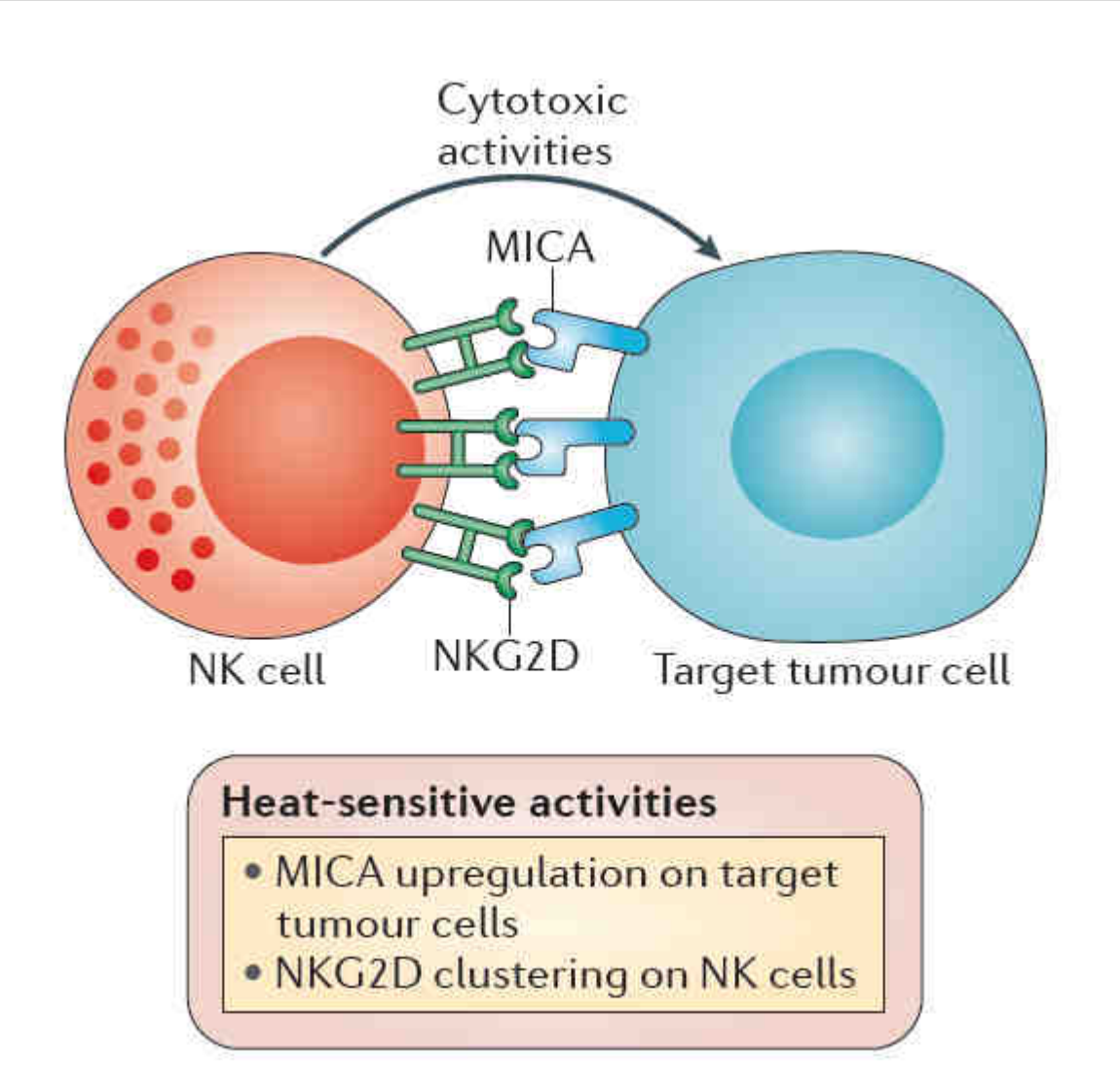
Human breast tumours were implanted into the gonadal fat pad of SCI mice, and apoptotic cells (arrows) were visualized in paraffin sections using the TUNEL method.

A: Tumour from a mouse not treated with 8 hr of whole body hyperthermia (WBH).
B: Tumour from a mouse treated with 8 hr of WBH.
C: Tumour from a mouse in which NK cell activity was depleted before 8 hr of WBH treatment.



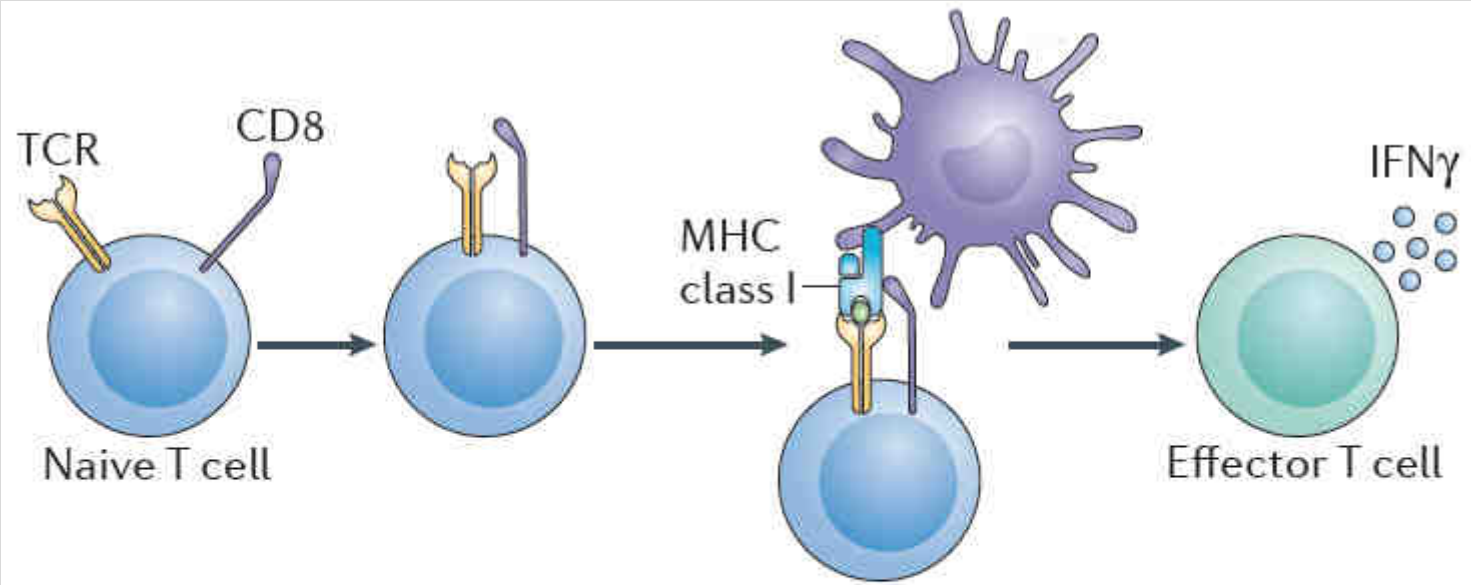
Burd R. et al. J Cell Physiol 177:137-147 (1998)

angeborenes Immunsystem



Evans, Repasky, Fisher (2015)

erworbenes Immunsystem

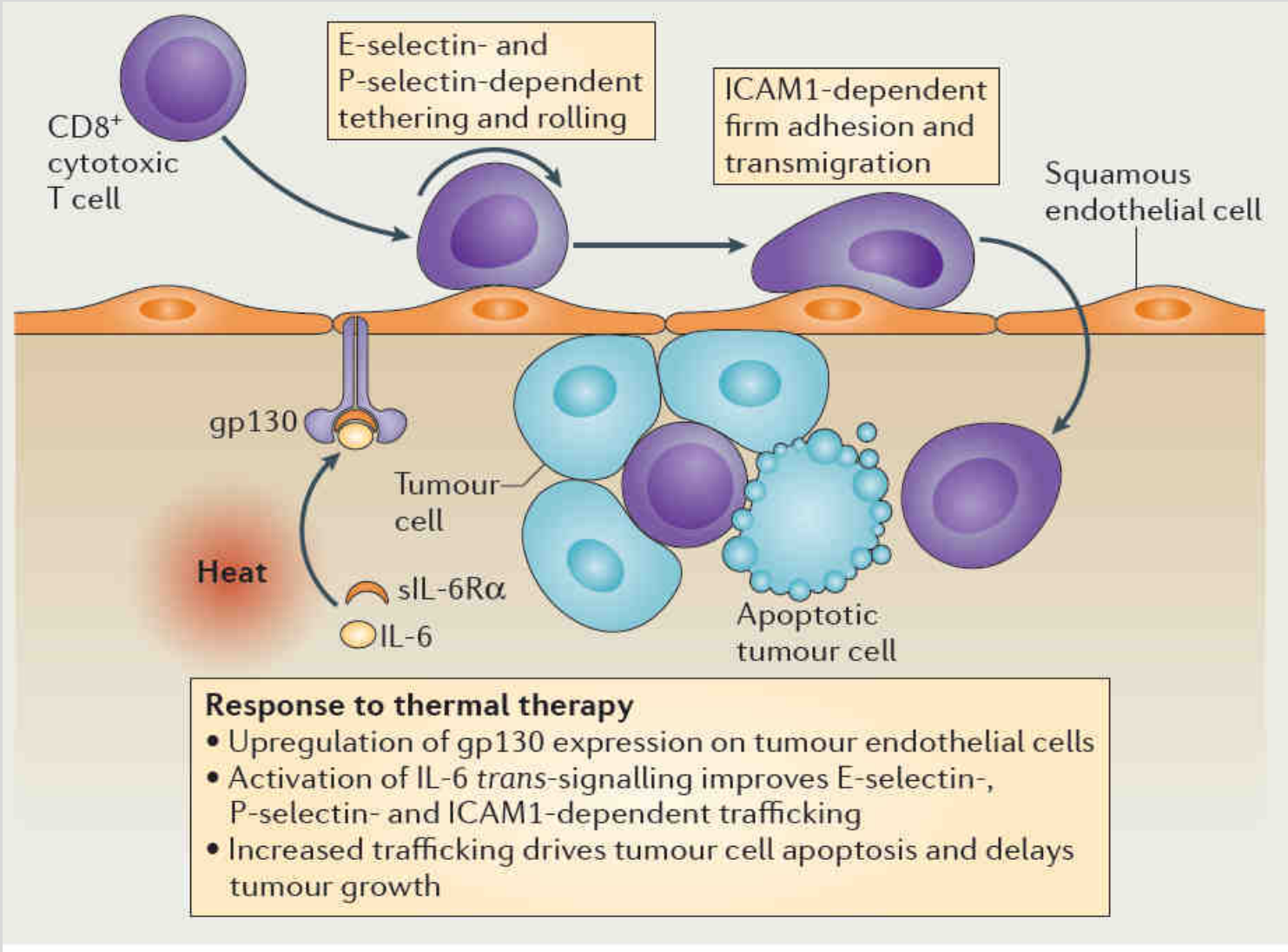


Heat-sensitive activities

- Pre-association of the TCR signalling complex
- Increased number and duration of T cell–APC interactions
- Enhanced generation of effector T cells (L-selectin loss, IFNγ production and cytotoxic activity)

