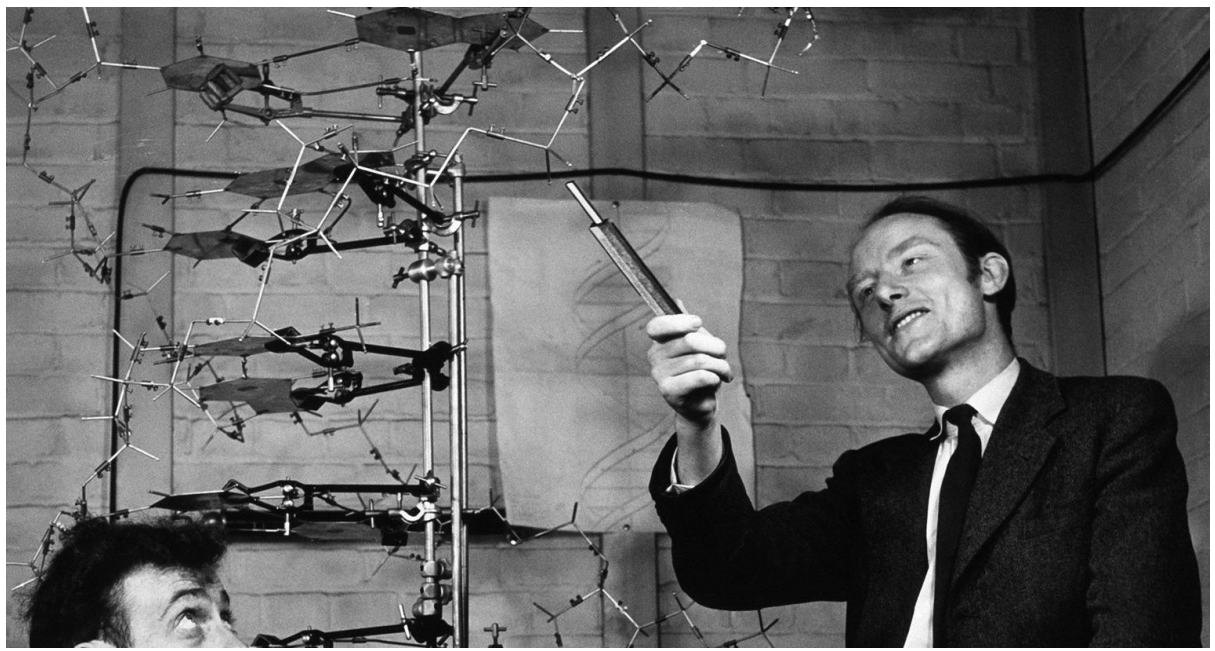
THE UNMET NEED

TRAVIS CHRISTOFFERSON

As Lewis Cantley, the director of the Cancer Center at Weill Cornell Medicine, once put it, “Metformin may have already saved more people from cancer deaths than any drug in history.” Nobel laureate James Watson (of DNA-structure fame), who takes metformin off-label for cancer prevention, once suggested that the drug appeared to be “our only real clue into the business” of fighting the disease.

SAM APPLE
07.01.1707:00 AM
FORGET THE BLOOD OF TEENS. THIS PILL PROMISES TO EXTEND LIFE FOR A NICKEL A POP
Wired Magazine




National Press Club
THE CANCER GENOME ATLAS

Program Overview

There are at least 200 forms of cancer, and many more subtypes. Each of these is caused by errors in DNA that cause cells to grow uncontrolled. Identifying the changes in each cancer's complete set of DNA – its genome – and understanding how such changes interact to drive the disease will lay the foundation for improving cancer prevention, early detection and treatment.

The Cancer Genome Atlas (TCGA), a collaboration between the National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI), has generated comprehensive, multi-dimensional maps of the key genomic changes in 33 types of cancer. The TCGA dataset, 2.5 petabytes of data describing tumor tissue and matched normal tissues from more than 11,000 patients, is publically available and has been used widely by the research community. The data have contributed to more than a thousand studies of cancer by independent researchers and to the TCGA research network publications.

TCGA created a genomic data analysis pipeline that can effectively collect, select, and analyze human tissues for genomic alterations on a very large scale. The success of this national network of research and technology teams serves as a model for future projects and exemplifies the tremendous power of teamwork in science.

Launch Data Portal

The Genomic Data Commons (GDC) Data Portal is an interactive data system for researchers to search, download, upload, and analyze harmonized cancer genomic data sets, including TCGA.

