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VISIONARY HEALTHCARE, LIFELONG WELLBEING

CANCER CAN STRIKE EVERYONE



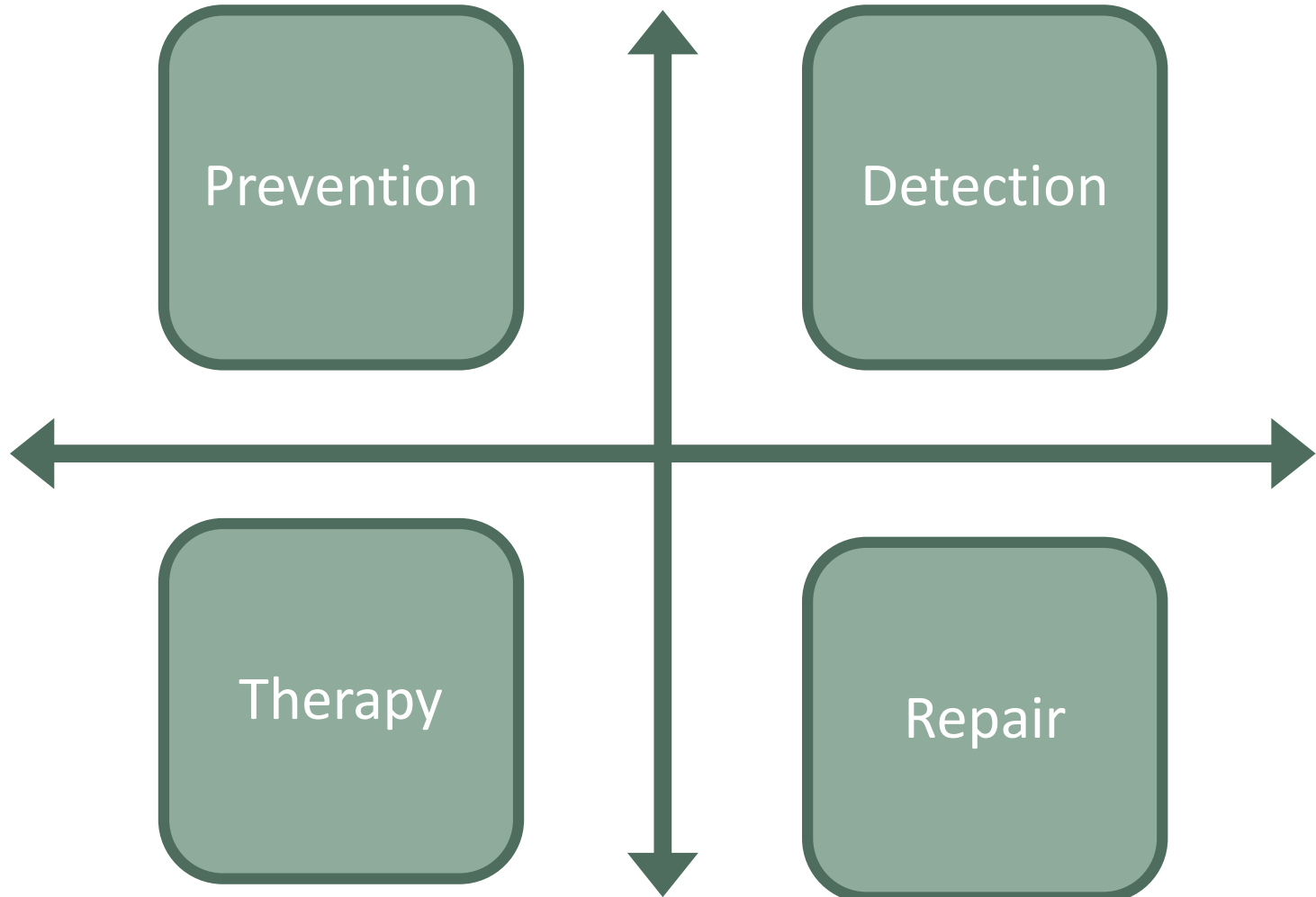


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MICC Miskawaan Individualised Cancer Concept





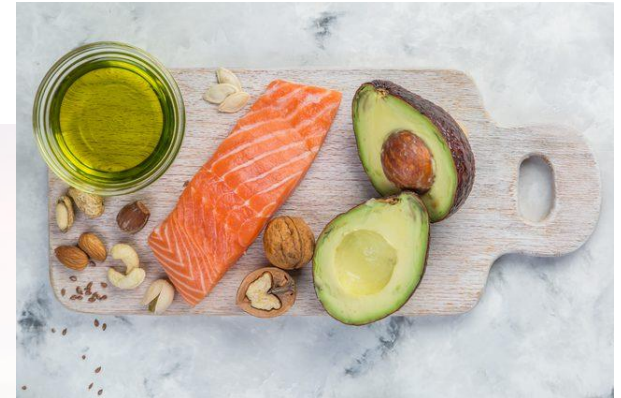
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Prevention

- Lifestyle: sports, smoking, alcohol
- Food: low carb , phytoprevention, microbiome, probiotics
- Genetics: Whole exome sequencing
- Heavy metal screening (hormone disruptors)
- Immune surveillance
- **SLEEP**





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Phytoprevention

natureOUTLOOK

CANCER PREVENTION

24 March 2011 / Vol 471 / Issue No. 7339



COVER ART:

Ask many people what they are afraid of, and cancer — the big C — will often top the list. Some forms of cancer have become easily treatable. But in many cases, by the time doctors deploy the weapons of surgery, chemotherapy or radiation, the cancer has already progressed past the point where medical intervention can cure the condition.

Many cancer specialists now contend that the best way to deal with cancer is to ensure it doesn't develop in the first place.

CONTENTS

- S2 **INTRODUCTION**
The prevention agenda
Addressing the research deficit
- S5 **CHEMOPREVENTION**
First line of defence
Using drugs to stop cancer in its tracks
- S8 **VACCINES**

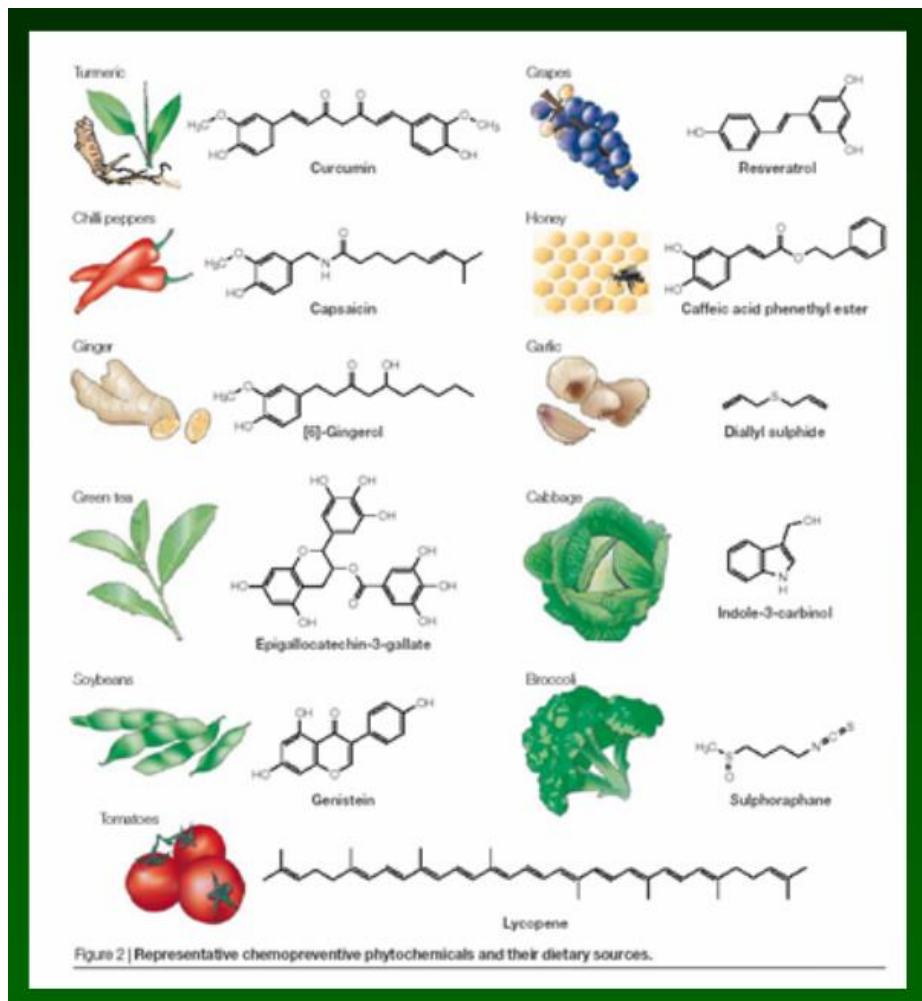


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Phytoprevention



Arch. Pharm. Chem. Life Sci. 2010, 9, 489–499

Review Article

Curcumin in Cancer Chemoprevention: Molecular Targets, Pharmacokinetics, Bioavailability, and Clinical Trials

Adeeb Shehzad, Fazli Wahid, and Young Sup Lee

“Sufficient data has been shown to advocate phase II and phase III clinical trials of curcumin for a variety of cancer conditions including multiple myeloma, pancreatic and colon cancer...”

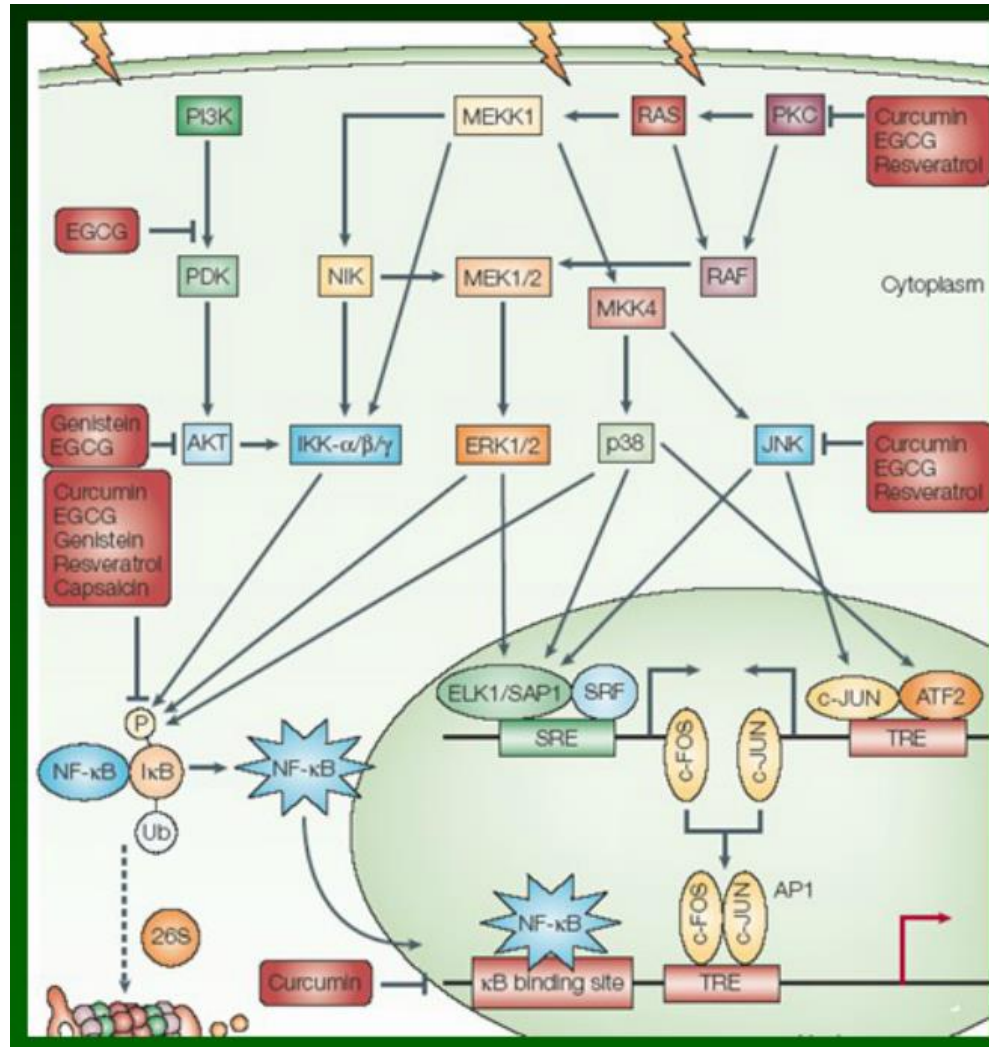


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Phytotherapy





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The Role of Probiotics

Gastroenterology 2017;152:1889–1900



Timely Use of Probiotics in Hospitalized Adults Prevents *Clostridium difficile* Infection: A Systematic Review With Meta-Regression Analysis

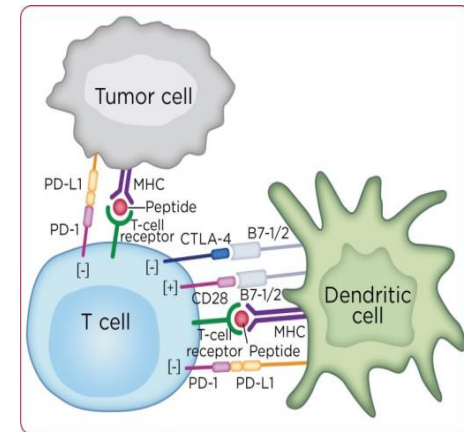
Nicole T. Shen,¹ Anna Maw,² Lyubov L. Tmanova,³ Alejandro Pino,⁴ Kayley Ancy,⁴ Carl V. Crawford,¹ Matthew S. Simon,^{5,6} and Arthur T. Evans⁵

“... the role of probiotics is clear

- in getting rid of mutagens,
- delaying the onset of tumors,
- alleviating the side effects of chemotherapy,
- pepping up chemotherapy,
- easing the postoperative complications,
- foiling remission and
- lifting the spirit of survivors.”