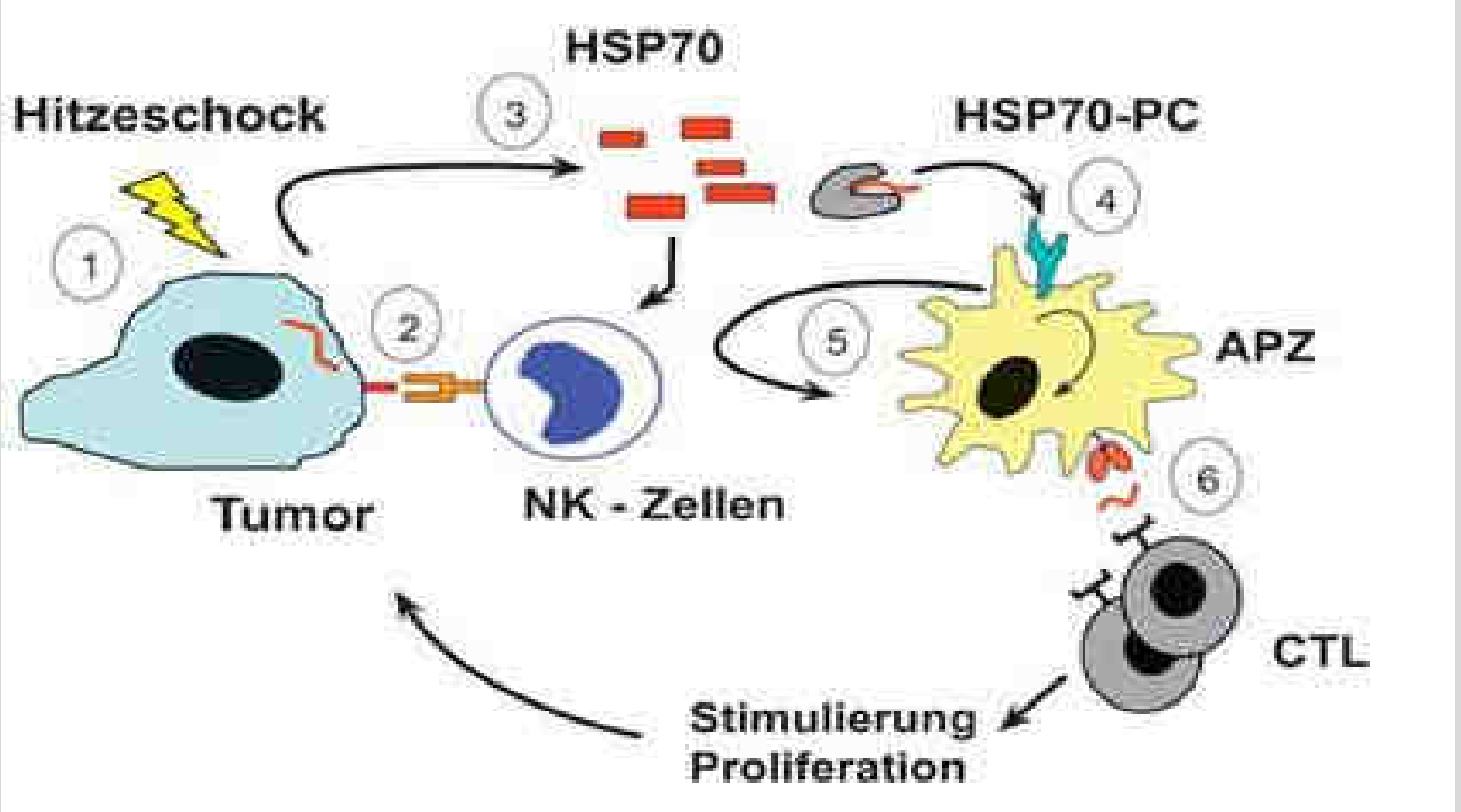
Evans, Repasky, Fisher (2015)

Wanderung der Immunzellen aus den Blutgefäßen zum Tumor



Evans, Repasky, Fisher (2015)

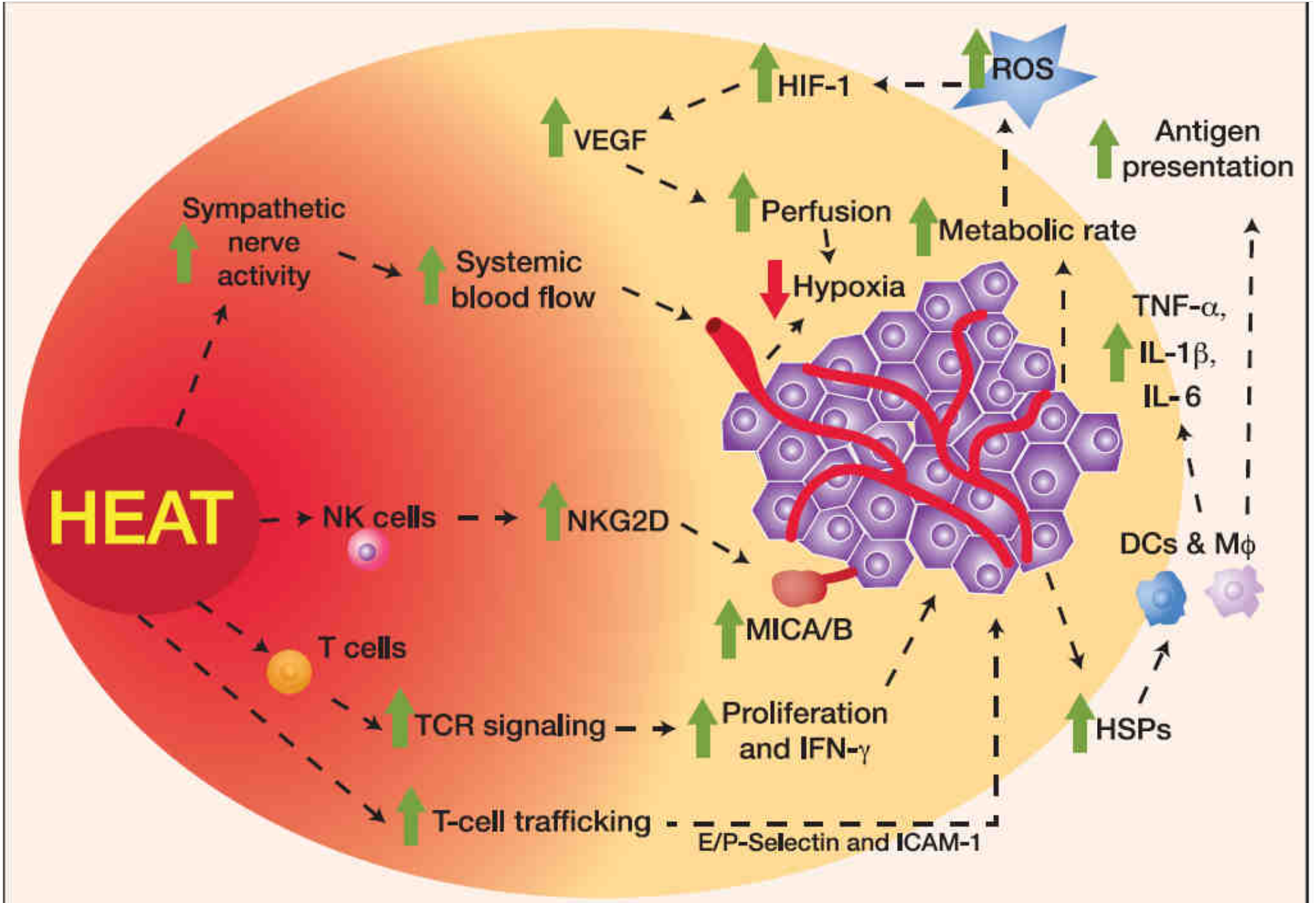
Doppelcharakter der Hitzeschock-Proteine (HSP)

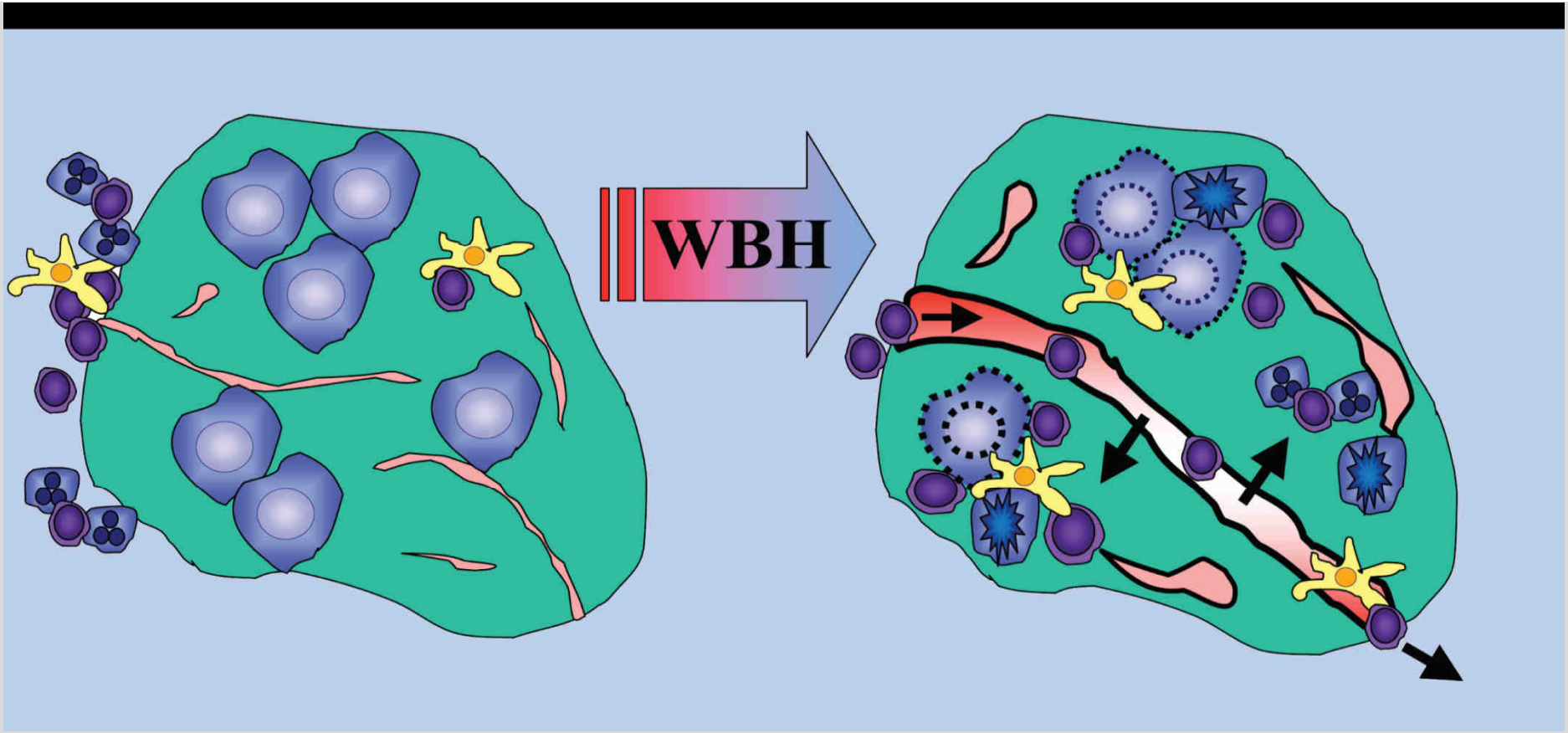


in der Zelle: Thermotoleranz

außerhalb der Zelle: immunaktivierendes „danger signal“

Gaipl (2011)





Synergistic effect of whole body hyperthermia (WBH) in antitumor immune response, by:

(1) Increased access of immune cells to the tumor bed through improved perfusion of compressed blood vessels facilitating immune cell entry and exit to draining lymph nodes, and increased function and expression of adhesion molecules regulating lymphocyte homing and trafficking to the tumor microenvironment.

