Back to the Future: Exploring Novel Research Directions

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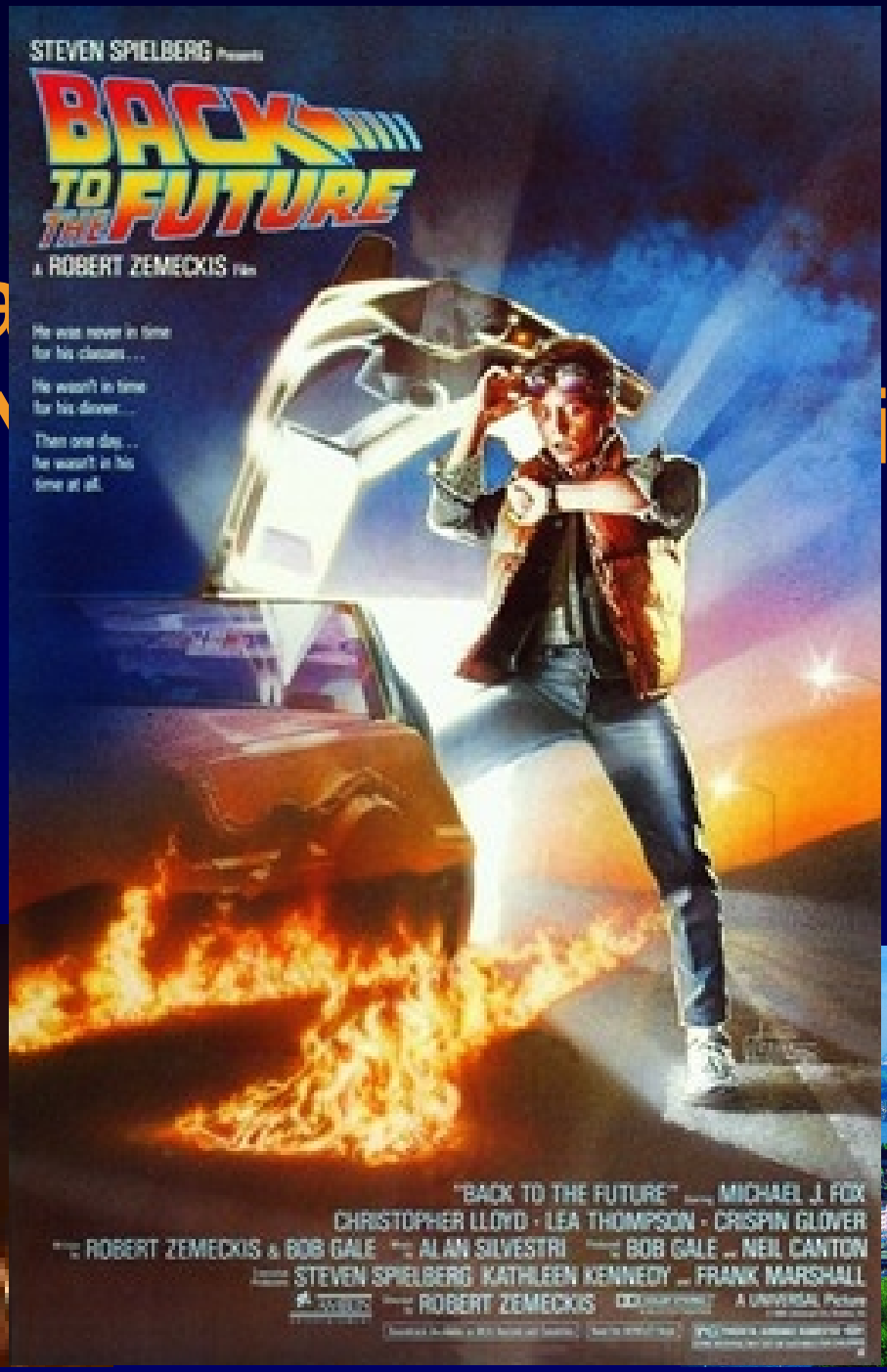
Exploring M irections