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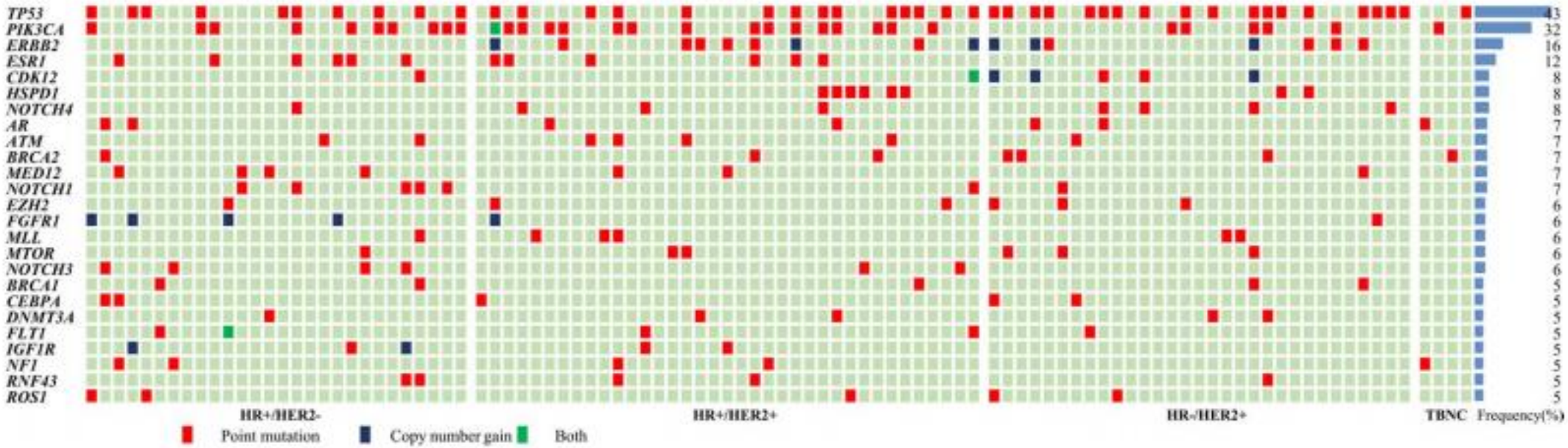
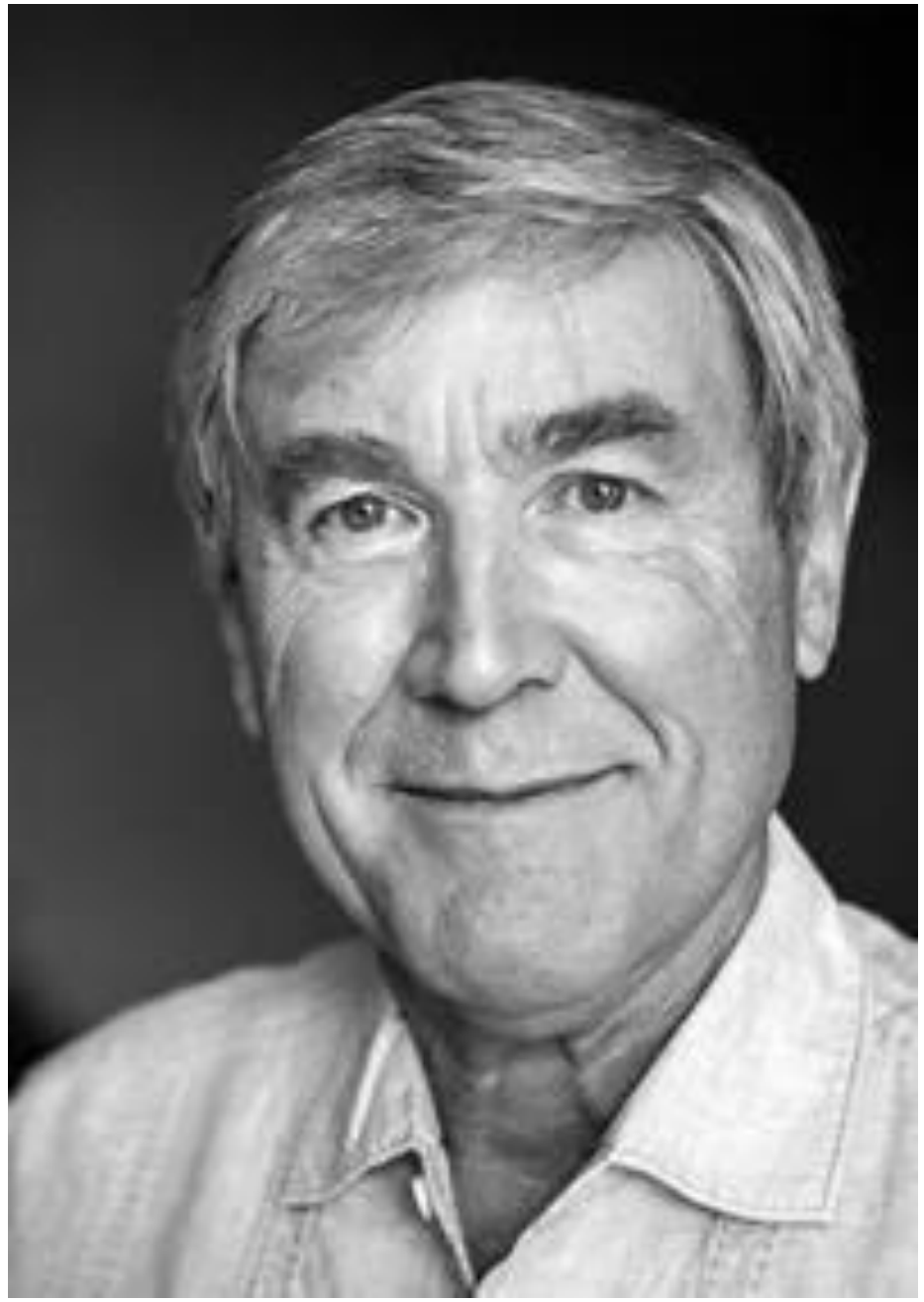
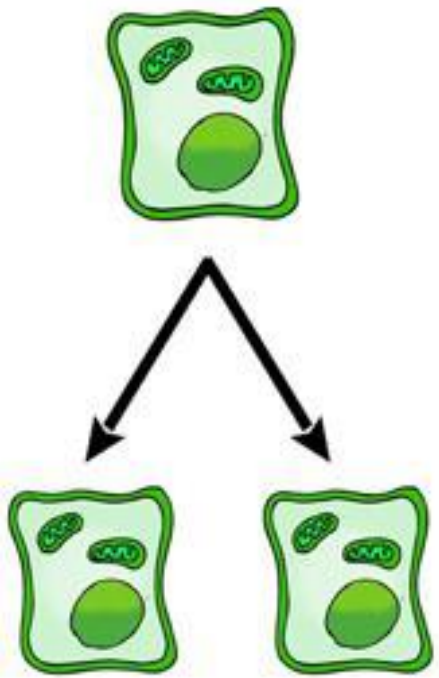