(2) Increased tumor cell killing through immune sensitization of tumor cells and enhanced immune effector activity by increased expression of heat stress-induced immune cell recognition targets on tumor cells (HSP70) and increased immune cell maturation, activation, and cytotoxic activity.

Int. J. Hyperthermia, September 2010; 26(6): 565–576

informa
healthcare

Fever-range whole body thermotherapy combined with oxaliplatin: A curative regimen in a pre-clinical breast cancer model

R. WANDA ROWE[1], FREDERICK R. STREBEL[1], JESSE M. PROETT[1], WANLENG DENG[1], DIANA CHAN[1], GUANGAN HE[2], ZAHID SIDDIK[2], & JOAN M. C. BULL[1]

[1]*University of Texas Medical School, Division of Oncology, Houston, Texas, and* [2]*M.D. Anderson Cancer, Department of Experimental Therapeutics, Houston, Texas, USA*

(Received 28 February 2010; Revised 28 March 2010; Accepted 1 April 2010)

Abstract

Purpose: Studies were conducted to test whether fever-range whole body thermal therapy would boost the efficacy of oxaliplatin chemotherapy without substantial toxicity.

Materials and methods: The effect of mild heat (40°C) on oxaliplatin cytotoxicity, cellular uptake, and platinum-DNA adduct formation was studied in vitro using the MTLn3 tumour cell line. In vivo oxaliplatin was administered at various doses and times before, during and after fever-range thermal therapy (6 h at 40°C) to rats bearing an MTLn3 mammary adenocarcinoma. Tumour growth, survival, and toxicity were measured to determine treatment outcome.

Results: Heating halved the oxaliplatin IC-50 dose for MTLn3 cells. Cellular uptake of platinum and platinum adducts increased by 34% and 36%, respectively, with heat. In vivo, 50% of all rats given 10 mg/kg oxaliplatin 24 h before thermal therapy were completely immunologically cured, while a further 11% regressed their primary tumour but ultimately succumbed to metastases, and 17% experienced a limited response with increased survival. The curative response occurred only in a narrow range of doses, with most cures at 10 mg/kg. Thermochemotherapy-treated, but uncured, animals had delayed incidence and slowed growth of metastases. Anti-tumour efficacy was greatest, and toxicity was least, when oxaliplatin was administered 12 or 24 h before fever-range whole body thermal therapy.

Conclusions: When properly dosed and scheduled, oxaliplatin thermochemotherapy achieved permanent eradication of all primary and metastatic tumours in 50% of animals, seemingly through an immune response. Successful clinical translation of this protocol would yield hitherto unseen cures and substantial improvement in quality of life.

Keywords: *breast cancer, cell death, hyperthermia, immune stimulation, low dose chemotherapy, oxaliplation, schedule, thermal therapy, thermochemotherapy, tumour cure*

FEVER-RANGE WHOLE-BODY THERMAL THERAPY ENHANCEMENT OF OXALIPLATIN EFFICACY *IN VIVO* IS SCHEDULE-DEPENDENT

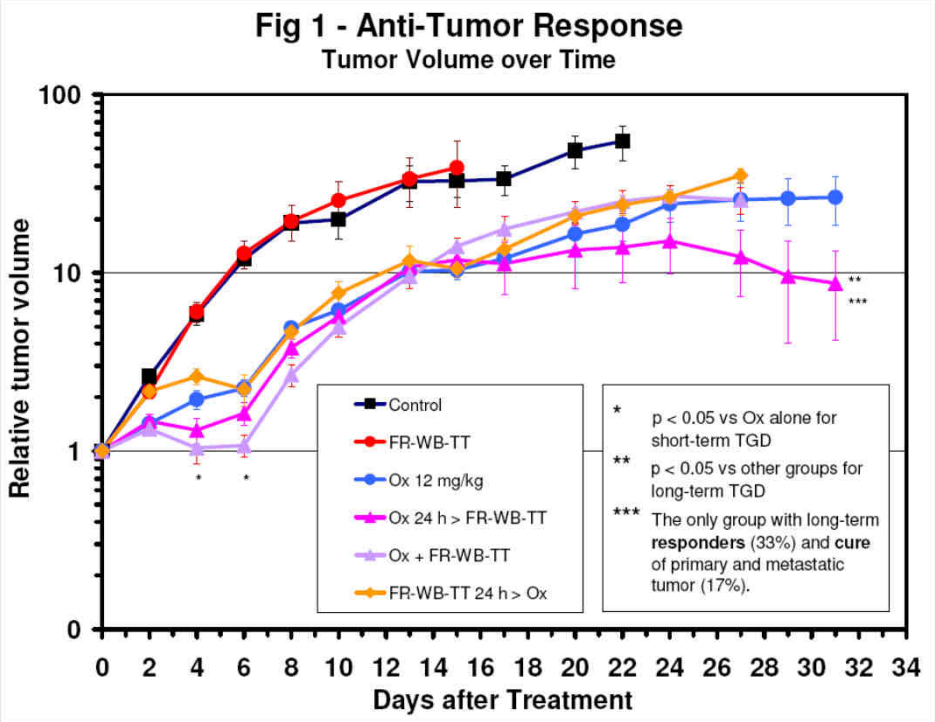
- **Frederick R. Strebel, Jesse M. Proett, R. Wanda Rowe, Wanleng Deng, and Joan M.C. Bull**
- ***Division of Oncology, University of Texas Medical School, Houston, TX***

Anti-tumor Response:

Ox-induced tumor growth delay was enhanced by combined Ox + FR-WB-TT for all sequencing schedules tested, compared to controls (Fig 1).

An early decrease in mean RTV, followed by tumor re-growth occurred with Ox before, during, and after FR-WB-TT (TT).

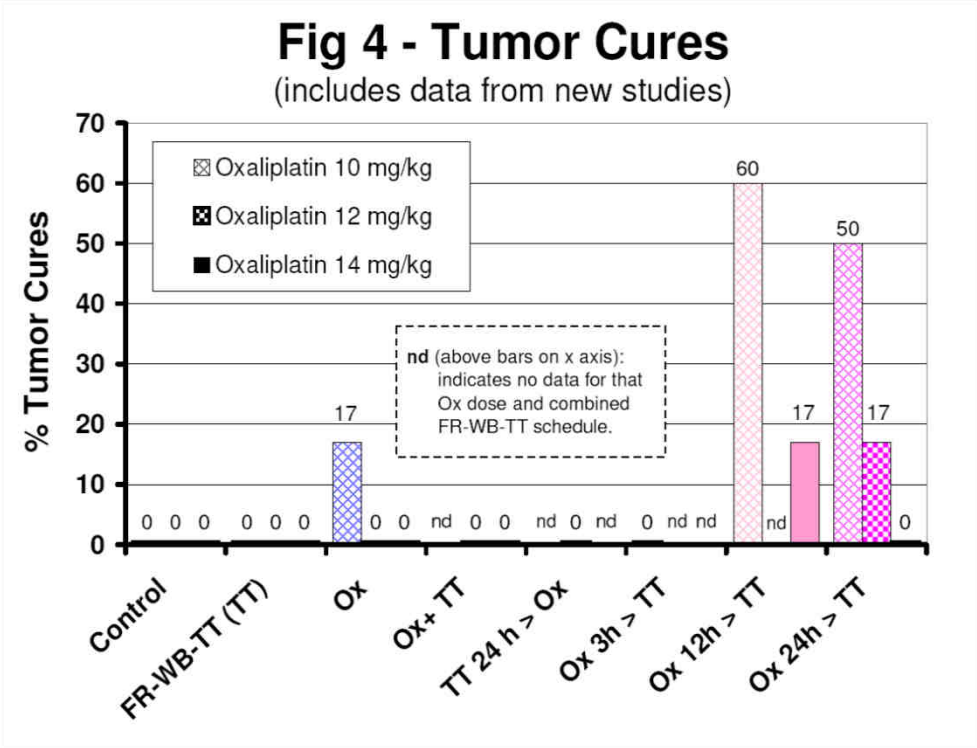
Ox before FR-WB-TT additionally had a late response with mean RTV decreasing after day 24, resulting in the only tumor cure.