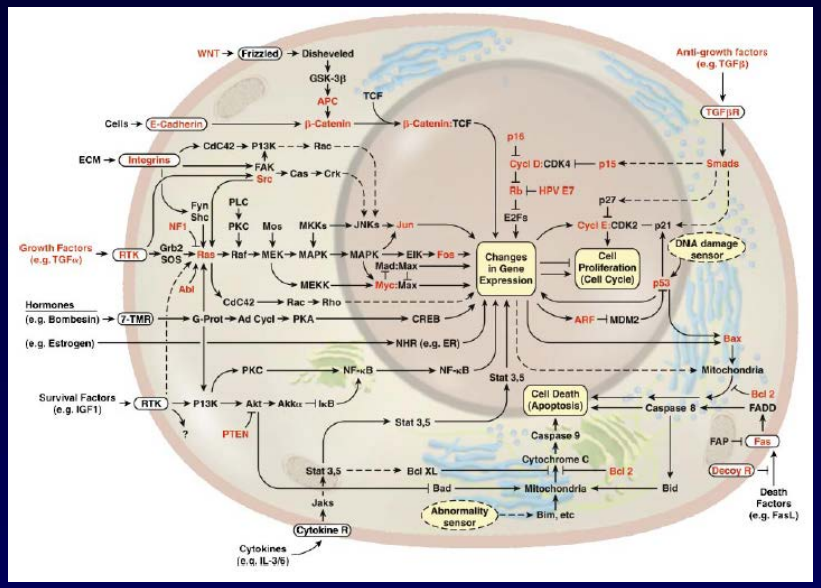
Novel Research Directions & Researchers

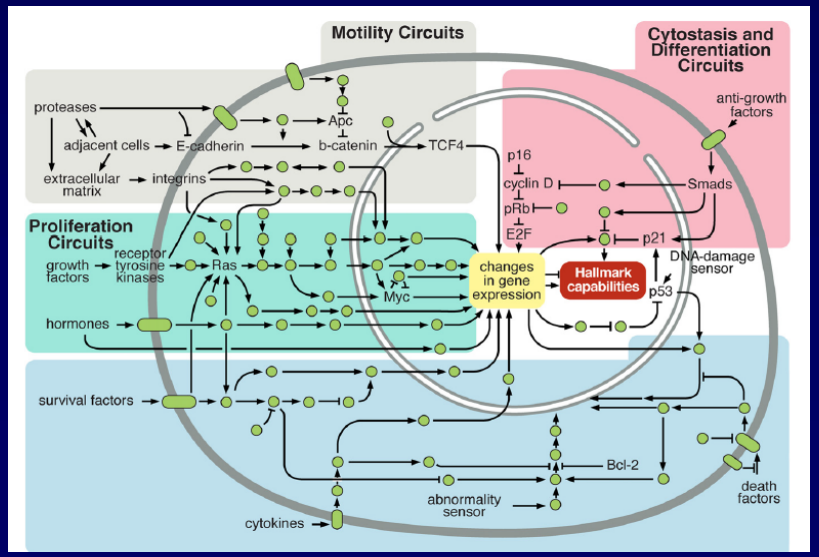
- The Pathfinder
- The Immunologist
- The Metabolomist
- The Device-ologist
- The Optimist

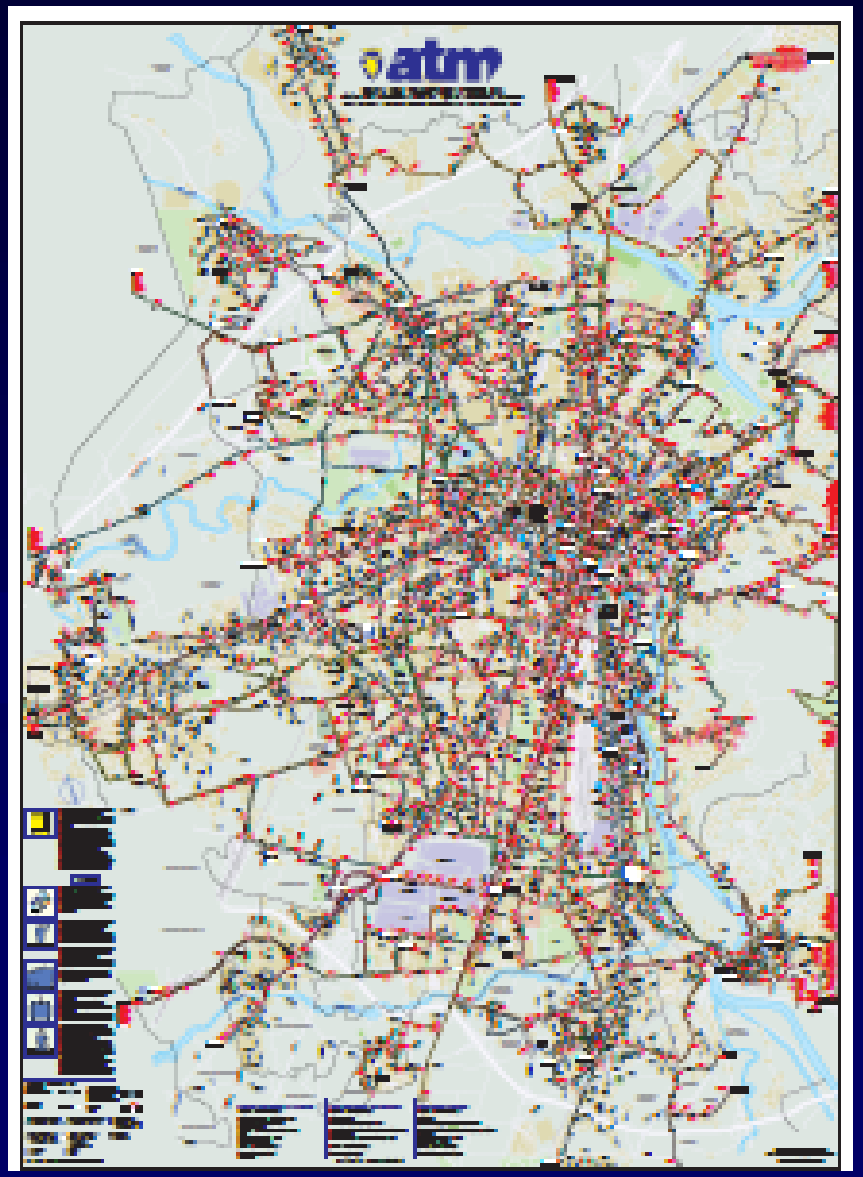
Glioblastoma & CCNU: Terminators for Drug Development?