Patel, 2013

[Probiotics and Antimicrobial Proteins Volume 5, Issue 1 , pp 59-67](#)



Gopalakrishnan V, Spencer CN, Nezi L, et al. [Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients.](#)

Science. 2018; 359(6371):97-103. doi: 10.1126/science.aan4236.

Matson V, Fessler J, Bao R, et al. [The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients.](#) *Science*. 2018; 359(6371):104-8. doi: 10.1126/science.aao3290.



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Yesterday's Immune





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Immune Stimulation

- Mistletoe (different kinds after testing)
- Peptides (from thymus, spleen)
- Arabinoxylan
- Cimetidin



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NK cell function

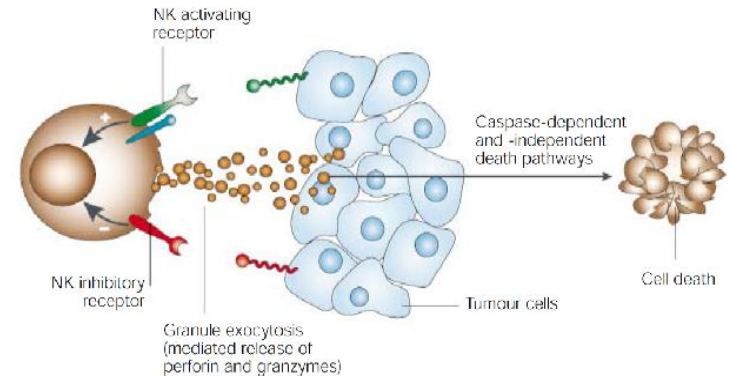
NK cells eliminate target cells by 2 major effector functions.

The direct cytotoxicity mechanism

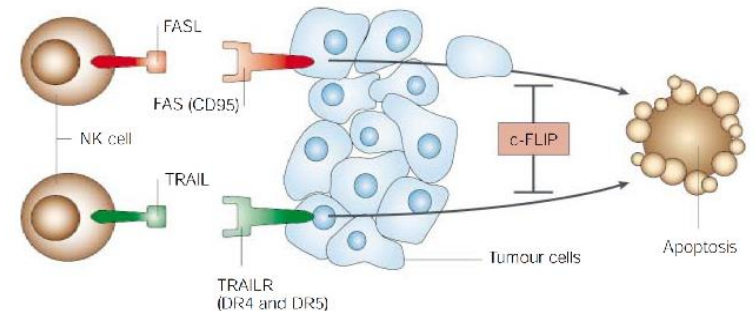
- Granule exocytosis pathway:
 - Perforin and Granzymes
- Death-receptor pathway : FasL / TRAIL
- ADCC : Antibody-Dependent
- Cellular Cytotoxicity
 - Cytokines secretion
- IFN-gamma, TNF- α , TNF- β , GM-CSF etc.

Mark J. Smyth et al, 2002

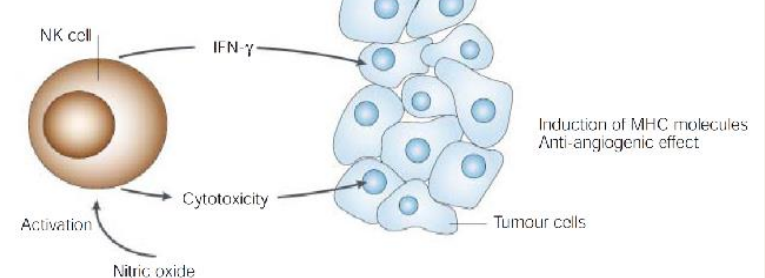
a Granule exocytosis pathway



b Death-receptor pathway



c IFN- γ , nitric oxide





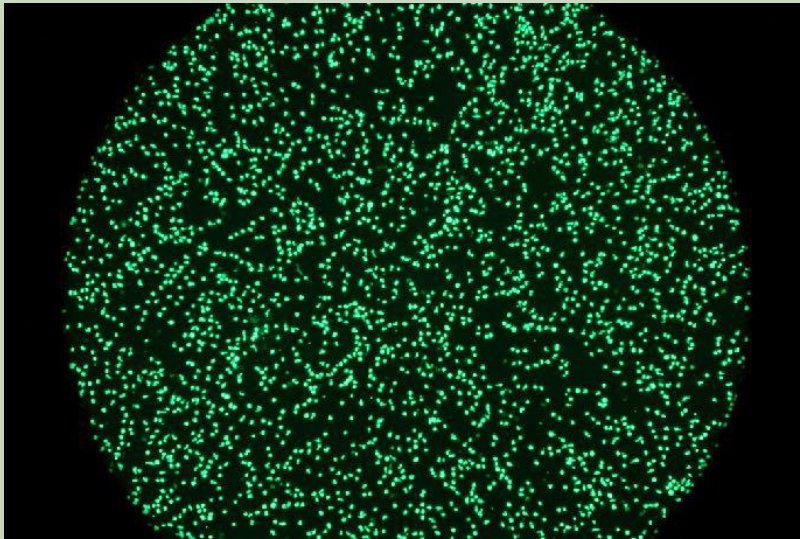
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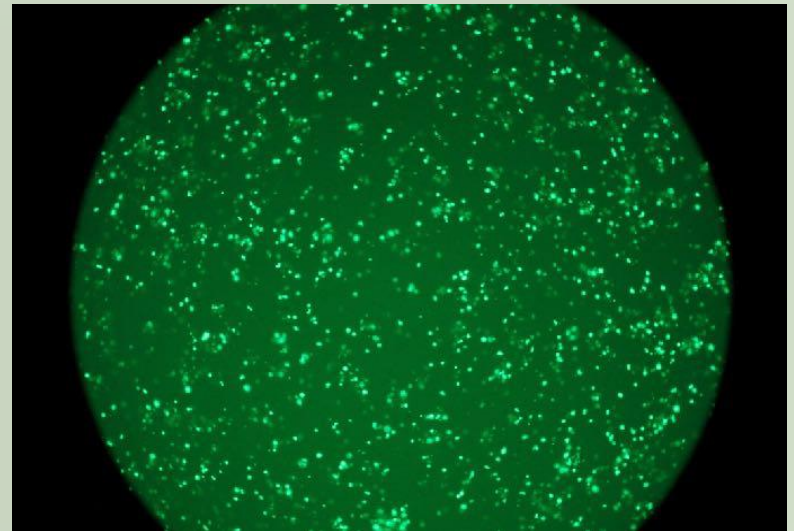
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NK Activity Test - WinCell

Before (0 hour)



After (4 hours)





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NK Activity Test - WinCell

Volker K. 45J.
Labor

02.2010
10.2010

NK-Zellfunktion

NK-SELECT®

NK-Check®

NK/Ctx: basal	12	19	% K562	> 20	
NK/Ctx: IL-2 stim	15	19	% K562	> 35	
NK-Zellen CD69 basal	17	14	% NK		
NK-Zellen CD 69 IL2	36	36	% NK		
MODULATOR 1	Iscucin Abiet				
NK-Zellen CD 69 Mod 1	14		% NK		
MODULATOR 2	Pini				
NK-Zellen CD 69 Mod 2	15		% NK		
MODULATOR 3	Populi				
NK-Zellen CD 69 Mod 3	15		% NK		
MODULATOR 4	MGN3				
NK-Zellen CD 69 Mod 4	12		% NK		
MODULATOR 5	Resveratrol				
NK-Zellen CD 69 Mod 5	13		% NK		
MODULATOR 6	Vitamin C				
NK-Zellen CD 69 Mod 6	17		% NK		
MODULATOR 7	Quercus				
NK-Zellen CD 69 Mod 7	16		% NK		
MODULATOR 8	Abnoba Visc				
NK-Zellen CD 69 Mod 8	16		% NK		
MODULATOR 9	Immuherbs				
NK-Zellen CD 69 Mod 9	16		% NK		
MODULATOR 10	Lektinol				
NK-Zellen CD 69 Mod 10	22		% NK		
MODULATOR 11	Iscador mali				
NK-Zellen CD 69 Mod 11	4		% NK		

NK-Zellfunktion

NK-SELECT®

NK-Check®

NK/Ctx: basal	46	20	% K562	> 20	
NK/Ctx: IL-2 stim	46	21	% K562	> 35	
NK-Zellen CD69 basal	22	7	% NK		
NK-Zellen CD 69 IL2	68	35	% NK		
MODULATOR 1	Lektinol	Immunpil			
NK-Zellen CD 69 Mod 1	25	15	% NK		
MODULATOR 2	Abnoba Mali	MGN3			
NK-Zellen CD 69 Mod 2	30	17	% NK		
MODULATOR 3	Iscucin Abietis	Mistel			
NK-Zellen CD 69 Mod 3	24	10	% NK		
MODULATOR 4	Abnoba Pini	Vitamin C			
NK-Zellen CD 69 Mod 4	30	6	% NK		
MODULATOR 5	Iscucin Populi				
NK-Zellen CD 69 Mod 5	34		% NK		
MODULATOR 6	Iscador ercus				
NK-Zellen CD 69 Mod 6	26		% NK		
MODULATOR 7	Abnoba Viscum				
NK-Zellen CD 69 Mod 7	31		% NK		
MODULATOR 8	MGN3				
NK-Zellen CD 69 Mod 8	69		% NK		
MODULATOR 9	Thymuvocal				
NK-Zellen CD 69 Mod 9	24		% NK		
NK-Zellen (relativ)	12	12	% Lympho	6 - 29	



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Melatonin and Cancer

Melatonin Reduces Cancer Progression and Metastasis

Russel J. Reiter, Ph.D., M.D (*h.c.*), D.Sc. (*h.c.*)