Tumor cure results of Oxaliplatin given **before** FR-WB-TT

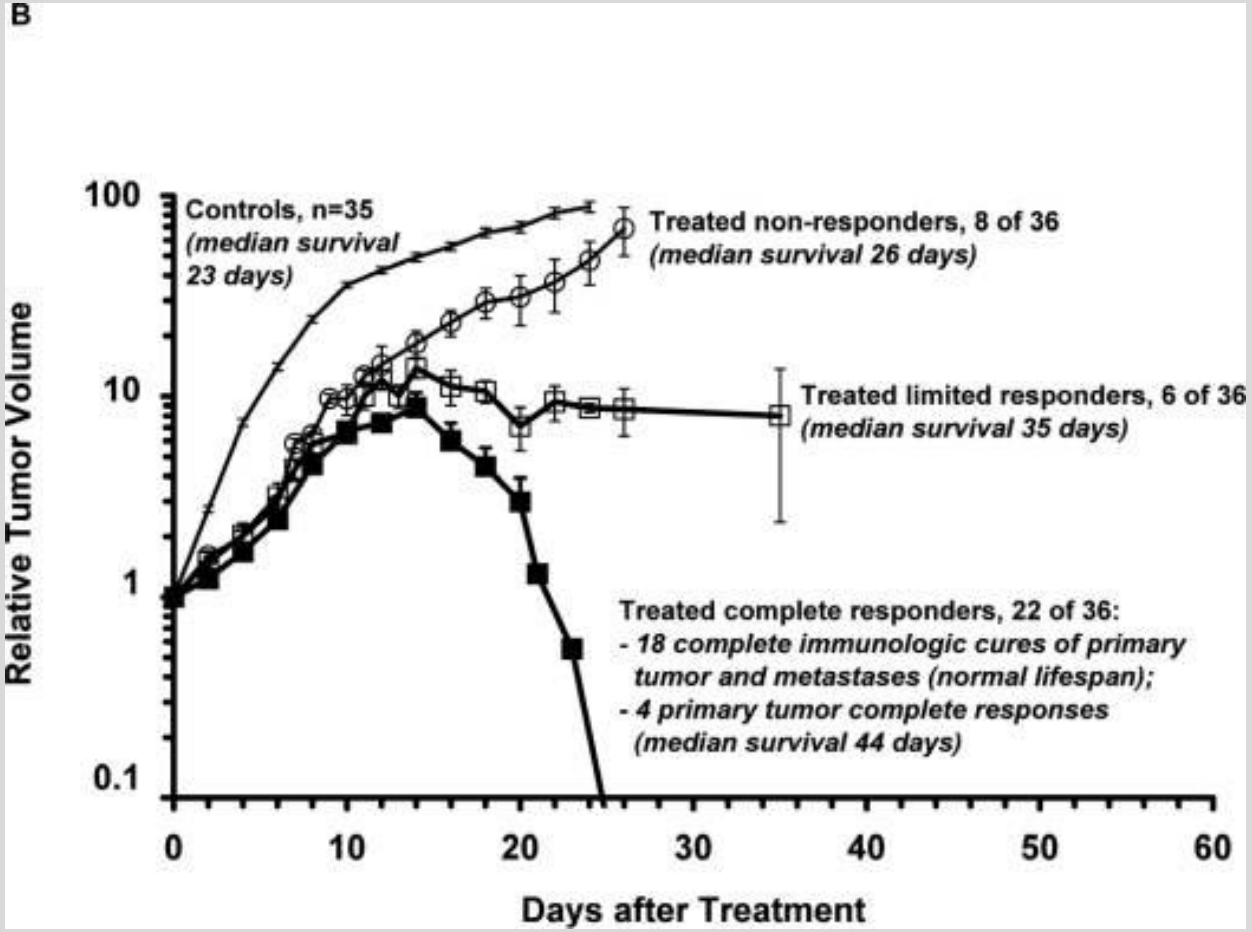
Reduced dose of Oxaliplatin (**10 mg/kg BW**) given **12 h** or **24 h before** FR-WB-TT

- ➢early anti-tumor response was reduced
- ➢long-term tumor control and eventual tumor **cures increased** from 17% to **60%** or **50%**
- ➢**Rats** that were **cured** and **tumor free** for 90 days or more
- ➢**completely rejected tumor re-challenge** with MTLn3 tumor cells



➢FR-WB-TT combined with sub-MTD Oxaliplatin can achieve lasting, immunological, cures in a model of advanced breast cancer.

➢Cures are accompanied by increased $CD8^+$ cell proliferation and activation; these properties may be predictive of thermo-chemotherapy outcome.



Oncoimmunology. 2014 Jan 1;3(1):e27878. Epub 2014 Mar 1.

Trial Watch: Chemotherapy with immunogenic cell death inducers.

Vacchelli E[1], Aranda F[1], Eggermont A[2], Galon J[3], Sautès-Fridman C[4], Cremer I[4], Zitvogel L[5], Kroemer G[6], Galluzzi L[7].

Author information

Abstract

Accumulating evidence suggests that the clinical efficacy of selected anticancer drugs, including conventional chemotherapeutics as well as targeted anticancer agents, originates (at least in part) from their ability to elicit a novel or reinstate a pre-existing tumor-specific immune response. One of the mechanisms whereby chemotherapy can stimulate the immune system to recognize and destroy malignant cells is commonly known as immunogenic cell death (ICD). Cancer cells succumbing to ICD are de facto converted into an anticancer vaccine and as such elicit an adaptive immune response. Several common chemotherapeutics share the ability of triggering ICD, as demonstrated in vaccination experiments relying on immunocompetent mice and syngeneic cancer cells. A large number of ongoing clinical trials involve such ICD inducers, often (but not always) as they are part of the gold standard therapeutic approach against specific neoplasms. In this Trial Watch, we summarize the latest advances on the use of cyclophosphamide, doxorubicin, epirubicin, oxaliplatin, and mitoxantrone in cancer patients, discussing high-impact studies that have been published during the last 13 months as well as clinical trials that have been initiated in the same period to assess the antineoplastic profile of these immunogenic drugs as off-label therapeutic interventions.

KEYWORDS: ATP, HMGB1, autophagy, calreticulin, dendritic cells, epothilone B

PMID: 24800173 [PubMed] PMCID: PMC4008470 [Available on 2015/1/1]

Proposed mechanism of action:

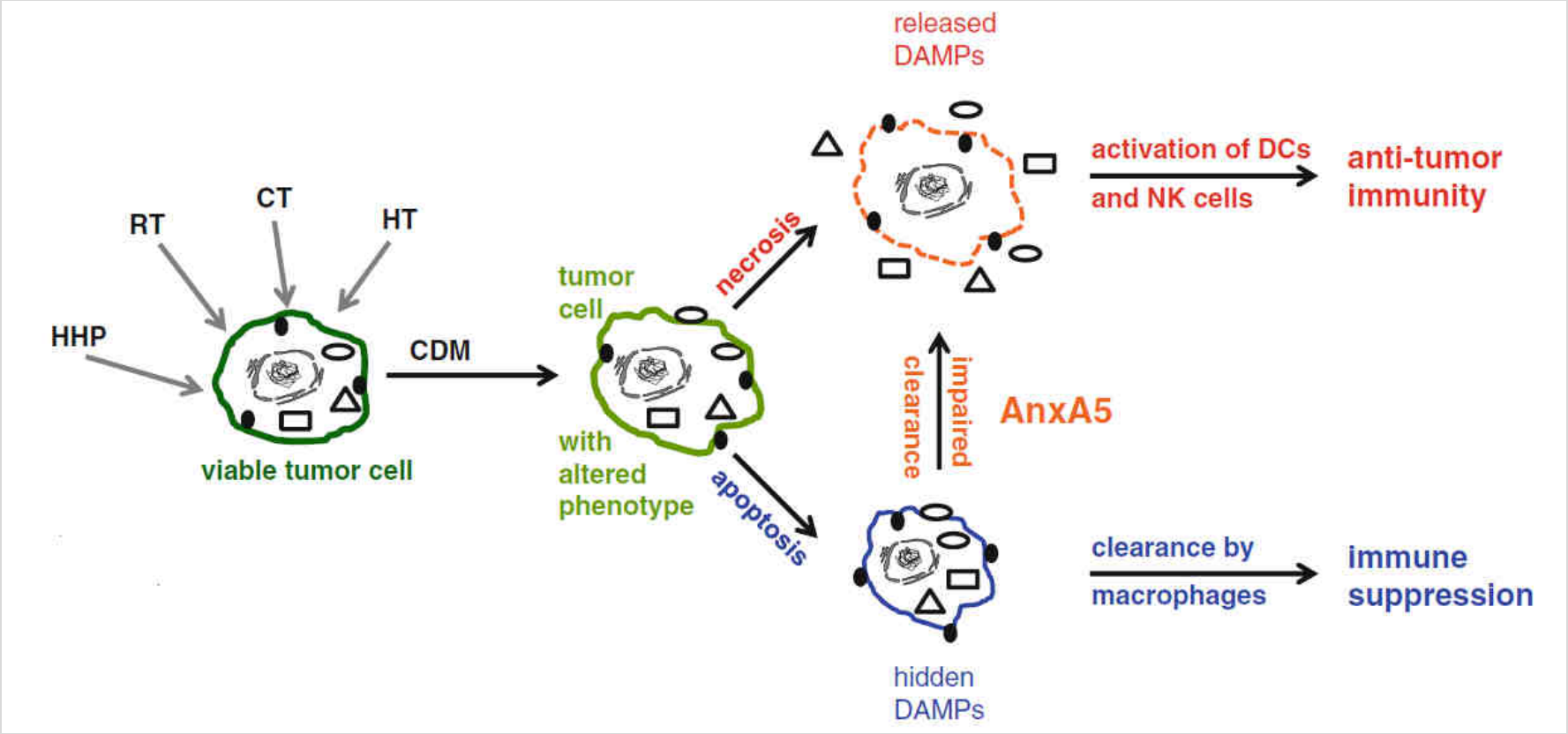
ICD – Immunogenic Cell Death induced by chemotherapy

A series of immunogenic signals delivered by tumor cells undergoing ICD stimulates DCs to take up antigens from dying tumor cells.

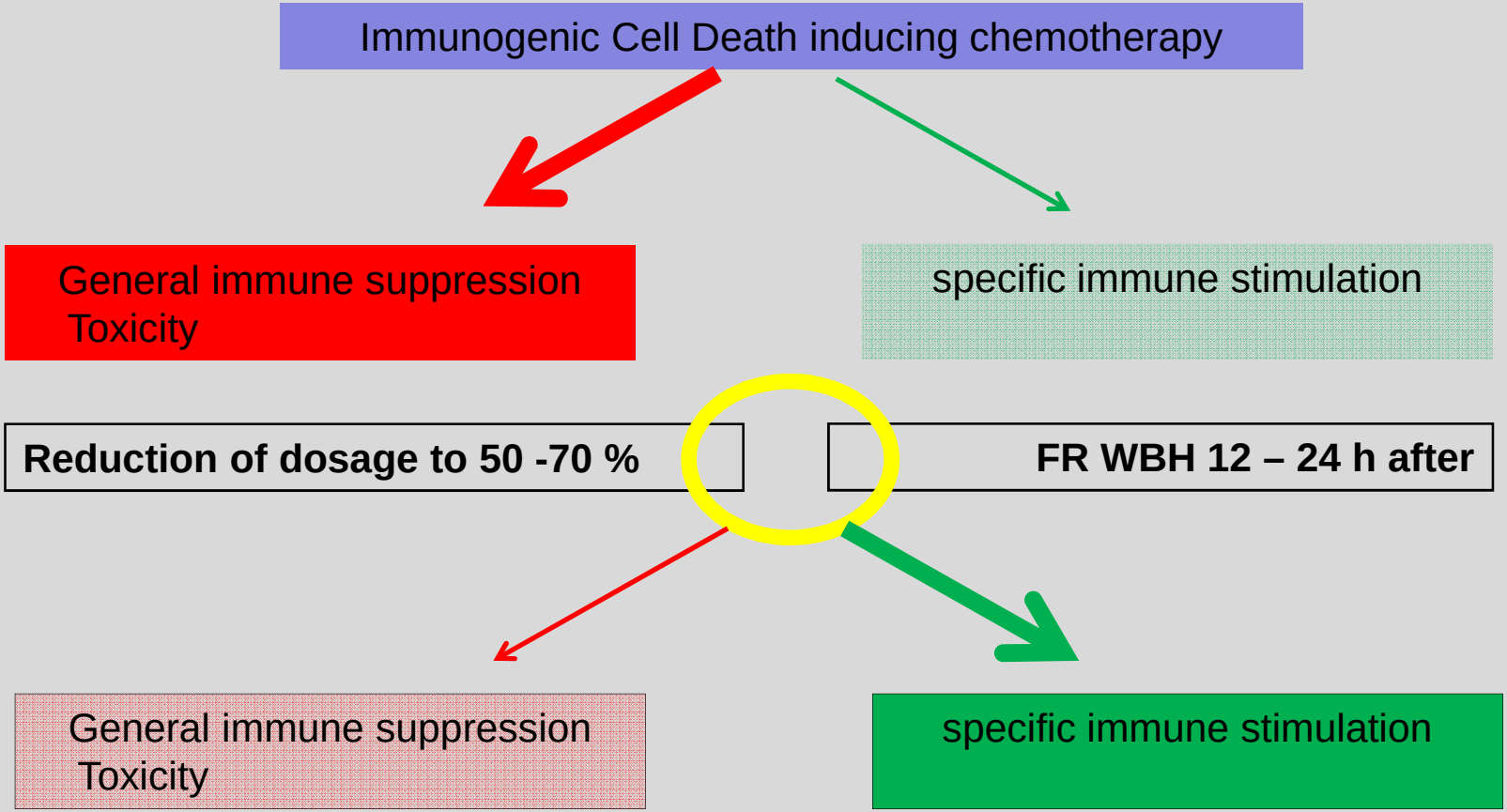
“Cancer cells succumbing to ICD are de facto converted into an anticancer vaccine and as such elicit an adaptive immune response.”