… just imagine, we would have had CCNU in the control arm of EORTC 26981 NCIC CE.3….

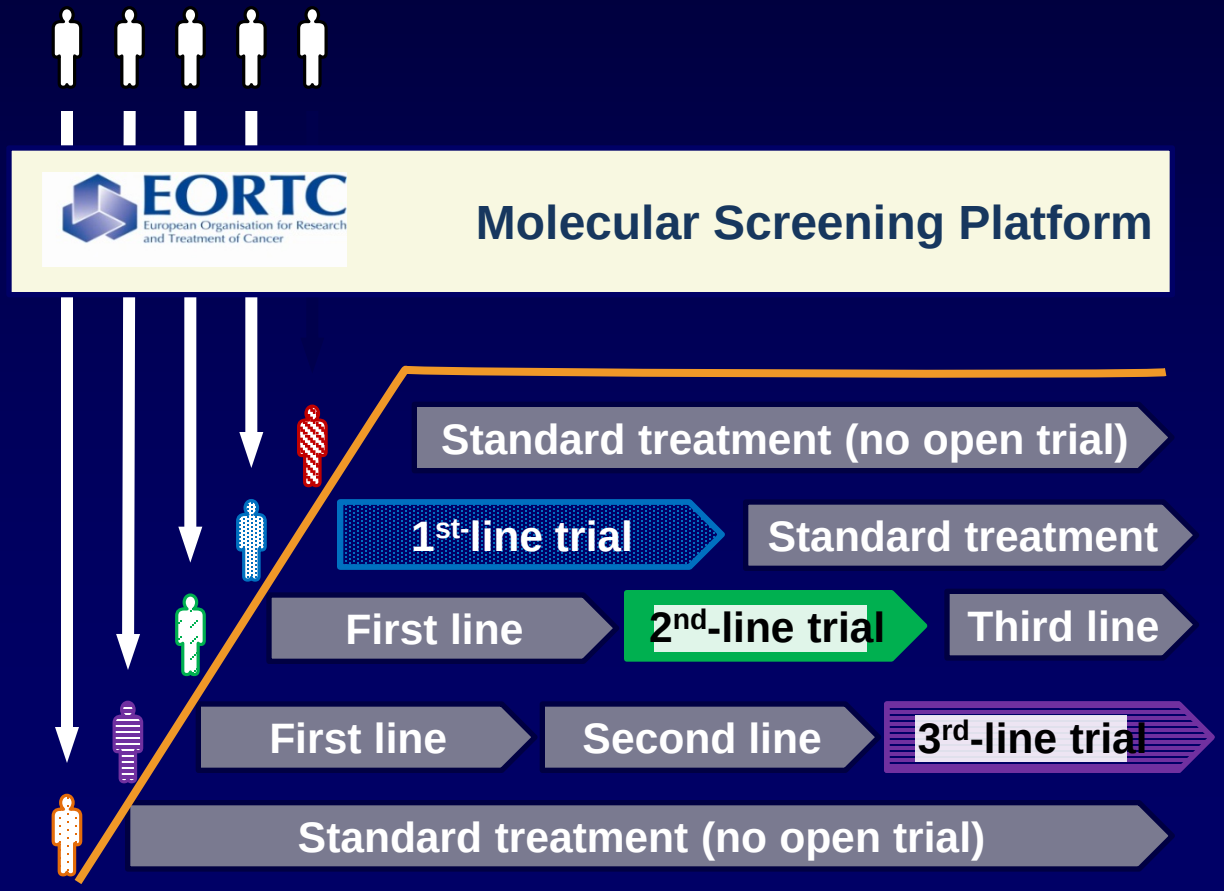
The Pathfinder







The SPECTA Collaborative Platform



Academia investment

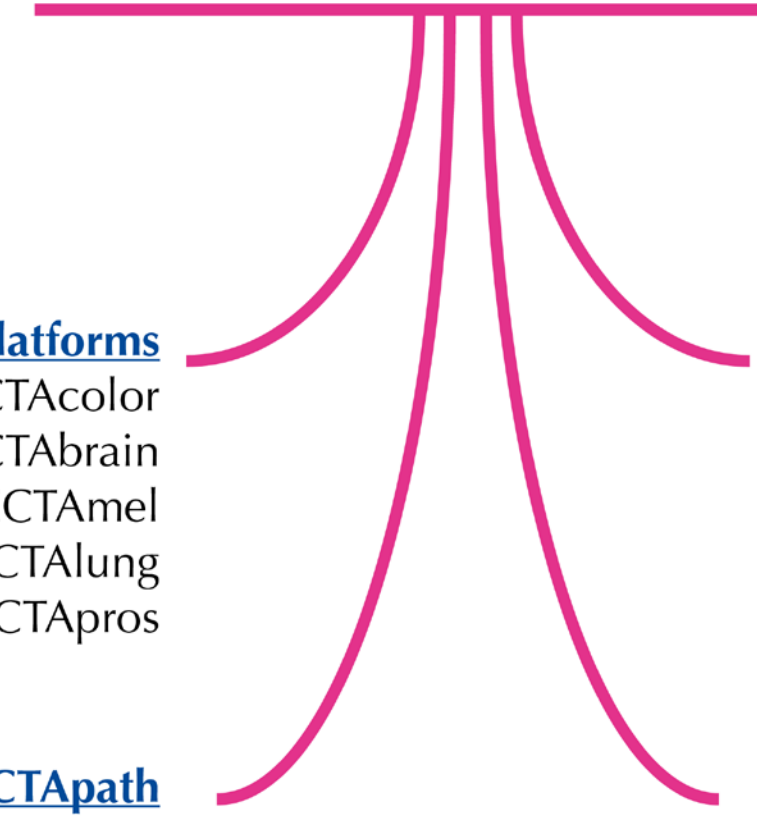
Industry cooperation

EORTC *The future of cancer therapy*

EORTC SPECTA

Screening Patients for Efficient Clinical Trial Access

Screen and Treat



SPECTAplatforms
SPECTAcolor
SPECTAbrain
SPECTAmel
SPECTAlung
SPECTApros

SPECTAforum
Patient representatives
Industry
Regulators
Technology companies