Professor of Cell Biology

UT Health San Antonio

San Antonio, Texas USA

Vienna, Austria: December 2019



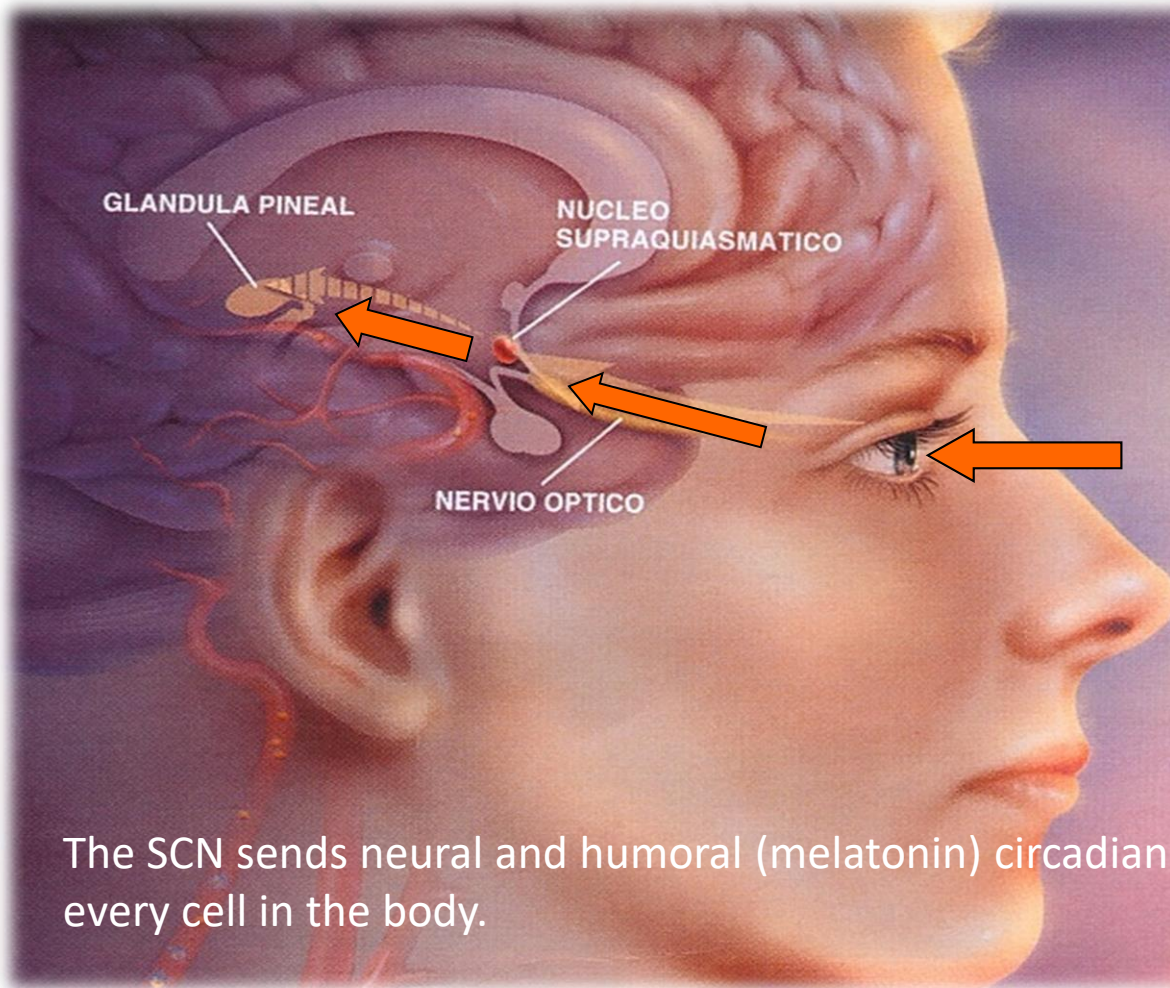


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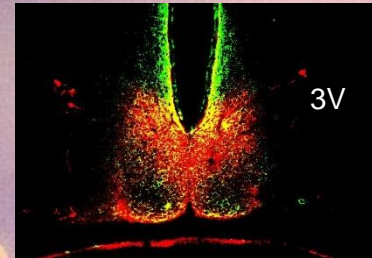
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Melatonin – The Biological Clock



Pineal melatonin is synthesized and released primarily at night **in darkness.**



The master biological clock

The SCN sends neural and humoral (melatonin) circadian information to every cell in the body.

Fuentes-Broto, 2009

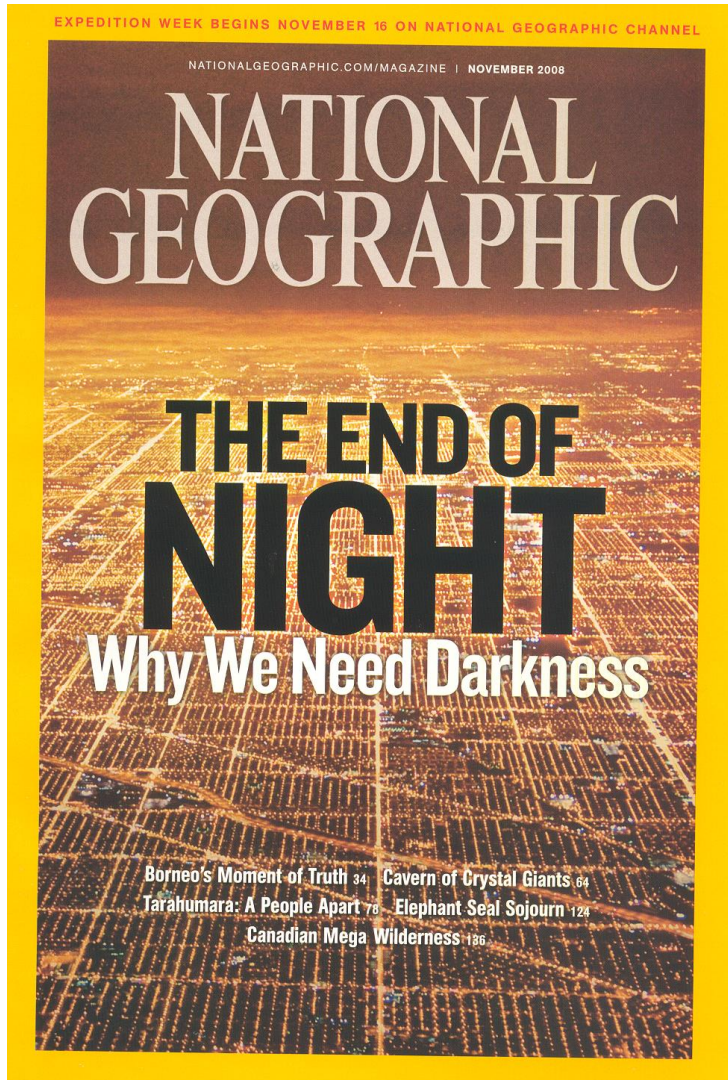


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Melatonin



The “end of night” means the loss/suppression of the melatonin rhythm

World Health Organization has classified light-at-night as a class 2A carcinogen

Significant consequences in terms of circadian misalignment (chronodisruption) and melatonin suppression



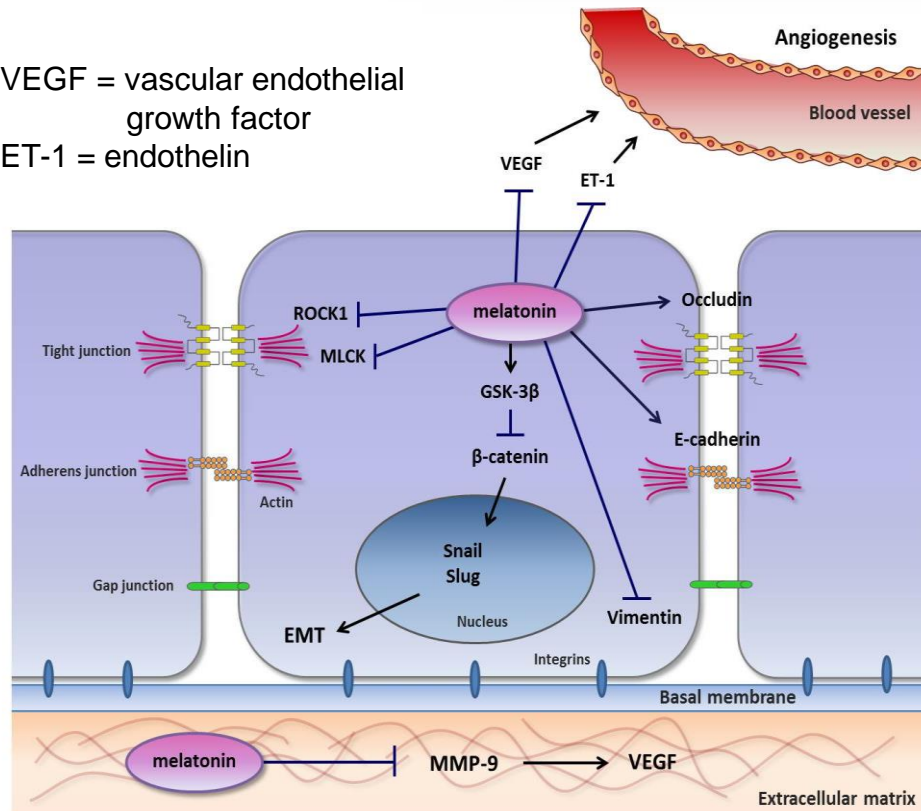
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Melatonin is a Potent Inhibitor of Cancer Metastasis

VEGF = vascular endothelial growth factor
ET-1 = endothelin



Reiter, 2017



Google image

Metastatic cancer is almost always worse than primary cancer.

Metastatic melanoma is an example of the increased danger of metastases.

Melatonin downregulates vimentin, ROCK & MLCK to reduce cytoskeletal reorganization.

Melatonin reduces cancer cells to a less invasive state by upregulating adhesion molecules.

Melatonin reduces angiogenesis by inhibiting VEGF and ET-1.

Melatonin activates GSK- β to decrease EMT transcription factors, snail and slug.

Melatonin inhibits MMP-9 in ECM to prevent invasion.

Yang et al, 2015



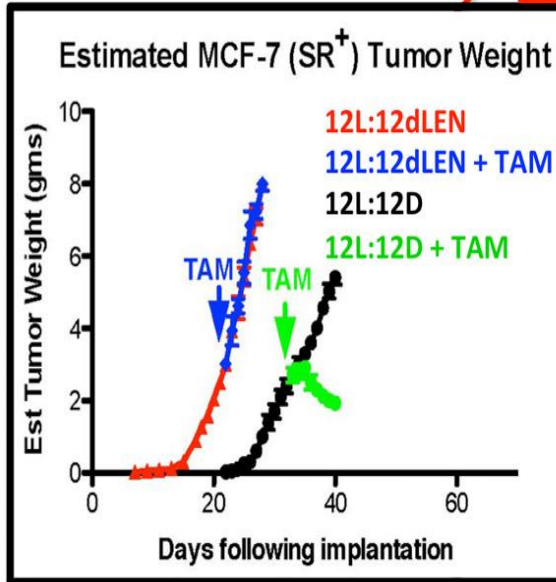
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Cancer and Melatonin

Study I



dLEN

Day
28



12L:12D

This illustrates the importance
of darkness at night



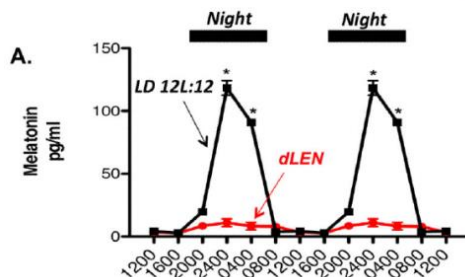
12L:12D
+ diluent

Day
40



12L:12D
+ TAM

Melatonin renders
treatment resistance
cancers sensitive to
chemotherapies
(tamoxifen)



Dauchy et al, 2014



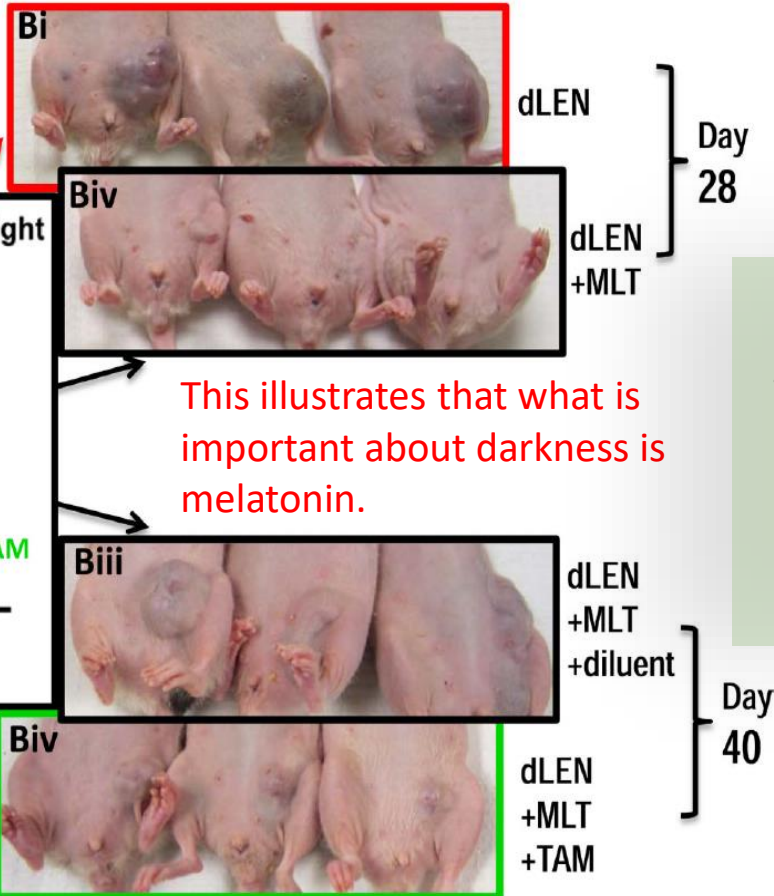
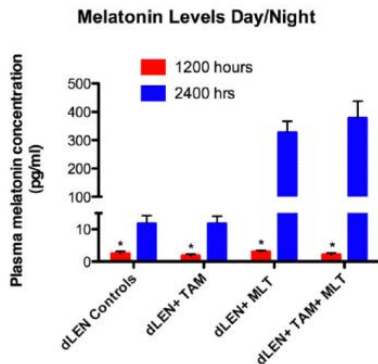
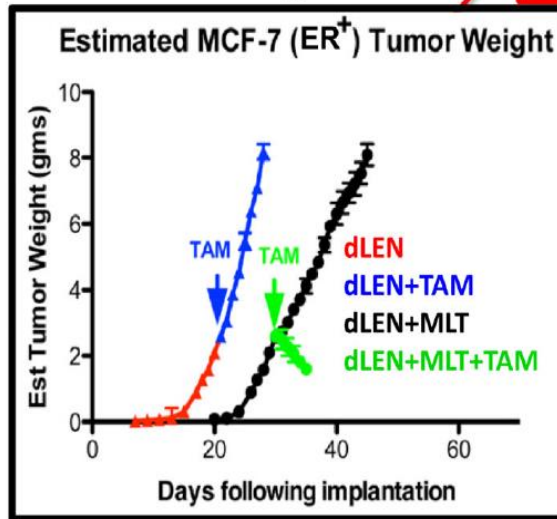
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Cancer and Melatonin

B. Study II



This illustrates that what is important about darkness is melatonin.