But:

This specific immune effect is considerably counteracted by the general immune-suppressive effect of chemotherapy.


RT
CT
HT
HHP
viable tumor cell
CDM
tumor cell
with altered phenotype
necrosis
apoptosis
released DAMPs
hidden DAMPs
activation of DCs and NK cells
anti-tumor immunity
impaired clearance
AnxA5
clearance by macrophages
immune suppression

Gaipl (2011)


Immunogenic Cell Death inducing chemotherapy
General immune suppression
Toxicity
specific immune stimulation
Reduction of dosage to 50 -70 %
FR WBH 12 – 24 h after
General immune suppression
Toxicity
specific immune stimulation

Immunogenic cell death inducing radiotherapy

Cancer Immunol Immunother
DOI 10.1007/s00262-013-1474-y

FOCUSSED RESEARCH REVIEW

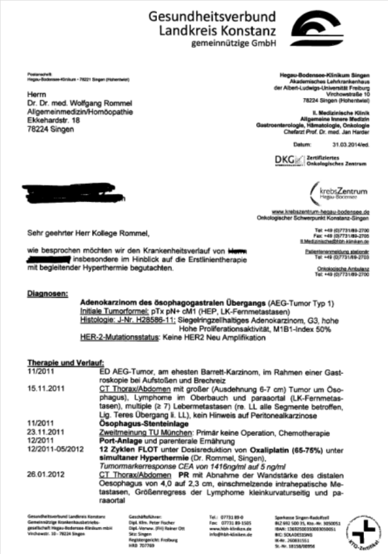
Antitumor immune responses induced by ionizing irradiation and further immune stimulation

Benjamin Frey · Yvonne Rubner · Lorenz Kulzer · Nina Werthmöller · Eva-Maria Weiss · Rainer Fietkau · Udo S. Gaipl

ICD inducing chemotherapeutics as to Kroemer / Zitvogel:

- Cyclophosphamide
- Doxorubicin
- Epirubicin
- Mitoxantrone
- Oxaliplatin → *pre-clinical evidence with FR WBH*

Clinical research and experiences



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Gastroenterologie, Hämatologie, Onkologie
Chefarzt Prof. Dr. med. Jan Harder

Datum: 31.03.2014/ed.

DKG Zertifiziertes Onkologisches Zentrum

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Herrn
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Allgemeinmedizin/Homöopathie
Ekkehardstr. 18
78224 Singen

[redacted]

Sehr geehrter Herr Kollege Rommel,

wie besprochen möchten wir den Krankenheitsverlauf von [redacted] insbesondere im Hinblick auf die Erstlinientherapie mit begleitender Hyperthermie begutachten.

Diagnosen:

Adenokarzinom des ösophagogastralen Übergangs (AEG-Tumor Typ 1)
Initiale Tumorformel: pTx pN+ cM1 (HEP, LK-Fernmetastasen)
Histologie: J-Nr. H28586-11: Siegelringzellhaltiges Adenokarzinom, G3, hohe Hohe Proliferationsaktivität, M1B1-Index 50%
HER-2-Mutationsstatus: Keine HER2 Neu Amplifikation

Therapie und Verlauf:

11/2011	ED AEG-Tumor, am ehesten Barrett-Karzinom, im Rahmen einer Gastroskopie bei Aufstoßen und Brechreiz
15.11.2011	CT Thorax/Abdomen mit großer (Ausdehnung 6-7 cm) Tumor um Ösophagus), Lymphome im Oberbauch und paraaortal (LK-Fernmetastasen), multiple (≥ 7) Lebermetastasen (re. LL alle Segmente betroffen, Lig. Teres Übergang li. LL), kein Hinweis auf Peritonealkarzinose
11/2011	**Ösophagus-Stenteinlage**
23.11.2011	Zweitmeinung TU München: Primär keine Operation, Chemotherapie
12/2011	**Port-Anlage** und parenterale Ernährung
12/2011-05/2012	**12 Zyklen FLOT** unter Dosisreduktion von **Oxaliplatin (65-75%)** unter **simultaner Hyperthermie** (Dr. Rommel, Singen), *Tumormarkerresponse CEA von 1416ng/ml auf 5 ng/ml*
26.01.2012	CT Thorax/Abdomen **PR** mit Abnahme der Wandstärke des distalen Oesophagus von 4,0 auf 2,3 cm, einschmelzende intrahepatische Metastasen, Größenregress der Lymphome kleinkurvaturseitig und paraaortal

Male, 34 years
Oesophagus-CA Type AEG I,
Primary tumour Ø 6-7cm
Distant lymphnode metastasis
Large liver metastasis
Inoperable

→ palliative chemotherapy

12 cycles FLOT (5-FU, Oxaliplatin, Docetaxel)
Oxaliplatin reduced to 65-75%
1 day after chemotherapy FR WBH (3hr > 39°C)

CEA: 1416 ng/ml → 5 ng/ml
PR (8 months), best Quality of Life

Oxaliplatin-related side effect (polyneuropathic) did not occur till the end of all scheduled cycles.
Nevertheless the protocol was changed to Folfiri after the expiry of the normal MTD of Ox.

EFFECT ↗
SIDE EFFECT ↘

Same clinc:

- 1 large CCC, inoperable
- 1 stomach cancer with peritoneal metastasis, inoperable
- 1 metastatic rectal cancer („forth line therapy“)

All of them much better response than expected…

Suggested therapy protocol 1

Oesophagus / Stomach / Colon – immunogenic cell death inducing chemotherapy

FR WBH (2-3hr > 39°C) 1 day after chemo (Ox 55 – 70%)

→ Anti-tumor effect by combination of antitumour cytotoxicity and immune response

Suggested therapy protocol 2

all tumours

FR WBH (1-3hr > 39°C) in the chemo break

→ Immune recovery; stabilization; decrease of side-effects (fatigue, polyneuropathy...)

Suggested therapy protocol 3

Peripheral tumours (e.g. head&neck)

FR WBH (1,5 - 2hr > 39°C) 1 day before radiotherapy resp. parallel to radiotherapy

→ Increase of tumour oxygenation, decrease of IFP

Suggested therapy protocol 4

all tumours after curative treatment

FR WBH (1 - 2hr > 39°C) asap after surgery (ca. 3 weeks),

either 6-10 trmts. 1-2x/week or 10-x treatm. 1x/month or 1 day after adjuvant chemo

→ Decrease of risk of recurrence by stimulation of anti-tumour immune response

Oncological Studies at Universities

Phase I/II studies at Roswell Park Cancer Institute Buffalo, E Repasky, W Kraybill

Phase 1- Study of Fever-Range Whole-Body Hyperthermia in Patients with Advanced Solid Tumours

⇨ Int J Hyperthermia, 2002,VOL.18,NO.3

Phase 1- Study of Doxil with Long Term Low Level WBH

⇨ Abstract STM 2007

INT. J. HYPERTHERMIA, 2002, VOL. 18, NO. 3, 253–266

A phase I study of fever-range whole body hyperthermia (FR-WBH) in patients with advanced solid tumours: correlation with mouse models

W. G. KRAYBILL†*, T. OLENKI¶, S. S. EVANS‡, J. R. OSTBERG‡, K. A. O'LEARY§, J. F. GIBBS† and E. A. REPASKY‡

† Division of Surgical Oncology
‡ Department of Immunology
§ Department of Anesthesiology and Pain Medicine, Roswell Park Cancer Institute, Buffalo, NY 14263, USA
¶ Department of Surgery, The Taussig Cancer Center, Cleveland Clinic Foundation, Cleveland, OH 44102, USA

(*Received 7 May 2001; revised 19 September 2001; accepted 8 November 2001*)

Various studies in animal tumour models have revealed the potential of fever-range whole body hyperthermia (FR-WBH) to be used in cancer therapy. To determine the safety of FR-WBH treatment in the clinic, patients with advanced solid tumours were heated in the out-