Governments
Payers

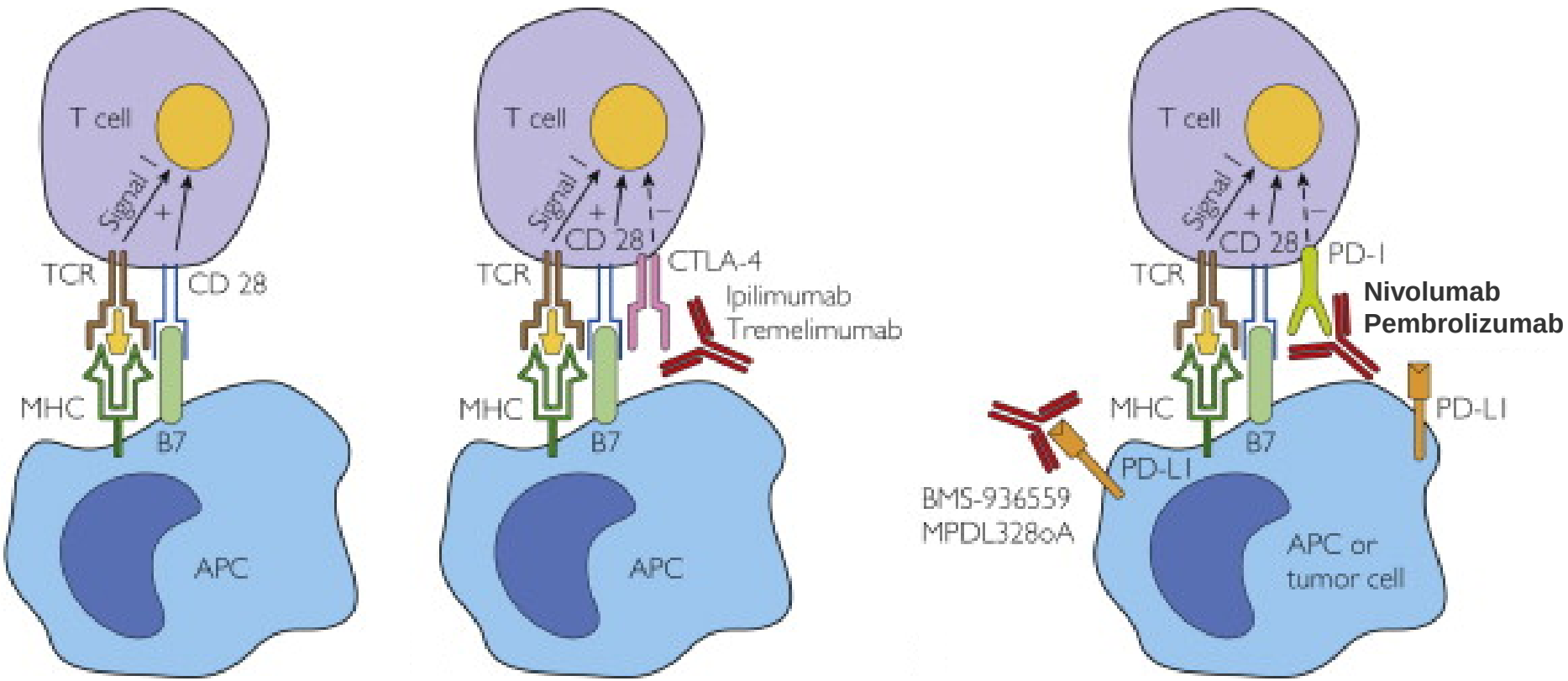
SPECTApath
PathoBiology
Biobanking
Scientific/operational support

SPECTAreg
Competent bodies
Regulatory affairs research

Immunotherapy for Glioblastoma

- Is attractive for scientists and clinicians because it promises cures for incurable cancers
- Is highly popular among patients and relatives
- Has been administered for decades, but not shown efficacy in a controlled clinical trial
- Needs to subscribe to the same standards of clinical trial science as any other approach