Melatonin renders treatment resistance cancers sensitive to chemotherapies (tamoxifen)



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Early Detection

- Pantum (EDIM Technology)
- Prescan (Whole Body MRI/CT)
- Metavectum (Liquid biopsy, drug test)



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Visualisation of Glucose Metabolism

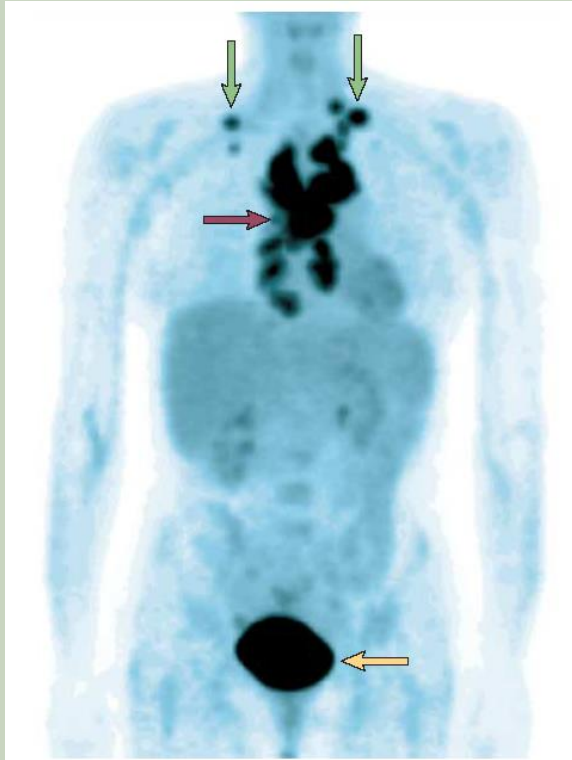


Figure 2 | Positron-emission tomography imaging with ^{18}F fluorodeoxyglucose of a patient with lymphoma. The mediastinal nodes (purple arrow) and supraclavicular nodes (green arrows) show high uptake of ^{18}F fluorodeoxyglucose (FdG), showing that tumours in these nodes have high levels of FdG uptake. The bladder (yellow arrow) also has high activity, because of excretion of the radionuclide.

Through ^{18}F -FDG-PET

a) Cancer ↑

b) Alzheimer ↓

Gatenby and Gillies, Nature Reviews Cancer 2004



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Warburg Effect

Fermentation of glucose despite the availability of oxygen

Über den Stoffwechsel der Carcinomzelle¹⁾.

Von

Otto Warburg, Karl Posener und Erwin Negelein.

(Aus dem Kaiser-Wilhelm-Institut für Biologie, Berlin-Dahlem, und aus der chirurgischen Universitätsklinik der Charité, Berlin.)

(Eingegangen am 10. September 1924.)

Mit 6 Abbildungen im Text.

Greift man das Carcinomproblem von der Seite der Stoffwechselphysiologie an, so ist die erste Frage: wodurch unterscheidet sich der Stoffwechsel wachsenden Gewebes von dem Stoffwechsel ruhenden Gewebes? Die Aussichten, eine Antwort auf diese Frage zu finden, sind groß. Ob ein Gewebe seine Substanz konstant hält oder ob es

Winner of the
Nobel Price
Otto Warburg
1924





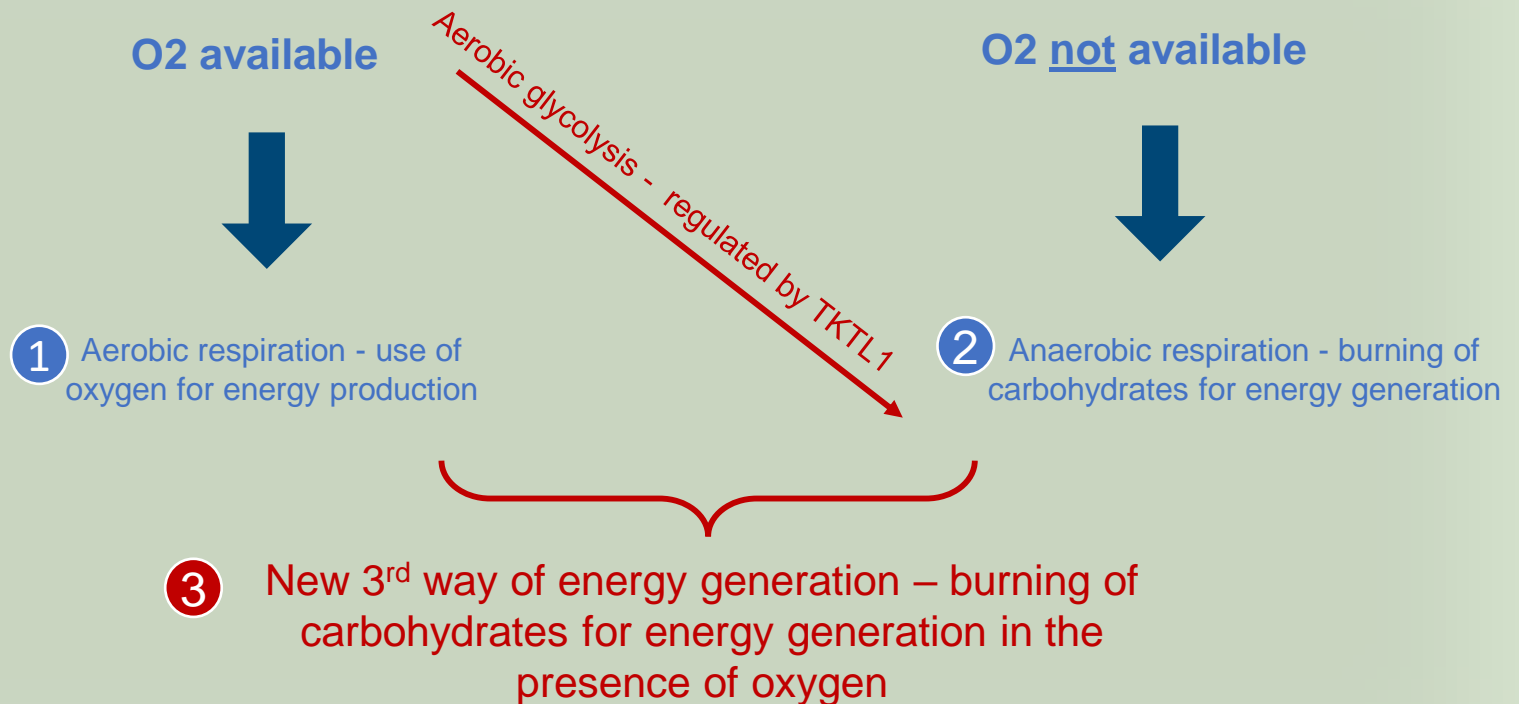
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Metabolism – Energy Generation in Cells

TKTL1-protein regulates aerobic glycolysis – a new, 3rd way of energy metabolism





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TKTL1 (Transketolase-like 1)

An increased TKTL1-Score is an indication of an aggressive tumour.

- TKTL1-gene discovered in 1995 by Dr Coy during his research at German Centre of Cancer Research (DKFZ), Heidelberg.
- TKTL1-metabolism describes long unknown **third way of energy generation** in the cell.
- TKTL1-protein regulated the **aerobic glycolysis** = fermentation process of glucose even in presence of oxygen.
- Tumour cells make use of this TKTL-1 metabolism as **growth becomes invasive/ aggressive**.
- Confirmed by analysis of more than 50 tumour entities in more than 110,000 blood samples.

Grimm et al. BMC Cancer 2013, 13:569
<http://www.biomedcentral.com/1471-2407/13/569>



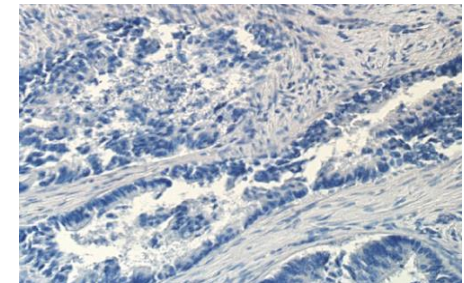
RESEARCH ARTICLE

Open Access

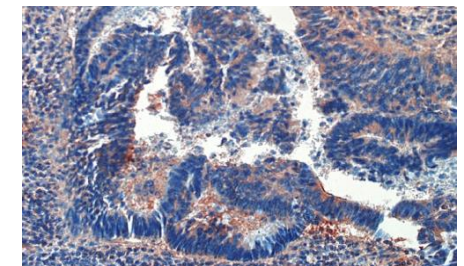
A biomarker based detection and characterization of carcinomas exploiting two fundamental biophysical mechanisms in mammalian cells

Martin Grimm^{1,2}, Steffen Schmitt², Peter Teriete³, Thorsten Biegner⁴, Arnulf Stenz⁵, Jörg Hennerlotter⁵, Hans-Joachim Muhl⁶, Adelheid Munz⁷, Tatjana Nadtochi¹, Klemens König⁸, Jörg Sängler⁹, Oliver Feyen⁹, Helko Hofmann⁹, Siegmund Reinert¹ and Johannes F. Coy⁹

TKTL1-negative tumor material



TKTL1-positive tumor material





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Apo10 (DNaseX)

An increased Apo10-Score is an indication of a proliferative disorder / tumor.

- Apo10 accumulates in cells due to **disordered apoptosis**.
- Independent from the type of tumour.
- Confirmed by analysis of more than 50 tumour entities in more than 90,000 blood samples.
- Disordered apoptosis is the **origin of malign degeneration** respectively a tumour.