Oncological Studies at Universities

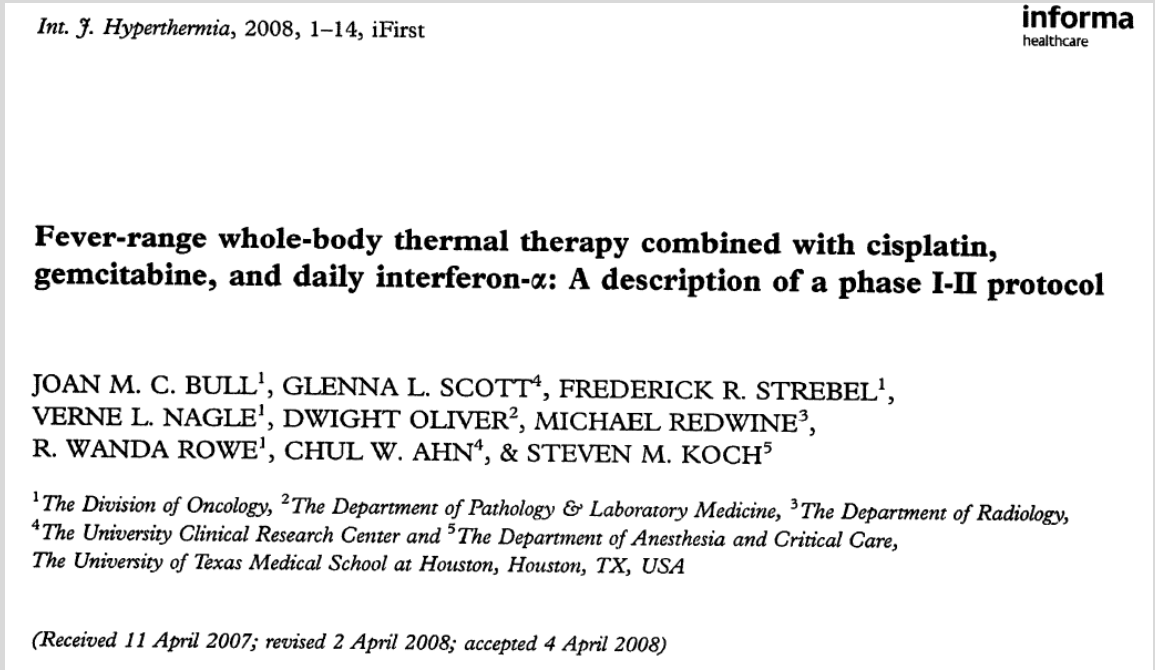
Phase I/II studies at Univ. of Texas, Medical School at Houston, JM Bull

FR-WBH + Cisplatin (CIS) + Gemcitabine (GEM) + Metronomic, Low-Dose Interferon-alpha

CIS 24h before FR WBH/GEM

Running protocol with various tumor entities, mainly pancreatic cancer

⇨ Int J Hyperthermia, Dec 2008



Int. J. Hyperthermia, 2008, 1–14, iFirst

informa
healthcare

Fever-range whole-body thermal therapy combined with cisplatin, gemcitabine, and daily interferon-α: A description of a phase I-II protocol

JOAN M. C. BULL[1], GLENNA L. SCOTT[4], FREDERICK R. STREBEL[1], VERNE L. NAGLE[1], DWIGHT OLIVER[2], MICHAEL REDWINE[3], R. WANDA ROWE[1], CHUL W. AHN[4], & STEVEN M. KOCH[5]

[1]*The Division of Oncology,* [2]*The Department of Pathology & Laboratory Medicine,* [3]*The Department of Radiology,* [4]*The University Clinical Research Center and* [5]*The Department of Anesthesia and Critical Care, The University of Texas Medical School at Houston, Houston, TX, USA*

(Received 11 April 2007; revised 2 April 2008; accepted 4 April 2008)

FR-WBH: Heckel Radiant Heat Device

Cisplatin 50-90 mg/m^2 (escalating dose)
Gemcitabine 60 mg/m^2 over 60 minutes

Interferon-α (IFN-α) 1 x 10^6 I.U. s.c. daily
GM-CSF (Leukine)

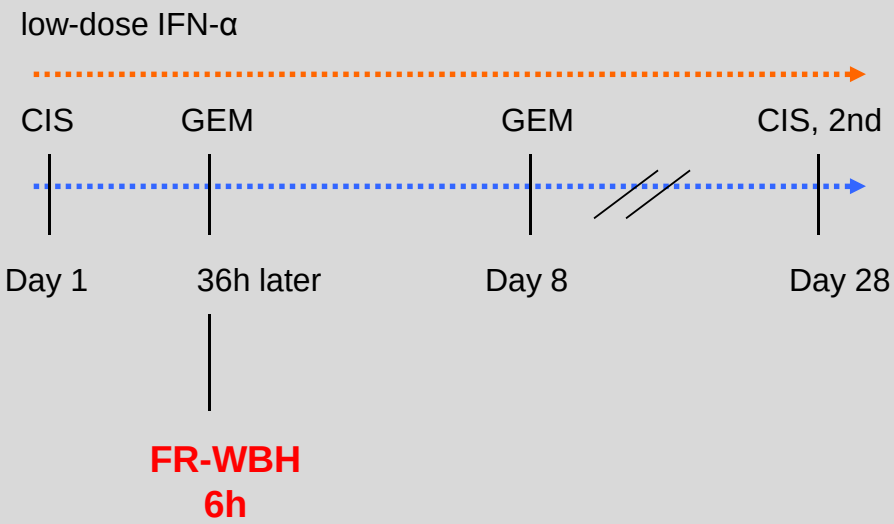


Table I. Tumor diagnosis of individual patients, age, sex, race, stage, number of treatment cycles, response, time to tumor progression (duration in months), and prior therapy

Diagnosis	Age	M/F	Race*	Stage	No. of cycles	Response	Duration (months)	Prior therapy
Pancreas	57	F	C	IV	3	PD	-	none
	62	F	C	III	3**	PR	9	gemcitabine, carboplatin
	74	F	AA	IV	2	PR	10	cisplatin/gemcitabine,
	64	M	C	III	2**	PR	6	cisplatin/gemcitabine
	61	M	C	IV	2	PR	7	radiation, gemcitabine, gene therapy
	70	F	C	IV	3	SD	4	gemcitabine
	55	M	AA	IV	3	PR	7	gemcitabine
Neuroendocrine	59	M	AA	III	2	PR	5	gemcitabine, carboplatin
	40	F	AA	IV	8	PR	10	cisplatin,/gemcitabine, irinotecan
	66	F	C	IV	4	CR	42	cisplatin/etoposide, paclitaxel
	56	M	AA	IV	1	PR	4	carboplatin/paclitaxel
	56	M	C	IV	8**	PR	15	cisplatin, leuprolide, bicalutamide
	63	M	C	III	5	PR	20	cisplatin, paclitaxel, taxotere, etoposide
Gastric	67	M	C	IV	1	PD	-	gemcitabine, capecitabine, 5-FU/irinotecan,
	64	M	C	IV	2	PR	5	Cisplatin/gemcitabine, doxorubicin
	47	F	H	IV	1	PD	-	doxorubicin/5-FU
	45	M	C	IV	2	PD	-	doxorubicin, etoposide
Lung	59	M	C	IV	2	PD	-	carboplatin/paclitaxel; vinorelbine, topotecan
	63	F	C	IV	1	PD	-	carboplatin/paclitaxel; topotecan
	50	M	C	IV	3	PR	8	radiation, carboplatin/paclitaxel, vinorelbine
Colon	51	M	C	IV	3	SD	4	5-FU/leucovorin; capecitabine/irinotecan
	46	M	AA	IV	3	PD	-	gemcitabine, carboplatin/5-FU/leucovorin, irinotecan
	71	F	C	IV	1	PD	-	radiation, oxaliplatin, capecitabine, 5-FU/levamsole
Breast	54	F	C	IV	2**	PR	5	gemcitabine, 5-FU/dox/cyclophsphamide, paclitaxel, vinorelbine, Doxil
	47	F	C	IV	2	PD	4	gemcitabine, 5-FU/doxorubicin/cyclophosphamide, paclitaxel, vinorelbine, capecitabine
Prostate	72	M	C	IV	1	PD	-	leuprolide, diethylstilbestrol, taxotere
	77	M	C	IV	1	SD	2	radiation, gemcitabine, capecitabine, leuprolide, genetherapy, diethylstilbesterol, iressa/docetaxel/thalidomide
Esophagus	73	M	C	IV	1	PD	-	cisplatin/5-FU
	56	M	C	IV	3	PR	5	radiation, irinotecan,
AUP*	66	F	C	IV	1	PD	-	cisplatin/gemcitabine, doxorubicin/cyclophosphamide
	46	F	AA	IV	1	PD	-	carboplatin/paclitaxel, doxorubicin, Doxil
Sarcoma	26	F	C	IV	5	PR	14	gemcitabine, vinblastine, thalidomide, BCNU, mesna/doxarubicin/ifosfamide/dacarbazine
Liver	33	M	C	IV	3	SD	5	cisplatin/gemcitabine, capecitabine/doxorubicin,
Hear & Neck	47	M	C	III	2**	SD	3	cisplatin/5-FU
Kidney	71	M	C	IV	3	SD	5	gemcitabine, paclitaxel
Bladder	57	M	H	IV	2	SD	4	cisplatin, interferon-alpha
Mesothelioma	78	M	C	IV	2	PD	-	cisplatin/paclitaxel, progesterone

*C, Caucasian; AA, African American; H, Hispanic; **adenocarcinoma unknown primary; ***treatment terminated because of 9 week facility closure for flood damage.

Table I. Tumor diagnosis of individual patients, age, sex, race, stage, number of treatment

Diagnosis	Age	M/F	Race*	Stage	No. of cycles	Response	Duration (months)
Pancreas	57	F	C	IV	3	PD	-
	62	F	C	III	3**	PR	9
	74	F	AA	IV	2	PR	10
	64	M	C	III	2**	PR	6
	61	M	C	IV	2	PR	7
	70	F	C	IV	3	SD	4
	55	M	AA	IV	3	PR	7
Neuroendocrine	59	M	AA	III	2	PR	5
	40	F	AA	IV	8	PR	10
	66	F	C	IV	4	CR	42
	56	M	AA	IV	1	PR	4
	56	M	C	IV	8**	PR	15
	63	M	C	III	5	PR	20
Gastric	67	M	C	IV	1	PD	-
	64	M	C	IV	2	PR	5
	47	F	H	IV	1	PD	-
	45	M	C	IV	2	PD	-
Lung	59	M	C	IV	2	PD	-
	63	F	C	IV	1	PD	-
	50	M	C	IV	3	PR	8
Colon	51	M	C	IV	3	SD	4
	46	M	AA	IV	3	PD	-
	71	F	C	IV	1	PD	-
Breast	54	F	C	IV	2**	PR	5
	47	F	C	IV	2	PD	4
Prostate	72	M	C	IV	1	PD	-
	77	M	C	IV	1	SD	2
Esophagus	73	M	C	IV	1	PD	-
	56	M	C	IV	3	PR	5
AUP*	66	F	C	IV	1	PD	-
	46	F	AA	IV	1	PD	-
Sarcoma	26	F	C	IV	5	PR	14
Liver	33	M	C	IV	3	SD	5
Hear & Neck	47	M	C	III	2**	SD	3
Kidney	71	M	C	IV	3	SD	5
Bladder	57	M	H	IV	2	SD	4
Mesothelioma	78	M	C	IV	2	PD	-

*C, Caucasian; AA, African American; H, Hispanic; **adenocarcinoma unknown primary; ***treatm

April 2008:

37 patients treated

(all of them in progress under standard therapy or no standard therapy available)

1 CR = 3%

15 PR = 40%

7 SD = 20%

14 PD = 37%

→ well-promising results

Oncological Studies at Universities

University Clinic of Vienna, I Sulyok, O Kimberger

Preoperative Whole-Body Hyperthermia in Patients Undergoing Major Abdominal Cancer Surgery: A Randomized Pilot Study

BJA Advance Access published July 31, 2012

British Journal of Anaesthesia Page 1 of 8
doi:10.1093/bja/aes248

BJA

Effect of preoperative fever-range whole-body hyperthermia on immunological markers in patients undergoing colorectal cancer surgery†

I. Sulyok[1], E. Fleischmann[1], A. Stift[2], G. Roth[1,3], D. Lebherz-Eichinger[1,3], D. Kasper[4], A. Spittler[5] and O. Kimberger[1]*

[1] Division of General Anaesthesia and Intensive Care, Department of Anaesthesiology, General Intensive Care and Pain Control, [2] Department of Surgery, [3] RAIC Laboratory 13C1, Department of Anaesthesiology, General Intensive Care and Pain Medicine, [4] Division of Pediatric Biochemistry and Analytics, Department of Pediatrics, and [5] Department of Surgery and Core Facility Flow Cytometry, Medical University of Vienna, Vienna, Austria

* Corresponding author. E-mail: study@kimberger.at

Editor's key points

- Therapeutic hyperthermia might have

Background. Previous studies have demonstrated beneficial immunological effects of fever-range whole-body hyperthermia (FR-WBH) as an adjunct to non-surgical cancer therapy. We conducted a study of preoperative FR-WBH in patients undergoing colorectal cancer surgery to evaluate perioperative, hyperthermia-induced immunomodulation.