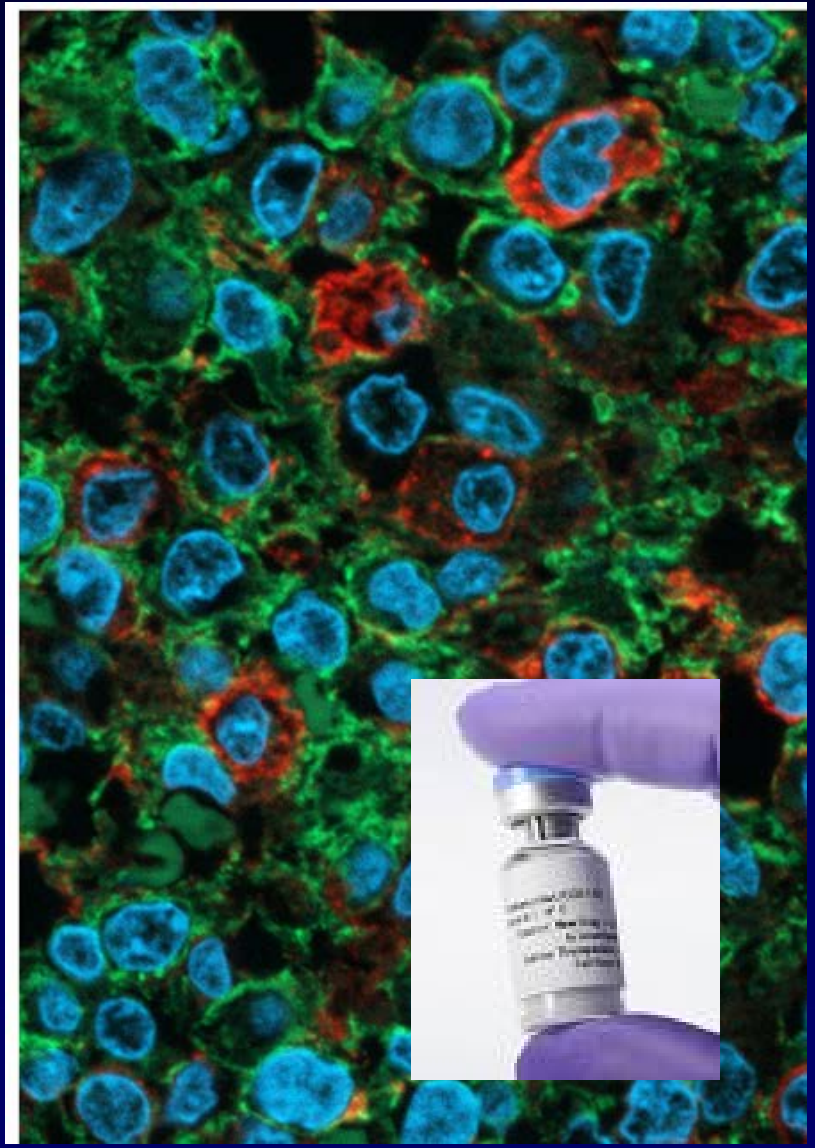
Checkpoint Inhibition

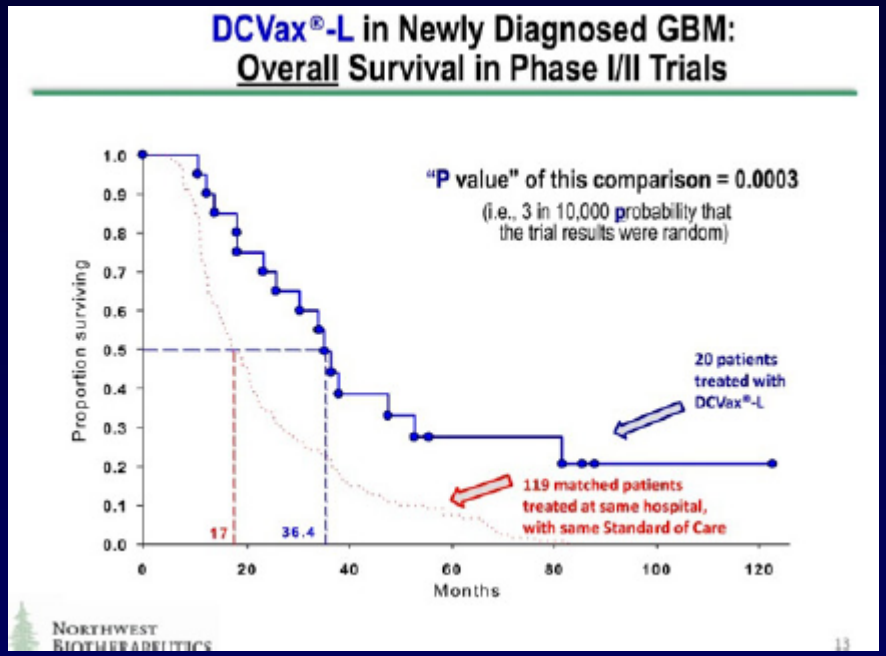


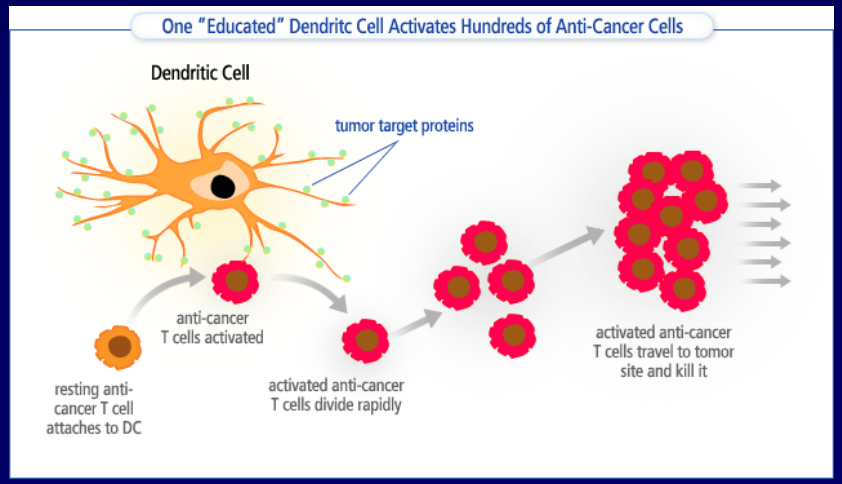
Engagement of CTLA-4 or PD-1 inhibits T-cell activity

=> Inhibition of these «checkpoint» molecules may boost immune responses against a tumor

Vaccination for Glioblastoma?







The Metabolomist

The Metabolomist

Dr. Warburg understood the relationship between oxygen and the pH of cancer cells and reported that cancer has a low pH (as low as 6.0) and therefore thrives when acid levels are high.

His research proves that cancer cannot live in an oxygen rich and an alkaline rich environment (a pH value greater than 7.0).

"Every single person who has cancer has a pH that is too acidic"

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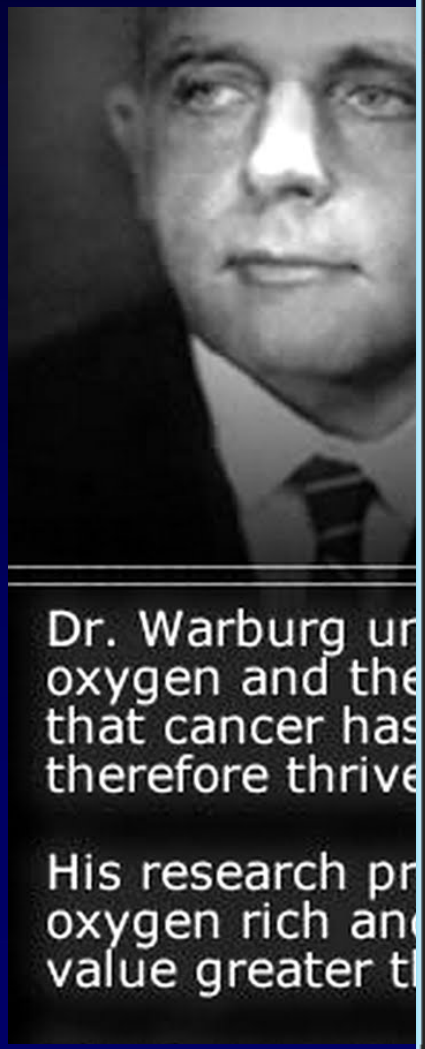
Dr. Otto Warburg won the Nobel Prize in 1931 for proving that cancer can't survive in an alkaline, oxygen rich environment but thrives in an acidic, low oxygen environment.
Dave Sommers



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Change Your Water, Change Your Life!™

Dr. Otto Warburg

Dr. Otto Heinrich Warburg
1931 Nobel Prize Winner
The Real Cause of Cancer

Discovering the Real Cause of Cancer!

Doctor Otto Warburg discovered the real cause of cancer in 1923 and he received the Nobel Prize for doing so in 1931. Dr Warburg was director of the Kaiser Wilhelm Institute (now Max Planck Institute) for cell physiology at Berlin.

He investigated the metabolism of tumors and the respiration of cells, particularly cancer cells.

> "Cancerous tissues are acidic, whereas healthy tissues are alkaline. Water splits into H+ and OH- ions, if there is an access of H+, it is acidic; if there is an excess of OH- ions, then it is alkaline."

In his work The Metabolism of Tumors he demonstrated that all forms of cancer are characterized by two basic conditions: Acidosis and Hypoxia (lack of oxygen). Lack of oxygen and acidosis are two sides of the same coin: where you have one, you have the other.

"All normal cells have an absolute requirement for oxygen, but cancer cells can live without oxygen – a rule without exception." – Dr. Otto Warburg

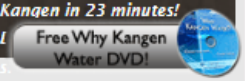
"Deprive a cell 35% of its oxygen for 48 hours and it may become cancerous."