Grimm et al. BMC Cancer 2013, 13:569
<http://www.biomedcentral.com/1471-2407/13/569>

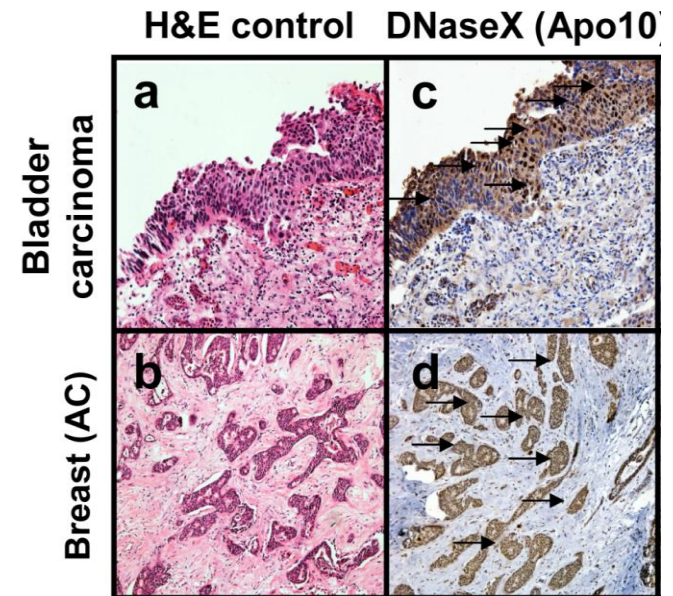


RESEARCH ARTICLE

Open Access

A biomarker based detection and characterization of carcinomas exploiting two fundamental biophysical mechanisms in mammalian cells

Martin Grimm^{1*}, Steffen Schmitt², Peter Teriete³, Thorsten Biegner⁴, Amulf Stenzl⁵, Jörg Hennenlotter⁵, Hans-Joachim Muhs⁶, Adelheid Munz¹, Tatjana Nadtootschi¹, Klemens König⁷, Jörg Sängers⁸, Oliver Feyen⁹, Heiko Hofmann⁹, Siegmund Reinert¹ and Johannes F Coy⁹



Immunohistochemistry of tumor material



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PanTum Application in Screening

Recommend: One PanTum Detect Test per year.

E
DIM
test result

Critical PanTum
detection point

Phase A: Tumor

Phase B: Cancer

Often successfully
treatable

Often lethal, rarely
treatable

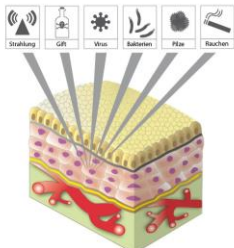
Ordinary tissue

Proliferating disorder

Carcinoma in situ

Carcinoma with matrix
degeneration

Metastasizing
Carcinoma





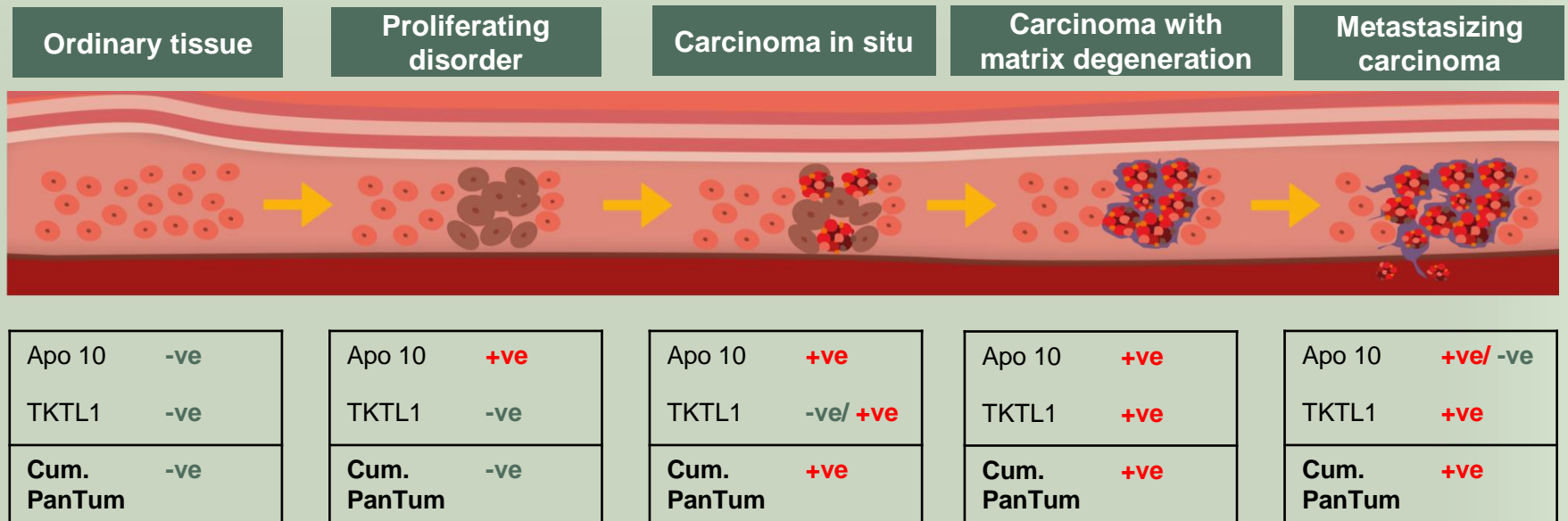
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PanTum Detect can detect all tumour stages

The combination of Apo10 and TKTL1 allows the detection of all tumor stages.



-ve = Negative
+ve = Positive



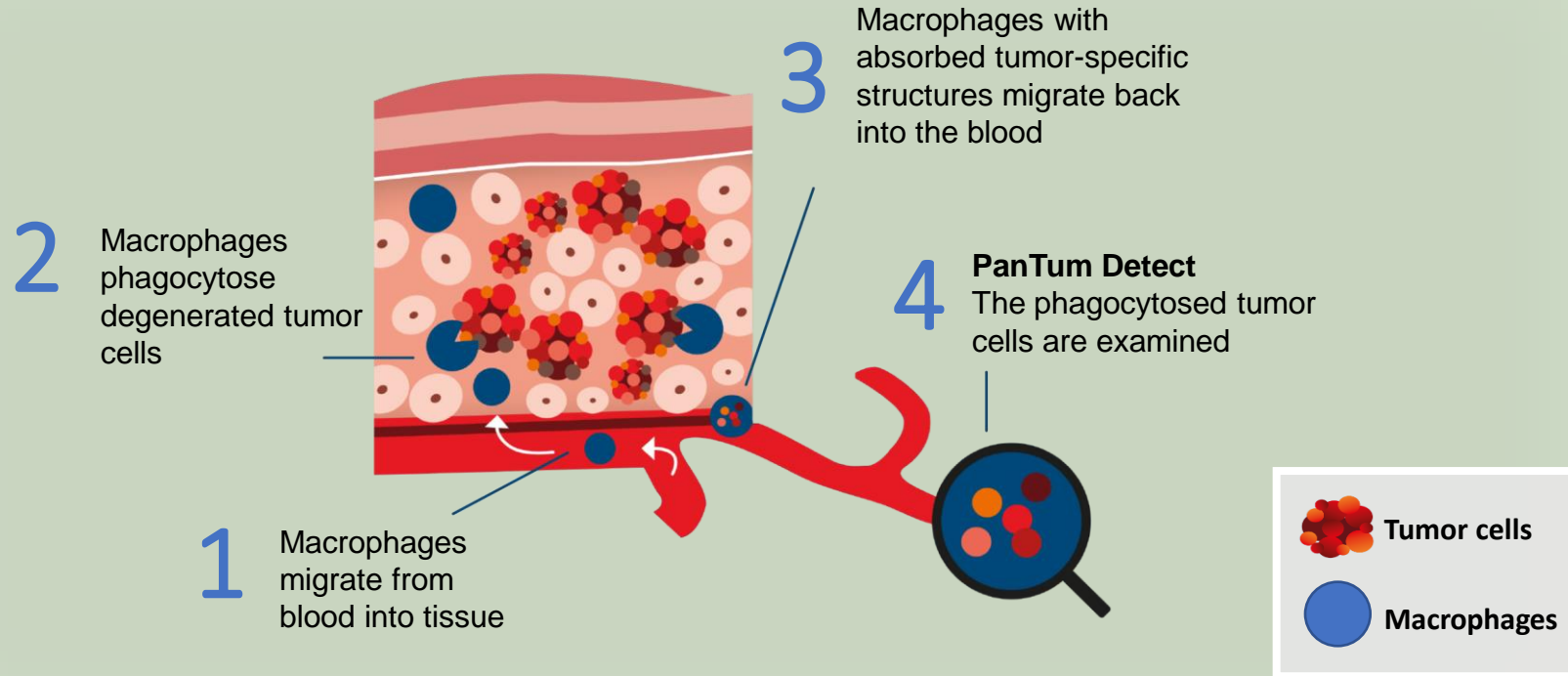
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Biological Biopsy – Leveraging the immune system

Highest test accuracy achieved by making use of the body's own immune system.





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PanTum Test - Supporting Studies

Supporting Studies in:

Dermatology, Endocrinology (thyroid cancer), Gastroenterology (colorectal & gastric cancer), Gynaecology (breast, ovarian, cervix cancer), Neurology (brain tumour), Ophthalmology, Otolaryngology (head & neck cancer), Pulmonology (lung cancer), Urology (prostate, urothelial & kidney cancer)

0 SEVERAL

Coy JF: EDIM-TKTL1/Apo10 Blood Test: An Innate Immune System Based Liquid Biopsy for Characterization and Targeted Treatment of Cancer. *Int J Mol Sci*. 2017 Apr 20;18(4): pii: E978. doi: 10.3390/ijms18040978. [Epub 2017 Apr 20].

Xu, L.M., Li, R.K., Lin, S.H., Tse, A.P., Chiu, D.K., Koh, H.Y., Law, C.T., Wong, C.M., Cai, Z., Wong, C. Counteracts oxidative stress to drive cancer development. *Proc Natl Acad Sci U S A*. 2016 Feb 22;113(8):2216-22. doi: 10.1073/pnas.1511111113. [Epub 2016 Feb 22].

Li, B., Iglesias-Pedraz, J.M., Chen, L.Y., Yin, F., Cadenas, E., Reddy, S., Comal, L. Downregulation of protein induces a metabolic shift that compromises redox homeostasis and limits proliferation. *Aging Cell*. 2014 Apr; 13, 367-378. University of Southern California, Los Angeles, USA / University of Southern California, Los Angeles, USA

1 DERMATOLOGY

Jayachandran, A., Lo, P.H., Chuah, A.C., Prithviraj, P., Molania, R., Davalos Salas, M., Anaka, M., W. Behnen, A. Transketolase-like 1 acetyl expression is associated with DNA hypomethylation and in melanoma cells. *BMC Cancer*. 2016 Feb 22;16:134. Ludwig Institute for Cancer Research, Heidelberg, Germany.

Li, J., Zhu, S.C., Li, S.G., Zhao, Y., Xu, J.R., Song, C.Y. TKTL1 promotes cell proliferation and metastasis in squamous cell carcinoma. *Biomed Pharmacother*. 2015 Aug;74:71-6. The Fourth Hospital of H. Shijiazhuang, China.

2 ENDOCRINOLOGY

THYROID CANCER:

Zerlilli M et al: Increased expression of transketolase-like-1 in papillary thyroid carcinomas diameter is associated with lymph-node metastases. *Cancer*. 2008 Sep 1;113(5):936-44. Univ. of Southern California, Los Angeles, USA

3 GASTROENTEROLOGY

COLORECTAL CANCER:

Ahpelio, K., Böökman, C., Hagström, J., Koskenvuo, S., Haglund, C. Transketolase-like protein 1 predicts prognosis in colorectal cancer. *Cancer Biol Ther*. 2016; 17, 163-168. University of Helsinki, Helsinki, Finland.

Bertz S et al: Hypoxia induces the expression of transketolase-like 1 in human colorectal cancer cells. *Int J Cancer*. 2013; 132, 182-192. University Hospital Zurich, Switzerland.

Jansen N and Coy JF: Diagnostic use of EDIM-blood test for early detection of colon cancer. *Int J Cancer*. 2015; 136, 665-9.

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Diaz-Morali S et al: Transketolase-like 1 expression is modulated during colorectal cancer cell formation. *PLoS One*. 2011; 6(9):e25323. Epub 2011 Sep 27. University of Barcelona, Spain.

Xu X et al: Transketolase-like protein 1 (TKTL1) is required for rapid cell growth and full viability. *Int J Cancer*. 2009 Mar 15;124(6):1330-7. DKFZ German Cancer Research Centre, Heidelberg, Germany.

Langhein S et al: Expression of transketolase TKTL1 predicts colon and urothelial cancer patient effect reinterpreted. *Br J Cancer*. 2006 Feb 27;94(4):578-85. University Hospital Mannheim, Germany.

GASTRIC CANCER:

Dong, Y., Wang, M. Knockdown of TKTL1 additively complements cisplatin-induced cytotoxic carcinoma cells by regulating the levels of NADPH and ribose-5-phosphate. *Biomed Pharmac*. 2016; 78, 329-338. University Hospital Tübingen, Germany / Sanford Burnham Preclinical Institute, La Jolla, CA, USA

Song, Y., Liu, D., Hu, G. TKTL1 and p63 are biomarkers for the poor prognosis of gastric cancer patients. *Cancer Biomark*. 2015; 15, 591-597. Central South University, Changsha, China.