Contents lists available at ScienceDirect

Immunology Letters

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

Fever-range whole-body heat treatment stimulates antigen-specific T-cell responses in humans

Yasunobu Kobayashi[a,*], Yusuke Ito[a], Valentina V. Ostapenko[a], Mayuko Sakai[b], Norimasa Matsushita[b], Kenichiro Imai[b], Koichi Shimizu[c], Atsushi Aruga[d], Keishi Tanigawa[a]

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[c] Shin-Itabashi Clinic, 4-4-4 Itabashi, Itabashi-ku, Tokyo 173-0004, Japan
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ARTICLE INFO

Article history:
Received 8 May 2014
Received in revised form 29 August 2014
Accepted 15 September 2014
Available online 26 September 2014

Keywords:
T cell
Hyperthermia
IFN-γ
IL-2

ABSTRACT

Increase in body temperature has been thought to play an important role in the regulation of immune responses, although its precise mechanisms are still under investigation. Here, we examined the effects of physiologically relevant thermal stress on the cytokine production from human peripheral T cells. Volunteers were heated using a whole-body hyperthermia device, the rectal temperature was maintained above 38.5 °C for more than 60 min, and peripheral blood mononuclear cells (PBMCs) were obtained before and after the treatment. When T cells were stimulated with anti-CD3/CD28 antibodies, marked increases in the production of interferon-γ (IFN-γ) and interleukin-2 were observed in PBMCs prepared immediately after and 24 h after the treatment. Similarly, enhanced production of IFN-γ in response to the tuberculin purified protein derivative or antigenic viral peptides was also observed immediately after and 24 h after the treatment. Fluorescence photo-bleaching analyses showed heat-induced increase of membrane fluidity in T cells, which probably enables them to induce rapid and efficient cluster formation of molecules involved in antigen recognition and signal transduction for T-cell stimulation. We concluded that physiologically relevant thermal stress could efficiently modify T-cell responsiveness to various stimuli, including enhanced responses to specific antigens.

Case Reports in Oncology

Case Rep Oncol 2012;5:212–215
DOI: 10.1159/000338617

Published online:
May 5, 2012

ISSN 1662–6575
www.karger.com/cro

Successful Treatment of Advanced Ovarian Cancer with Thermochemotherapy and Adjuvant Immune Therapy

R. Kleef S. Kekic N. Ludwig

Dr. Kleef – Hyperthermie, Stiftung Integrative Onkologie, Vienna, Austria

Dr. Stephan Wey, Lauf:

Since 2002 adjuvant treatment of 63 patients after curative therapy to minimize the risk of recurrences (1x/month, number of trmts: 3-14)

Evaluation 09/2012:

- 59 patients NED (No Evidence of Disease).

Body Warming in Improving Blood Flow and Oxygen Delivery to Tumors in Patients With Cancer

This study is currently recruiting participants. (see Contacts and Locations)

Verified April 2015 by Roswell Park Cancer Institute

Sponsor:
Roswell Park Cancer Institute

Collaborators:
National Cancer Institute (NCI)
Braun Foundation

Information provided by (Responsible Party):
Roswell Park Cancer Institute

ClinicalTrials.gov Identifier:
NCT01896778

First received: July 8, 2013
Last updated: April 23, 2015
Last verified: April 2015
History of Changes

Purpose

This randomized pilot clinical trial studies **body warming** in improving blood flow and oxygen delivery to tumors in patients with cancer. Heating tumor cells to several degrees above normal **body** temperature may kill tumor cells.

Condition	Intervention
Adult Primary Liver Cancer Breast Cancer Colon Cancer Head and Neck Cancer Kidney Tumor Lung Cancer Malignant Neoplasm Melanoma Ovarian Neoplasm Soft Tissue Sarcoma	Procedure: hyperthermia treatment Other: laboratory biomarker analysis

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Basic Science

Official Title: **Body Warming** to Alter [Thermo] Regulation and the Microenvironment [B-**WARM**] Therapy: A Pilot Study

Treatment of chronic inflammatory diseases by fever-range WBH

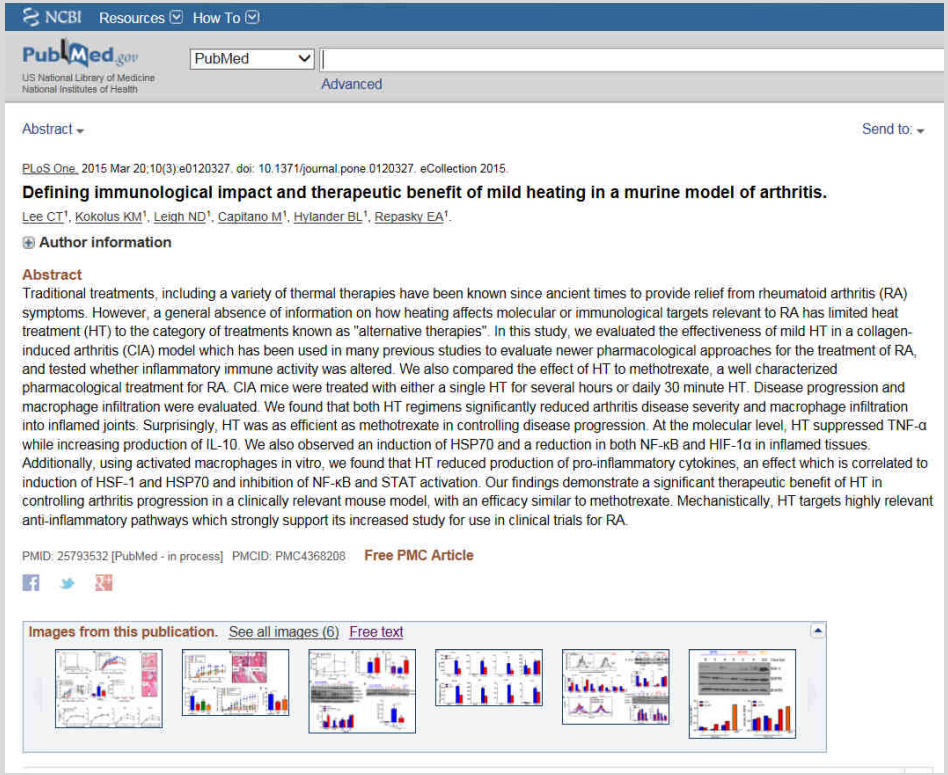
e.g. chronic sinu-bronchitis, sinu-broncho-pulmonal syndrom, endogene asthma bronchialis, colitis ulcerosa, osteomyelitis, neurodermitis, psoriasis, acne

Chronic inflammatory processes show a local dysregulation of the immune system. Because of the huge number of different inflammatory and immune moleculs it is difficult (or very expansive) to make a specific drug therapy.

The **regulative systemic effect of a WBH** provides an activating push to the immune system and stops the blockade of a too high or too low activitiy of the immune system.

Mild Hyperthermia for orthopedic diseases

- Arthrosis, Fibromyalgia, low-back pain,
- Morbus Bechterew
  - relaxation of deep-seated muscles
  - improved blood perfusion of bradytrophic tissue



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Abstract

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PLoS One. 2015 Mar 20;10(3):e0120327. doi: 10.1371/journal.pone.0120327. eCollection 2015.

Defining immunological impact and therapeutic benefit of mild heating in a murine model of arthritis.

Lee CT[1], Kokolus KM[1], Leigh ND[1], Capitano M[1], Hylander BL[1], Repasky EA[1].

Author information

Abstract

Traditional treatments, including a variety of thermal therapies have been known since ancient times to provide relief from rheumatoid arthritis (RA) symptoms. However, a general absence of information on how heating affects molecular or immunological targets relevant to RA has limited heat treatment (HT) to the category of treatments known as "alternative therapies". In this study, we evaluated the effectiveness of mild HT in a collagen-induced arthritis (CIA) model which has been used in many previous studies to evaluate newer pharmacological approaches for the treatment of RA, and tested whether inflammatory immune activity was altered. We also compared the effect of HT to methotrexate, a well characterized pharmacological treatment for RA. CIA mice were treated with either a single HT for several hours or daily 30 minute HT. Disease progression and macrophage infiltration were evaluated. We found that both HT regimens significantly reduced arthritis disease severity and macrophage infiltration into inflamed joints. Surprisingly, HT was as efficient as methotrexate in controlling disease progression. At the molecular level, HT suppressed TNF-α while increasing production of IL-10. We also observed an induction of HSP70 and a reduction in both NF-κB and HIF-1α in inflamed tissues. Additionally, using activated macrophages in vitro, we found that HT reduced production of pro-inflammatory cytokines, an effect which is correlated to induction of HSF-1 and HSP70 and inhibition of NF-κB and STAT activation. Our findings demonstrate a significant therapeutic benefit of HT in controlling arthritis progression in a clinically relevant mouse model, with an efficacy similar to methotrexate. Mechanistically, HT targets highly relevant anti-inflammatory pathways which strongly support its increased study for use in clinical trials for RA.