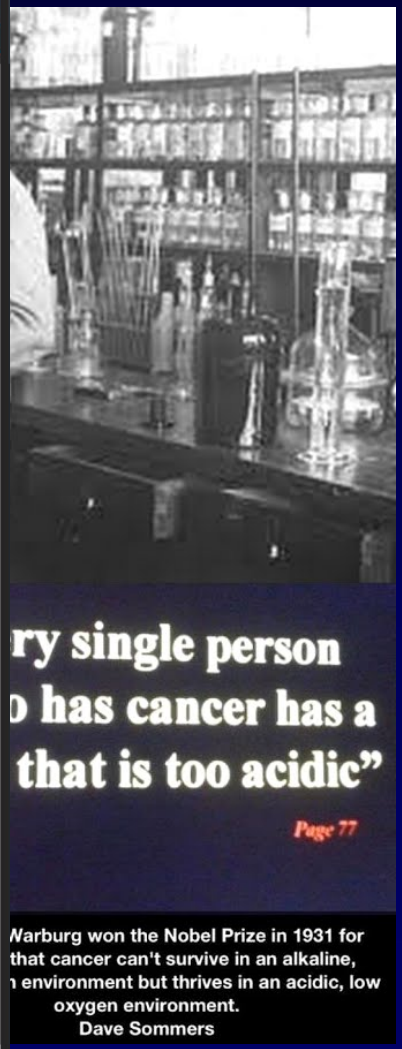
Otto Warburg. Dr Warburg has made it clear that the prime cause of cancer is oxygen deficiency (brought about by Toxemia). Dr Warburg discovered that cancer cells are anaerobic (do not breathe oxygen) and cannot survive in the presence of high levels of oxygen.

Notice how Dr. Warburg states that healthy tissues are alkaline whereas cancerous tissues are acidic. Cancer cannot survive in an alkaline state! What Dr. Warburg discovered is that Alkalinity and longevity go hand in hand.

> The closer one's body is to being alkaline, the healthier that person is. The closer one's body is acidic, the more sick and unhealthy that individual is.

According to Dr Warburg, " Cancers are characterized by two basic conditions: Acidosis and hypoxia (lack of oxygen)" Kangen water fights acidosis and is loaded with oxygen





More From the Metabolomists

EMBARGOED UNTIL 2:00 PM US ET WEDNESDAY, 12 MAY 2010

RESEARCH ARTICLE

CANCER

Metabolic Modulation of Glioblastoma with Dichloroacetate

E. D. Michelakis,[1]* G. Sutendra,[1] P. Dromparis,[1] L. Webster,[1] A. Haromy,[1] E. Niven,[2] C. Maguire,[2] T.-L. Gammer,[1] J. R. Mackey,[3] D. Fulton,[3] B. Abdulkarim,[3] M. S. McMurtry,[1] K. C. Petruk[4]

(Published 12 May 2010; Volume 2 Issue 31 31ra34)

Solid tumors, including the aggressive primary brain cancer glioblastoma multiforme, develop resistance to cell death, in part as a result of a switch from mitochondrial oxidative phosphorylation to cytoplasmic glycolysis. This metabolic remodeling is accompanied by mitochondrial hyperpolarization. We tested whether the small-molecule and orphan drug dichloroacetate (DCA) can reverse this cancer-specific metabolic and mitochondrial remodeling in glioblastoma. Freshly isolated glioblastomas from 49 patients showed mitochondrial hyperpolarization, which was rapidly reversed by DCA. In a separate experiment with five patients who had glioblastoma, we prospectively secured baseline and serial tumor tissue, developed patient-specific cell lines of glioblastoma and putative glioblastoma stem cells ($CD133^+$, $nestin^+$ cells), and treated each patient with oral DCA for up to 15 months. DCA depolarized mitochondria, increased mitochondrial reactive oxygen species, and induced apoptosis in GBM cells, as well as in putative GBM stem cells, both in vitro and in vivo. DCA therapy also inhibited the hypoxia-inducible factor–1α, promoted p53 activation, and suppressed angiogenesis both in vivo and in vitro. The dose-limiting toxicity was a dose-dependent, reversible peripheral neuropathy, and there was no hematologic, hepatic, renal, or cardiac toxicity. Indications of clinical efficacy were present at a dose that did not cause peripheral neuropathy and at serum concentrations of DCA sufficient to inhibit the target enzyme of DCA, pyruvate dehydrogenase kinase II, which was highly expressed in all glioblastomas. Metabolic modulation may be a viable therapeutic approach in the treatment of glioblastoma.

More From the Metabolomists

ARTICLES

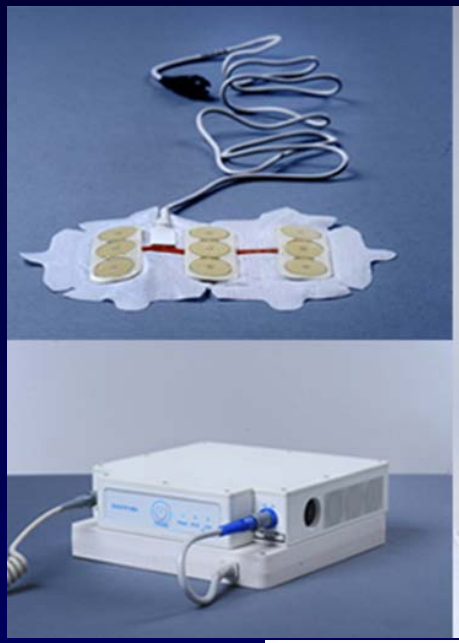
nature medicine

BCAT1 promotes cell proliferation through amino acid catabolism in gliomas carrying wild-type IDH1