Yuan W et al: Silencing of TKTL1 by siRNA inhibits proliferation of human gastric cancer cells. *Cancer Biol Ther*. 2010 May;9(5):710-6. Epub 2010 May. Central South University, Changsha, China.

Stäger W et al: Expression of the mutated transketolase TKTL1, a molecular marker in gastric cancer. *Int J Cancer*. 2012 Aug 10; 132(12):2738-44. University Hospital Mannheim, Heidelberg, Germany.

4 GYNAECOLOGY

BREAST CANCER:

Rotmann A et al: A new diagnostic approach for the early detection and monitoring of breast cancer. *Proc Natl Acad Sci U S A*. 2012 Mar 26;109(12):4710-5. Epub 2012 Mar 26. University of Southern California, Los Angeles, USA

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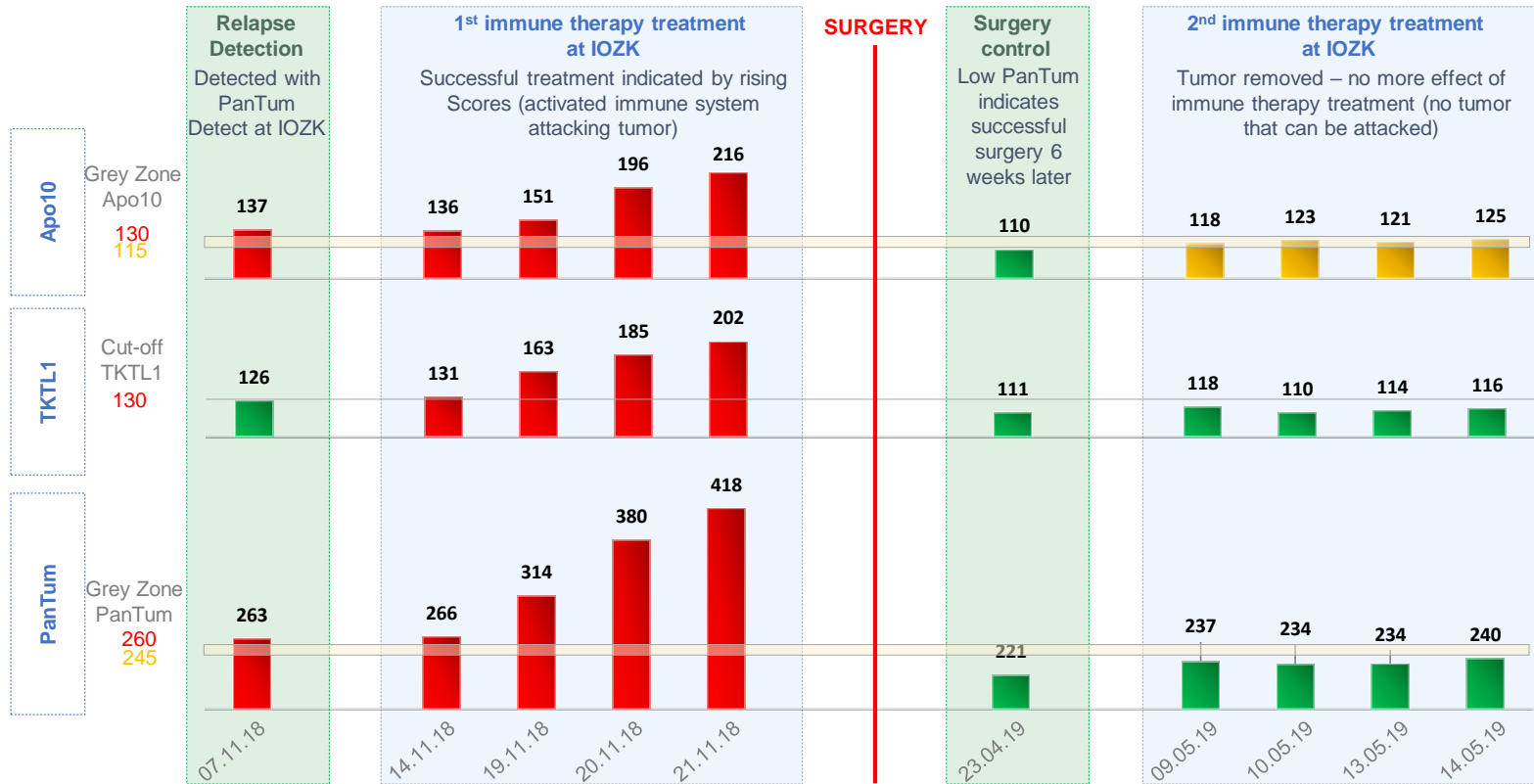


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Patient Case Example – PanTum Surveillance





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Cancer therapy approach

Cancer Therapy Approach

**FOOD &
MICROBIOME**

**IMMUNE
THERAPY**

LIQUID BIOPSY

INFUSION

**COMBINATION
OF CHEM,
BIOLOGICAL,
HYPERThERMIA**



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Stem Cell Metro Map

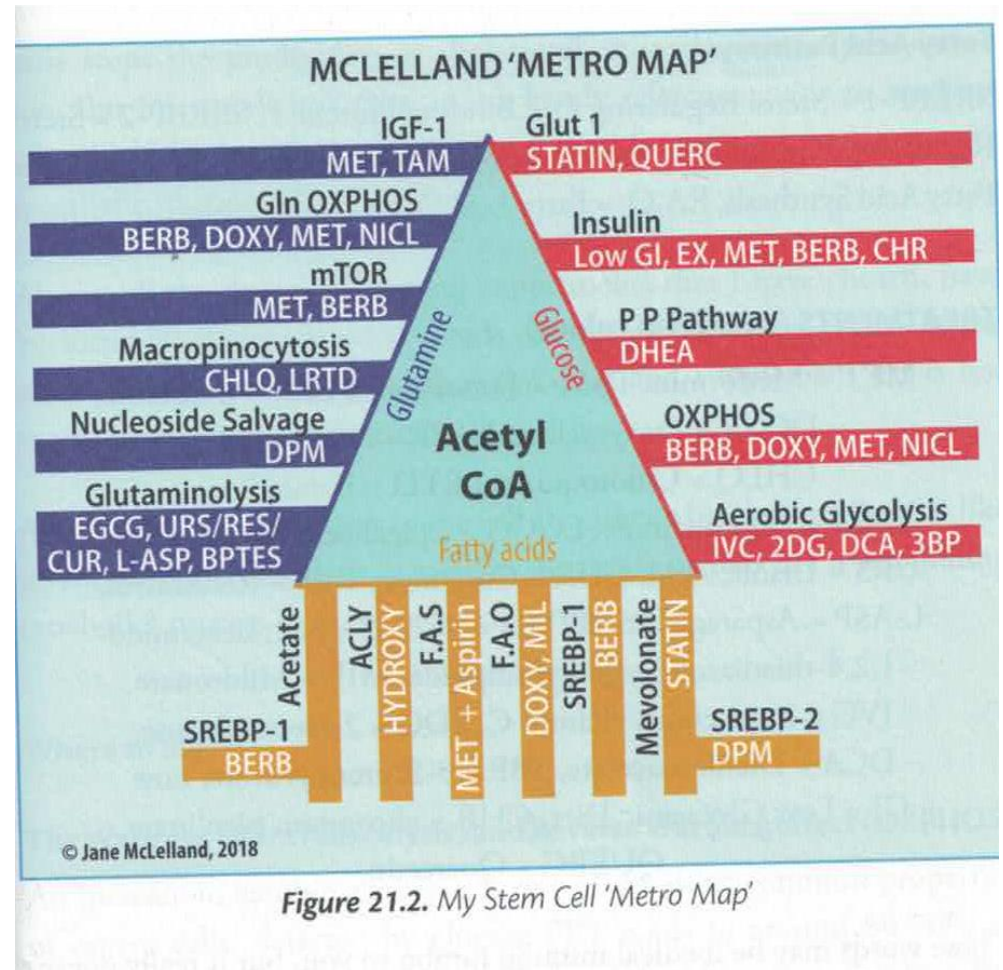
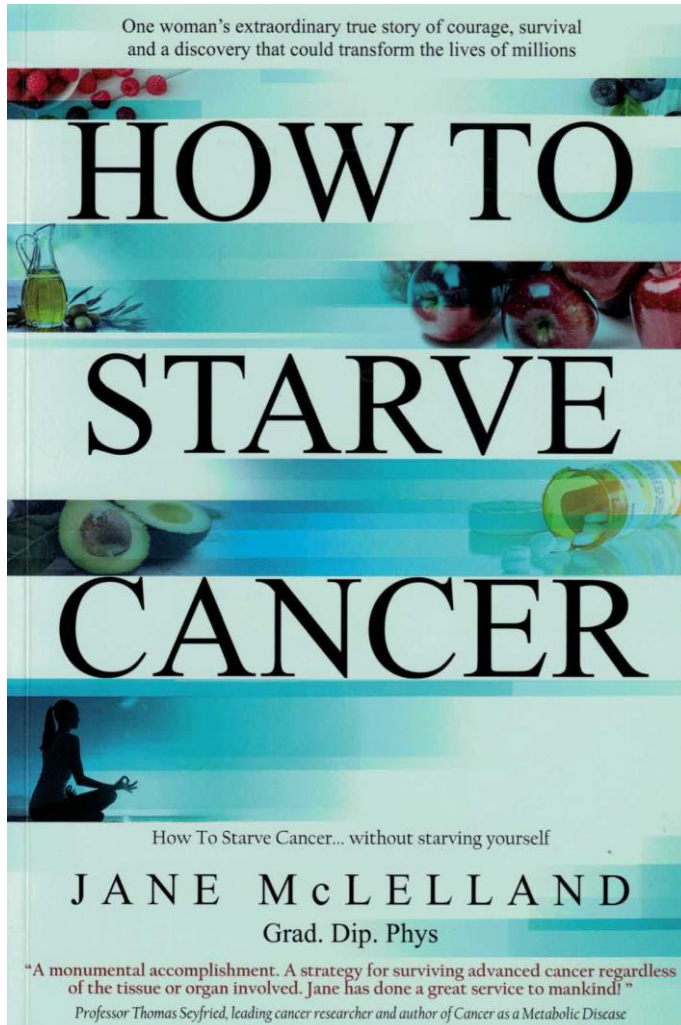


Figure 21.2. My Stem Cell 'Metro Map'



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Janus-faced Character of Sugar

Role in Healthy cells:

- Prevents and neutralizes radicals
- Fast glucose degradation
- Protection from glucose-associated cell-damages / advanced glycation end products (AGEs) in endothelial cells nerves retina.



Role in Cancer cells:

- Energy release without oxygen
- Degradation of surrounding matrix
- Invasion and metastasis
- Resistance towards radio and chemotherapy



8. Andere Kohlehydrate. α - und β -Glucose.

In den bisher beschriebenen Versuchen war der Zucker der Ringerlösung eine im Gleichgewicht befindliche Mischung von α - und β -Glucose. Wir haben uns gefragt, wie spezifisch die Zelle auf ihr natürliches Substrat eingestellt ist, und verschiedene Kohlehydrate auf ihre glykolytische Spaltbarkeit geprüft. Es zeigte sich, daß nur Hexosen angegriffen werden und von ihnen außer Glucose nur Mannose, Fructose und Galaktose. Dabei waren die Geschwindigkeiten

	$Q_{CO_2}^{N_2}$
für d-Glucose	23,9
„ d-Mannose	21,6
„ d-Fructose	3,3
„ d-Galaktose	1,3

Was die beiden Formen der Glucose, ihre α - und β -Form, anbetrifft, so haben wir einen wesentlichen Unterschied der glykolytischen Spaltbarkeit nicht gefunden. Da sich beide Formen, in Wasser gelöst,

Carcinomas are fermenting GALACTOSE much more slowly than GLUCOSE.



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PanTum Application in Screening

Elimination of TKTL1 leads to lower cisplatin-induced cytotoxicity.

Knockdown of TKTL1 additively complements cisplatin-induced cytotoxicity in nasopharyngeal carcinoma cells by regulating the levels of NADPH and ribose-5-phosphate



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ARTICLE INFO

Article history:

Received 10 August 2016

Received in revised form 15 November 2016

Accepted 16 November 2016

Keywords:

TKTL1

Cisplatin

Cytotoxicity

Pentose phosphate pathway

Nasopharyngeal carcinoma

ABSTRACT

Background: Transketolase-like 1 (TKTL1) plays an important role in pentose phosphate pathway (PPP) branch, the main pathway generating nicotinamide adenine dinucleotide phosphate (NADPH) and nucleotides for DNA synthesis. TKTL1 is closely related to DNA damage and has a close relationship with incidence and progression of cancers. Cisplatin is the main chemotherapeutic drug by inducing DNA damage. Whether TKTL1 knockdown additively complements cisplatin-induced cytotoxicity in nasopharyngeal carcinoma cells, however, remains largely undefined.