PMID: 25793532 [PubMed - in process] PMCID: PMC4368208 **Free PMC Article**

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WBH
6h, 2x/week or 30min, 5x/week:

- significantly reduced arthritis disease severity and macrophage infiltration into inflamed joints
- as efficient as methotrexate in controlling disease progression

- suppressed TNF-α while increasing production of IL-10
- induced HSP70
- reduced in both NF-κB and HIF-1α in inflamed tissues

Pilotstudy 6 AS patients and 6 healthy volunteers

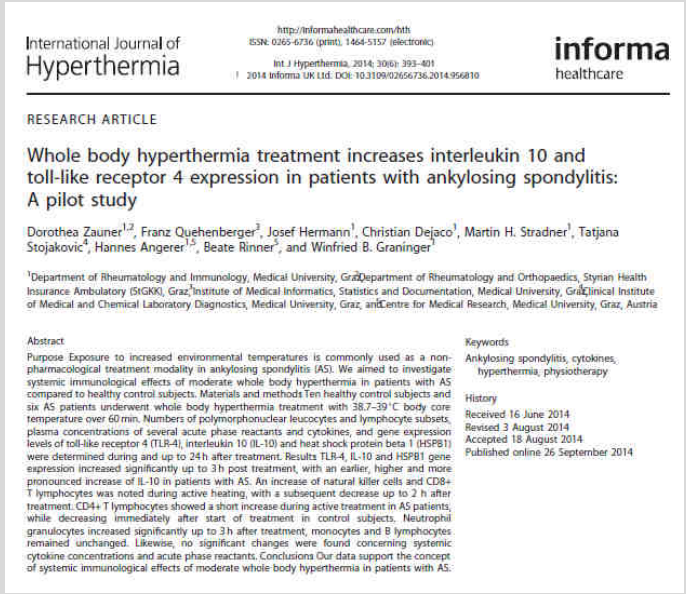
University of Graz, Austria, Dept. of Rheumatology
Zauner D et al, not yet published

1 single treatment
1h heating up to 39°C, 1h plateau
Blood samples before WBH, at 39°C, 1h, 2h, 3h, 24h after ?

Increase of neutrophile granulocytes
Decrease of T-Lymphocytes and NK-cells

No change of
CRP, Alpha-1-Antitrypsin, Haptoglobin, Transferrin, C3, C4
IFN-gamma, IL-12, TNF-alpha, sIL-2R, IL-6, IL-10, IL-1beta

Significant increase of IL-10, TLR4, HSPB1 mRNA



International Journal of Hyperthermia
http://informahealthcare.com/hth
ISSN: 0265-6736 (print), 1464-5157 (electronic)
Int J Hyperthermia, 2014; 30(6): 393–401
! 2014 Informa UK Ltd. DOI: 10.3109/02656736.2014.956810
informa healthcare

RESEARCH ARTICLE

Whole body hyperthermia treatment increases interleukin 10 and toll-like receptor 4 expression in patients with ankylosing spondylitis: A pilot study

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Abstract

Purpose Exposure to increased environmental temperatures is commonly used as a non-pharmacological treatment modality in ankylosing spondylitis (AS). We aimed to investigate systemic immunological effects of moderate whole body hyperthermia in patients with AS compared to healthy control subjects. Materials and methods Ten healthy control subjects and six AS patients underwent whole body hyperthermia treatment with 38.7–39 °C body core temperature over 60 min. Numbers of polymorphonuclear leucocytes and lymphocyte subsets, plasma concentrations of several acute phase reactants and cytokines, and gene expression levels of toll-like receptor 4 (TLR-4), interleukin 10 (IL-10) and heat shock protein beta 1 (HSPB1) were determined during and up to 24 h after treatment. Results TLR-4, IL-10 and HSPB1 gene expression increased significantly up to 3 h post treatment, with an earlier, higher and more pronounced increase of IL-10 in patients with AS. An increase of natural killer cells and CD8+ T lymphocytes was noted during active heating, with a subsequent decrease up to 2 h after treatment. CD4+ T lymphocytes showed a short increase during active treatment in AS patients, while decreasing immediately after start of treatment in control subjects. Neutrophil granulocytes increased significantly up to 3 h after treatment, monocytes and B lymphocytes remained unchanged. Likewise, no significant changes were found concerning systemic cytokine concentrations and acute phase reactants. Conclusions Our data support the concept of systemic immunological effects of moderate whole body hyperthermia in patients with AS.

Keywords
Ankylosing spondylitis, cytokines, hyperthermia, physiotherapy

History
Received 16 June 2014
Revised 3 August 2014
Accepted 18 August 2014
Published online 26 September 2014

Whole Body Hyperthermia and Major Depression (MDD)

This study is currently recruiting participants. (see Contacts and Locations)

Verified December 2014 by University of Arizona

Sponsor:
University of Arizona

Collaborators:
Dr. med. h.c. Erwin Braun Foundation
The Depressive and Bipolar Disorder Alternative Treatment Foundation
Brain & Behavior Research Foundation

Information provided by (Responsible Party):
University of Arizona

ClinicalTrials.gov Identifier:
NCT01625546

First received: June 19, 2012
Last updated: December 4, 2014
Last verified: December 2014
History of Changes

Purpose

Major depressive disorder (MDD) is predicted to be the second leading cause of disability worldwide by the year 2020. The economic burden of depression in the United States is significant: $83.1 billion in 2000 and increasing. Much of this burden comes from the high rate of sub-optimal treatment outcomes associated with the disorder. Indeed, only 50% of MDD patients recover in less than 12 weeks with adequate treatment, and up to 20% of patients will fail to adequately respond to all currently available interventions. Moreover, current treatments come at the cost of significant central nervous system (CNS) side effects, further highlighting the need for more effective treatments with fewer side effects. This study will compare temperature ranges from the investigators preliminary studies involving thermoafferent pathways resulting in antidepressant actions with lower temperature ranges not expected to activate these pathways as a control condition, with the goal to evaluate whether previous observations were related to the temperature range in question or can be achieved with other levels.

Condition	Intervention
Depressive Disorder, Major	Device: **Whole Body Hyperthermia** system

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Single Blind (Subject)
Primary Purpose: Treatment

Official Title: **Whole Body Hyperthermia** and Major Depression (MDD)

Sedation

FR-WBH short duration (1-3 hr > 39°C): if necessary

Diazepam (drops)

TCM ?

FR-WBH long duration (4-6 hr), extreme WBH: mandatory

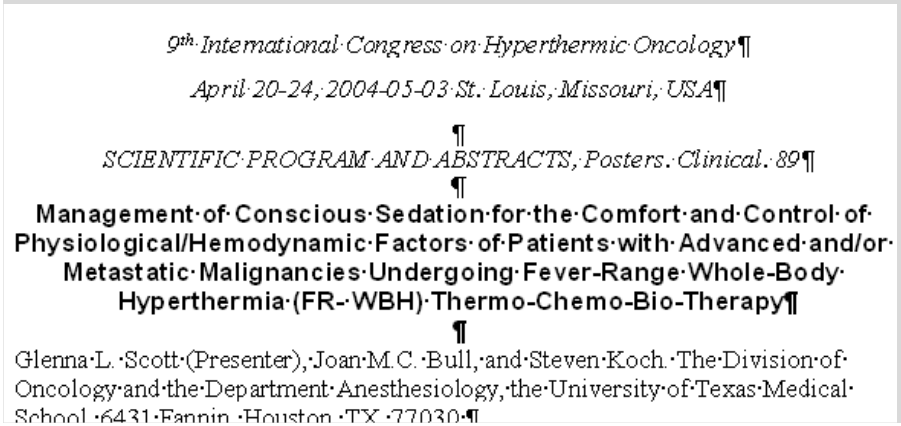
Applied drugs: Fentanyl, DHB, Propofol

Midazolam, Lorazepam

Promethazine, Pronabinol

3.000 – 5.000 ml solution (NaCl, Ringer lactate, glucose); preheated to 41°C

Detailed information on sedation of FR-WBH long-duration available in:



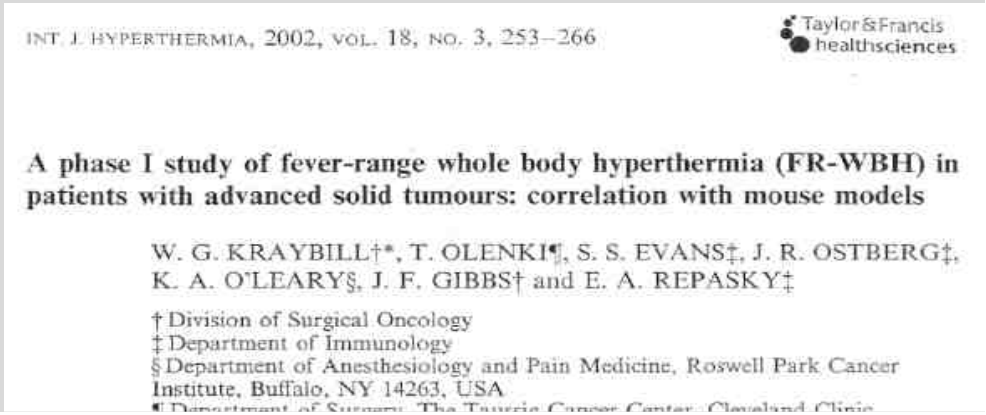
9th International Congress on Hyperthermic Oncology

April 20-24, 2004-05-03 St. Louis, Missouri, USA

SCIENTIFIC PROGRAM AND ABSTRACTS, Posters. Clinical. 89

Management of Conscious Sedation for the Comfort and Control of Physiological/Hemodynamic Factors of Patients with Advanced and/or Metastatic Malignancies Undergoing Fever-Range Whole-Body Hyperthermia (FR-WBH) Thermo-Chemo-Bio-Therapy

Glenna L. Scott (Presenter), Joan M.C. Bull, and Steven Koch. The Division of Oncology and the Department Anesthesiology, the University of Texas Medical School 6431 Fannin Houston TX 77030



INT. J. HYPERTHERMIA, 2002, VOL. 18, NO. 3, 253–266

Taylor & Francis healthsciences

A phase I study of fever-range whole body hyperthermia (FR-WBH) in patients with advanced solid tumours: correlation with mouse models

W. G. KRAYBILL†*, T. OLENKI¶, S. S. EVANS‡, J. R. OSTBERG‡, K. A. O'LEARY§, J. F. GIBBS† and E. A. REPASKY‡

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Main contra-indications for WBH above ca. 38°C

- cardiac insufficiency and severe irregularity
- severe cerebral circulatory deficiency, brain tumors, brain edemas *(spasmodic conditions occurring during oncological hyperthermia may be indicative of undiscovered cerebral metastases)*
- existing or impending thrombosis, anticoagulant medication
- acute infections
- advanced destructive inflammations
- erratically progressive diseases such as multiple sclerosis
- hormonal and metabolic crisis situations
- pronounced dehydration with disruptions in the balance of water and electrolytes, inability to perspire
- existing lymphedemas may be increased by vasodilatation caused by hyperthermia. A careful consideration of this risk as well as special medication is required.
- Gravity

Main side effects

relate primarily

a) to the strain on the central thermo-regulatory system, with an elevated actual temperature being applied to the body at its temperature setpoint of 37°C and

b) to the thermal load imposed on the areas of skin exposed to infrared radiation.

- unrest
- hyperventilation tetany
- herpes labialis
- Small burns caused by
  - neurological disorders with deficient thermosensitivity of the skin in the areas exposed to infrared radiation
  - heavy medicative sedation, analgesia or general anesthetic
  - disruption of sweat secretion
  - premedication with photo-sensitizing drugs

Thank you very much for your attention !

heckel

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