Martje Tönjes[1,20], Sebastian Barbus[1,20], Yoon Jung Park[2,3], Wei Wang[1], Magdalena Schlotter[1], Anders M Lindroth[2], Sabrina V Pleier[1,4], Alfa H C Bai[1], Daniela Karra[5], Rosario M Piro[6,7], Jörg Felsberg[5], Adele Addington[8], Dieter Lemke[9], Irene Weibrecht[1], Volker Hovestadt[1], Claudio G Rolli[10], Benito Campos[11,12], Sevin Turcan[13], Dominik Sturm[1,4,14], Hendrik Witt[1,4,14], Timothy A Chan[13], Christel Herold-Mende[11,12], Ralf Kemkemer[10,15], Rainer König[6,7], Kathrin Schmidt[16], William-Edmund Hull[17], Stefan M Pfister[1,4,14], Manfred Jugold[18], Susan M Hutson[8], Christoph Plass[2], Jürgen G Okun[16], Guido Reifenberger[5,19], Peter Lichter[1] & Bernhard Radlwimmer[1]

Here we show that glioblastoma express high levels of branched-chain amino acid transaminase 1 (BCAT1), the enzyme that initiates the catabolism of branched-chain amino acids (BCAAs). Expression of BCAT1 was exclusive to tumors carrying wild-type isocitrate dehydrogenase 1 (IDH1) and IDH2 genes and was highly correlated with methylation patterns in the *BCAT1* promoter region. BCAT1 expression was dependent on the concentration of α-ketoglutarate substrate in glioma cell lines and could be suppressed by ectopic overexpression of mutant IDH1 in immortalized human astrocytes, providing a link between IDH1 function and BCAT1 expression. Suppression of BCAT1 in glioma cell lines blocked the excretion of glutamate and led to reduced proliferation and invasiveness *in vitro*, as well as significant decreases in tumor growth in a glioblastoma xenograft model. These findings suggest a central role for BCAT1 in glioma pathogenesis, making BCAT1 and BCAA metabolism attractive targets for the development of targeted therapeutic approaches to treat patients with glioblastoma.

The Device-ologist



Tumor Treating Fields

A New Treatment for Newly Diagnosed Glioblastoma Brain Tumors

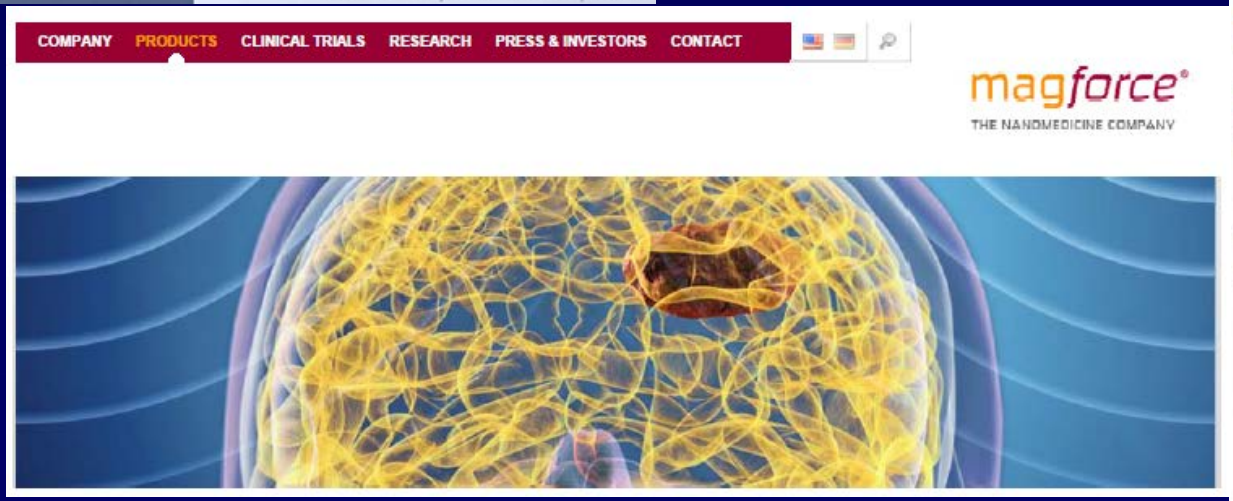
Overview

Thank you for visiting NovoCureTrial.com to learn about our newly diagnosed glioblastoma clinical trial. This glioblastoma trial, also known as a GBM clinical trial or simply a GBM trial, is an FDA approved Pivotal/Phase III clinical trial evaluating the safety and efficacy of the Novo-TTF device, a non-invasive device. NovoCure Ltd., the trial sponsor, maintains this website to help recruit patients for the trial.

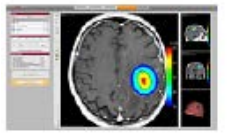
The Device and Treatment

The NovoTTF-100A is a portable, investigational device for cancer treatment using TTFields - Tumor Treating Fields (SCIENCE). The device is intended for continuous home use by patients (TREATMENT) with a newly diagnosed GBM tumor (ELIGIBILITY). Results from a pilot study of the device suggest that the investigational treatment may increase the length of time before disease progression and increase median overall survival newly diagnosed GBM patients. These results were from a small study and have not yet been validated. The device has not yet been proven to be safe and effective for any indication. (CLINICAL EXPERIENCE).

CLINICAL EXPERIENCE



NanoTherm™



NanoPlan®

NanoActivator®

Brain Tumor Funders Collaborative: Long-Term Survival in Glioblastoma