Methods: Lipofectamine 2000 was used to transfect si-TKTL1s with different sequences into the CNE2 and HONE1 cells. The mRNA and protein levels of TKTL1 were determined by qRT-PCR and western blot, respectively. MTT assay and flow cytometry were used to access the viability and apoptosis of CNE2 and HONE1 cells. The NADPH and ribose-5-phosphate levels in both CNE2 and HONE1 cells were determined by NADPH examination kit and HPLC analysis, respectively. The effect of TKTL1 knockdown and NADPH/ribose-5-phosphate supplement on DNA damage was assessed by using Comet assay.

Results: TKTL1 knockdown significantly decreased TKTL1 level in CNE2 and HONE1 cells. A significant decrease in cell viability and an obvious increase in cell apoptosis rate were found in si-TKTL1 + cisplatin group compared with si-TKTL1 group or si-control + cisplatin group. The levels of NADPH and ribose-5-phosphate in CNE1 and HONE1 cells were dramatically decreased in si-TKTL1 group compared with si-control group. TKTL1 knockdown additively complemented cisplatin-induced cytotoxicity, which was partly reversed by the supplements of NADPH and ribose-5-phosphate, including the increased survival rate, decreased apoptosis and DNA damage.

Conclusions: Knockdown of TKTL1 additively complements cisplatin-induced cytotoxicity in the nasopharyngeal carcinoma cells by inhibiting the levels of NADPH and ribose-5-phosphate, indicating that TKTL1 may be a promising target to improve the therapeutic effect combining with cisplatin for the patients with nasopharyngeal carcinoma.

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PanTum Application in Screening

TKTL1 leads to resistance to paclitaxel.

TKTL1 modulates the response of paclitaxel-resistant human ovarian cancer cells to paclitaxel

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ARTICLE INFO

Article history:

Received 26 May 2018

Accepted 6 June 2018

Available online xxx

Keywords:

Ovarian cancer

Paclitaxel resistance

TKTL1

RNA interference

Redox

ABSTRACT

Transketolase-like 1 (TKTL1) plays an important role in the pentose phosphate pathway (PPP) branch. The main obstacle of ovarian cancer treatment is chemotherapeutic resistance. We investigated whether inhibiting TKTL1 in OC3/TAX300 cells could re-sensitize paclitaxel-resistant cells to paclitaxel and proposed a mechanism of action. Western blotting revealed that TKTL1 expression levels in OC3/Tax300 cells were significantly higher than those in OC3 cells. Inhibition of TKTL1 significantly decreased the cellular proliferation rate and IC50 for paclitaxel. Metabolomics revealed that NADPH levels were reduced in the si-TKTL1 group, whereas NADP⁺ was increased compared with the level in the negative si-TKTL1 group. A 2.2-fold increase in the ROS level and an obvious increase in the cell apoptosis rate were observed in the si-TKTL1+paclitaxel group compared with those in the negative si-TKTL1+paclitaxel and OC3/Tax300 + paclitaxel groups. Western blotting revealed that Bax and Caspase 3 proteins were up-regulated, whereas Bcl-2 expression was down-regulated. Quantitative RT-PCR revealed no changes in *gst-π* or *mrp1* gene expression in the three groups, whereas GSH levels were reduced in the si-TKTL1 group as verified by metabolomics. TKTL1 inhibition also reduced tumor growth *in vivo*. Collectively, TKTL1 down-regulation sensitized paclitaxel-resistant OC3/Tax300 ovarian cancer cells to paclitaxel.

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Biochem Biophys Res Commun. 2018 Sep5;503(2):572-579



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PanTum Application in Screening

TKTL1 association with carcinoma carcinogenesis.

Published Online First on January 26, 2010 as 10.1158/1078-0432.CCR-09-2604

Human Cancer Biology

Clinical
Cancer
Research

TKTL1 Is Activated by Promoter Hypomethylation and Contributes to Head and Neck Squamous Cell Carcinoma Carcinogenesis through Increased Aerobic Glycolysis and HIF1 α Stabilization

Wenyue Sun¹, Yan Liu², Chad A. Glazer¹, Chunbo Shao¹, Sheetal Bhan¹, Semra Demokan¹, Ming Zhao³, Michelle A. Rudek³, Patrick K. Ha¹, and Joseph A. Califano^{1,4}



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TKTL1 and Phytotherapy

RESVERATROL INHIBITS EXPRESSION OF CANCER-SPECIFIC PENTOSE PHOSPHATE PATHWAY ENZYME TKTL1

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Received: 30 January 2018, Revised and Accepted: 19 March 2018

Resveratrol treatment in HeLa cells inhibited proliferation, promoted ROS, and reduced intracellular GSH levels. In TKTL1 promoter activity assay, resveratrol treatment was found to directly inhibit promoter activity of TKTL1.

Resveratrol inhibited both mRNA and protein expression of TKTL1 in a dose-dependent manner.



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TKTL1 and Oxythiamin (OT)

Transketolase counteracts oxidative stress to drive cancer development

Iris Ming-Jing Xu^a, Robin Kit-Ho Lai^a, Shu-Hai Lin^{b,c}, Aki Pui-Wah Tse^a, David Kung-Chun Chiu^a, Hui-Yu Koh^a, Cheuk-Ting Law^a, Chun-Ming Wong^{a,d}, Zongwei Cai^{b,c}, Carmen Chak-Lui Wong^{a,d,1}, and Irene Oi-Lin Ng^{a,d,1}

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Edited by Tak W. Mak, The Campbell Family Institute for Breast Cancer Research at Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, and approved December 24, 2015 (received for review May 5, 2015)

We next examined the sensitization effect of the TKT inhibitor oxythiamine (OT), a thiamine antagonist, for Sorafenib.

Cell proliferation assay revealed that OT drastically sensitized SMMC and MHCC97L cells to Sorafenib treatment in vitro and increased ROS accumulation in the Sorafenib-treated HCC cells.

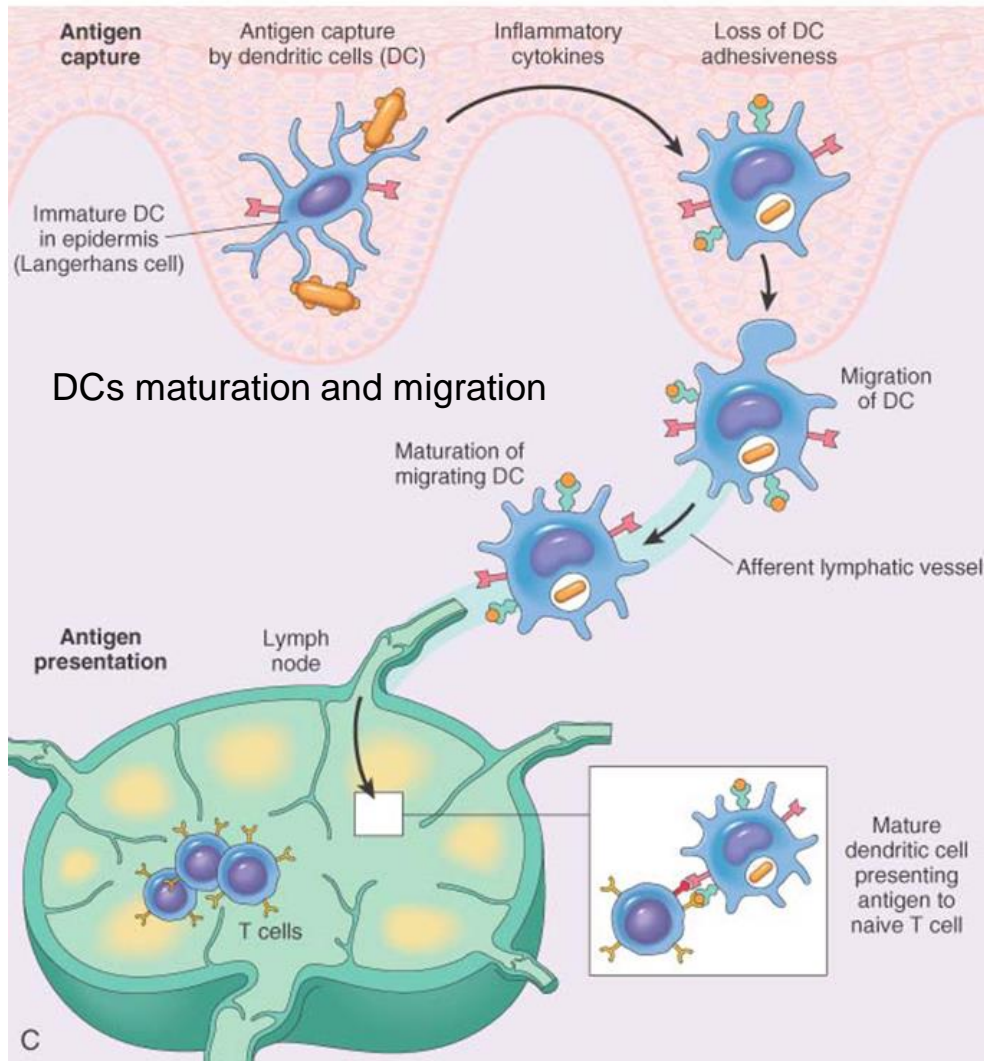


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Dendritic Cells (DC)



Immature DCs

- Residing in tissue and unable to stimulate naïve T-cells.
- The functions of immature DCs are antigen uptake and processing.

Mature DCs

- Residing in Lymphoid organs and able to stimulate naïve T-cells.
- The functions of mature DCs are presenting antigen to naïve T-cells.



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Peptide Vaccine VS DC Vaccine Therapy

Peptide vaccine therapy

Cancer markers peptides is injected.



Dendritic cell vaccine therapy

Dendritic cells are educated and strengthened outside the body and then injected.



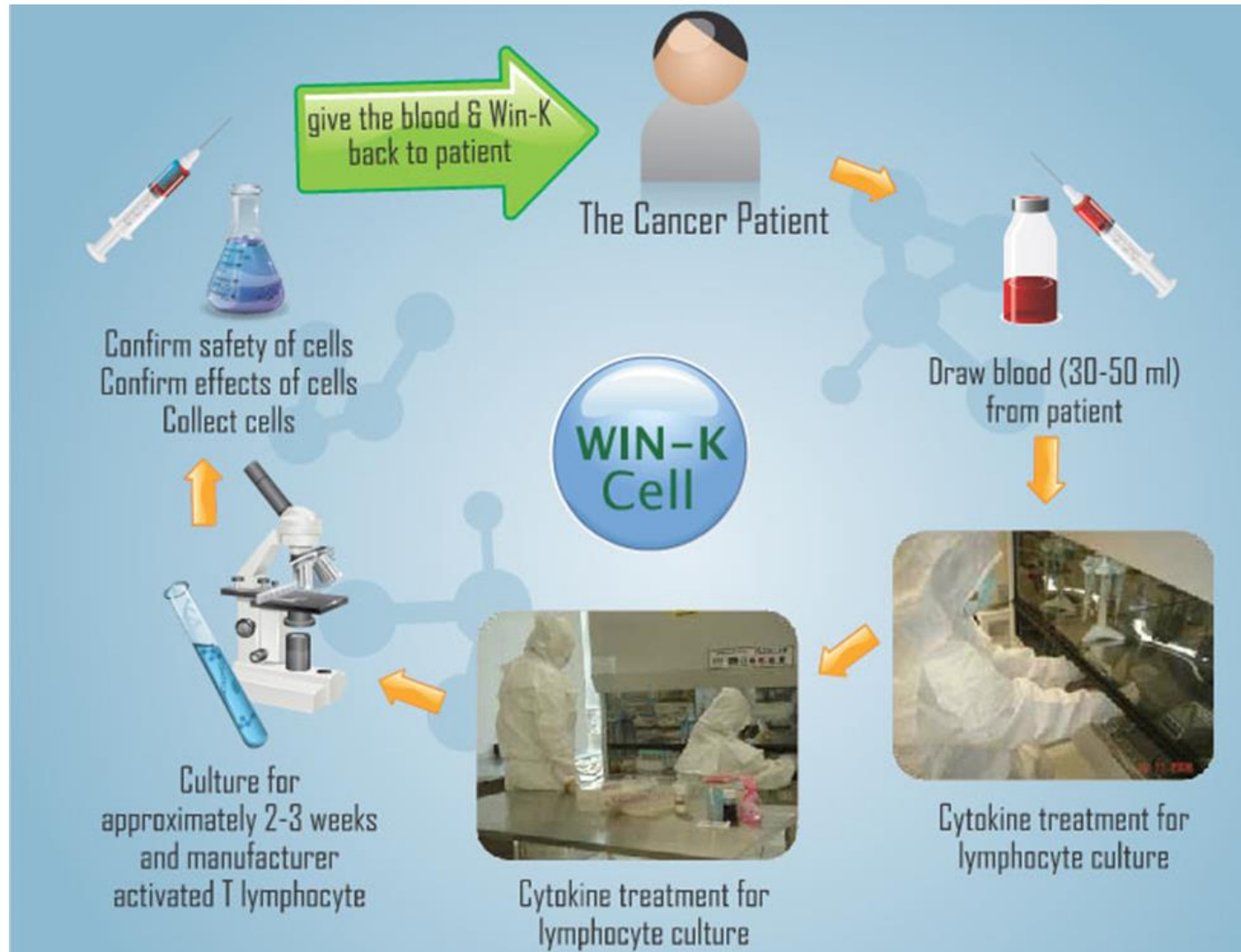


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Immune Therapy with NK cells





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Liquid Biopsy

The **Metavectum Tumour-Therapy Test** pinpoints the "Achilles' heel" of the tumor on a genomic, proteomic and metabolomic level and based on the results a therapy proposal is submitted.

Tumors develop a unique individual profile which differs from person to person. Consequently the medical treatment for tumor must be carried out **individually**.





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Therapy: IV or Orally

I.V.
Infusions



+

Oral
Supplements



- Curcumin
- DCA
- Amygdalyn
- Artesunate
- Vitamin C
- ECGC
- Germanium
- Procain
- **Silibinin, Apigenin, Berberin in progress**
- Phytotherapy
- Salvestroles
- Cannabis
- Methadon
- Metformin
- Melatonin



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Metavectum Report (Part I)

Anti-Cancer Agent	Gene Profile (+)	Gene Profile (-)	Gene Profile normal
5-FU	TS +	TP (-), DPD (-)	
Adriamycin, Epirubicin	TOPOIIA1 ≈+		
Alkylators (Ifosphamid, Cyclophosphamid etc.)	GCS +, GSTpi +		
Apigenin			STAT1 n
Aromatase-Inhibitoren			CYP19A1 n
Artesunate			TF n
Atezolizumab etc.	PDL-1 +		
Avastin	VEGFA ≈+		
Berberin	TOPOIIA1 ≈+		
Busulfan, Treosulfan	GCS +, GSTpi +		
Carmustin, Lomustin etc. Nitrosoharnstoffe	GCS +, GSTpi +		
Capecitabin, Xeloda		TP (-)	
Cabozantinib, Cometriq	MET ≈+, MDM2 +		MET ≈+
Crizotinib, Alectinib	MET ≈+, ALK +		
Celebrex etc.			COX2 n
Curcumin	NFKB +		
Dabrafenib, Trametinib	MEK ≈+		
Dacarbazin	CD133 +		MGMT n
Denosumab	RANKL +		
Digoxin	HIF +		
Enzalutamid, Bicalutamid	ARFL + <> ARV7 +		
Enzalutamid, plus Niclosamid	ARFL + <> ARV7 +		



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Metavectum Report (Part II)

Erlotinib, Gefitinib etc.	EGFR ≈+		
Estramustin	BCL2 +		
Etoposid	TOPOIIA1 ≈+		
Everolimus	mTOR +		
Glivec, Imatinib	C-KIT +, MDR1 +		
Gemcitabine, Cytarabin	RRM1 ≈+, DCK ≈+		
Herzeptin, Lapatinib			ERBB2 n
Hydroxyharnstoff	RRM1 ≈+		
Hyperthermie			HSP27 n
IFN-alpha, IL2			IFNAR1 n, IFNGR1 n
IP-6	TERT +		
Methotrexat, Pemetrexed	DHFR +, MSH2 +		
Mitomycin C	GCS +, GSTpi +		
Mitoxantron	TOPOIIA1 ≈+		
Niclosamid	AEV7 +		
Nivolumab, Pembrolizumab	PD1 +, CYP3A4 ≈+		
Palbociclib			CDK4/6 n
Platinverbindungen	CD133 +, CD44+, GSTpi +	ERCC1 (-)	
Quercetin, Sulforaphan	CD133+		
Salinomycin etc.	CD133+		
Sorafenib, Sunitinib	PDGFRbeta +, C-KIT +		
Tamoxifen, Raloxifen			ER1 n
Taurolidin	TNF ≈+		
Taxane	MDR1 +		
Temozolomid			
Topo-, Irinotecan	TOPOI ≈+, MDR1 +		
Vinca-Alkaloide	GCS +, GSTpi +		
Vitamin C Hochdosis	SVCT-2 +, HIF +		



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Metavectum Report (Part III)

META-V-20181932325-R1

Natural Product	Gene Profile (+)	Gene Profile (-)	Gene Profile normal
Amygdalin			Beta-Glucosidase n
Apigenin			STAT1 n
Artesunate			TF n
Berberin	TOPOIIA1 ≈+		
Cannabinoide	CB2 +		
Celebrex etc.			COX2 n
Curcumin	NFKB +		
DCA			LDHA n
Digoxin	HIF +		
Genistein			uPAR n
Hyperthermia			HSP27 n
IFN-alpha, IL2			IFNAR1 n, IFNGR1 n
IP-6	TERT +		
Isoflavone, Estriol			ER1 n
Niclosamid	ARV7 +		
Quercetin/Sulforaphan	CD133 +		
Resveratrol	BIRC5 +		
Salinomycin	CD133 +		
Silibinin	CD44 +		
Taurolidin			TNF n
Vitamin C	HIF +, SVCT-2 +		
Zileuton			5LOX n



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Metavectomy Report (Part IV)

CD133/CD44: "...CD133+CD44+ cancer stem cells previously isolated from laryngeal squamous cell carcinoma (LSCC) cell lines showed strong malignancy and tumorigenicity..." [Lit.: Whole-Transcriptome Analysis of CD133+CD144+ Cancer Stem Cells Derived from Human Laryngeal Squamous Cell Carcinoma Cells. Yongyan Wu et al., Cell Physiol Biochem (2018) 47 pp 1696-1710; Identification of molecular signature of head and neck cancer stem-like cells. S. Shrivastava et al., Nature SCIENTIFIC REPORTS (2015) 5:7819].

Salinomycin >> CD133: "...The combination of salinomycin targeting stem cells with current chemotherapeutic drugs i.e., doxorubicin or paclitaxel directed to cancer cells..." [Lit.: Targeting breast cancer stem cells in triple-negative breast cancer using a combination of LBH589 and salinomycin. M. Kai, et al., Breast Cancer Res. Treat. (2015) 151, 281–294; Targeting Breast Cancer Stem Cells to Overcome Treatment Resistance. Sònia Palomeras et al., Molecules (2018) 23(9): 2193].

Silibinin >> CD44 >: [Lit.: Anti-metastatic Efficacy of Silibinin: Molecular Mechanisms and Therapeutic Potential against Cancer. G. Deep et al., Cancer Metastasis Rev. (2010) 29(3): 447–463].

Atezolizumab / Nivolumab: It was shown in the literature, that the combination of Atezolizumab (>PDL-1) and Nivolumab (>PD1) is more effective than the respective monotherapy. Therapy should be started with low dose to evaluate possible side effects.



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Circulating Tumour Cells Detection Case Study

Patient: FEMALE - 69 years old

Primary Tumour: Head and neck squamous cell carcinoma

1 Isolation of circulating tumour cells (CTC) / micrometastases

Epithelial cells were isolated from the patient's peripheral blood. Mononuclear cells (MNC) served as a control. mRNA was isolated from all cell isolates and the expression of the tumour-relevant genes and chemo sensitivity markers was measured using RT-PCR.

Conclusion: Proof of the increased expression of TERT, C-MYC, BIRC5, EpCAM, CD44, CD133 and CK8/18 refers to the presence of circulating tumor cells (CTC) in the examined blood sample.



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Therapy D.F.

I.V.
Infusions



+

Oral
Supplements



I.V.

- Curcumin
- ECGC
- Vitamin C
- Hyperthermia

Oral

- Niclosamid
- **Salinomycin**
- **Possible combination:**
Atezolizumab,
Nivolumab



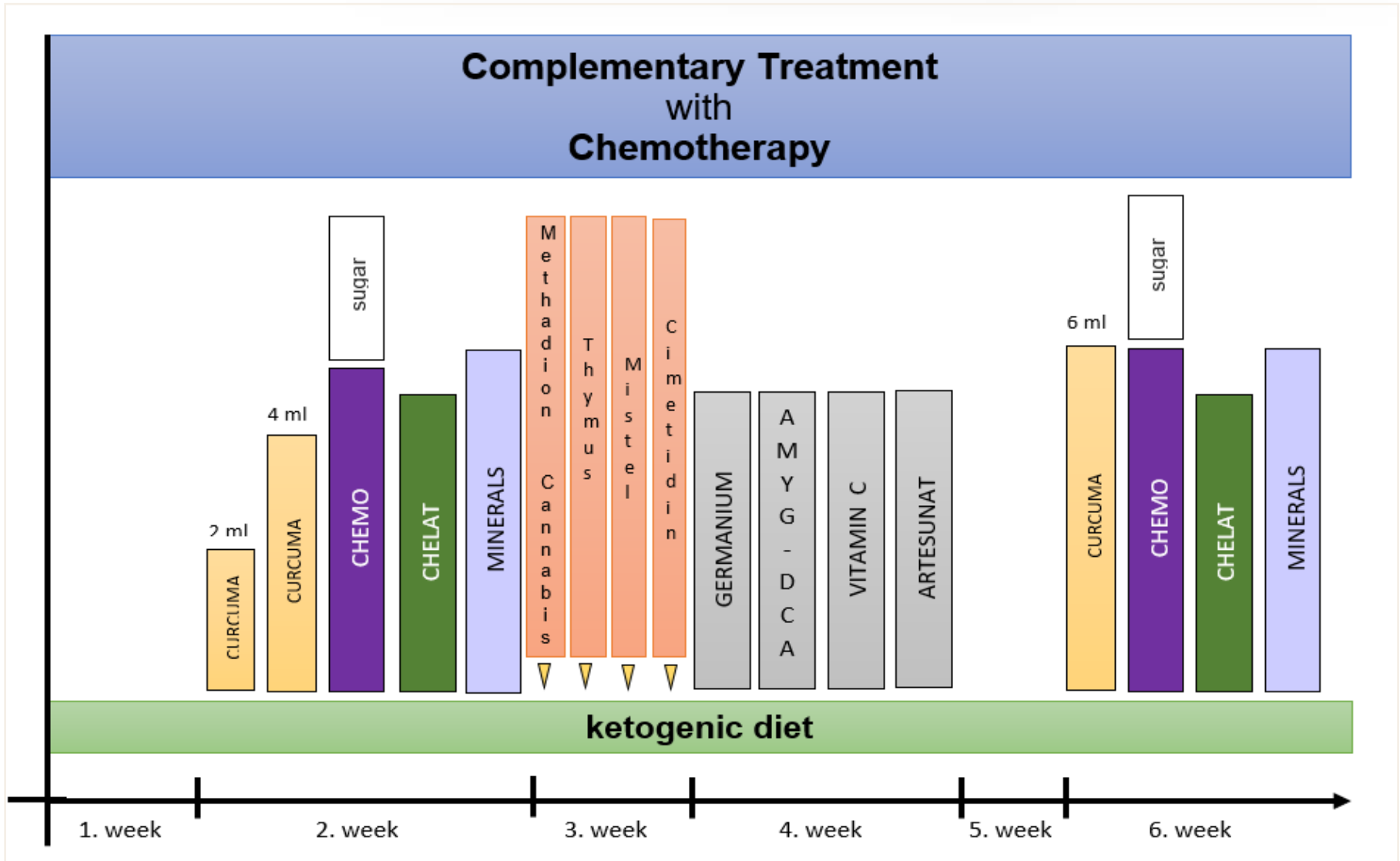


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Complementary Treatment with Chemotherapy






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Thank you for your attention.