Figure 1. The landscape of hotspot mutations in advanced breast cancer. Each of the 25 hotspot gene mutations has been identified in more than 5 patients listed to the left of the figure. The number of mutations in each gene among the 100 patients is shown (rows). Point mutations, copy number changes and both are colored red, blue and purple, respectively.

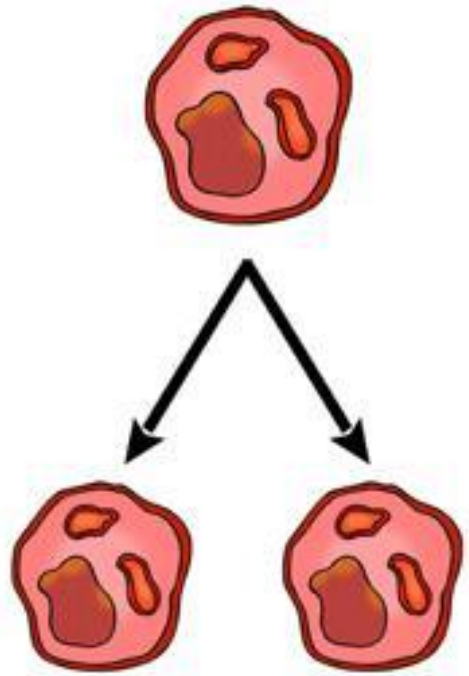


1. Normal Cell



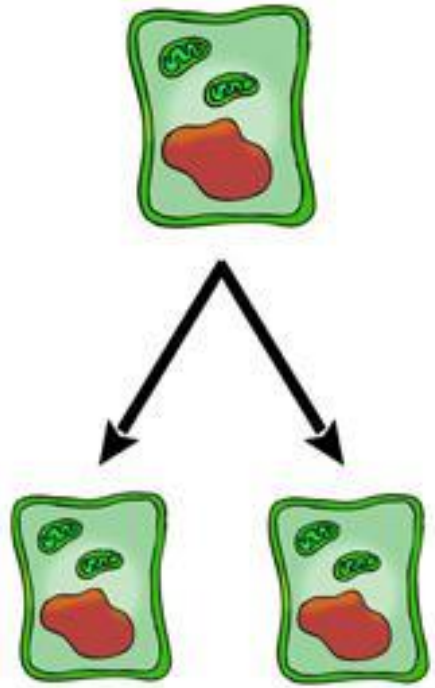
Normal Cells

2. Tumor Cell



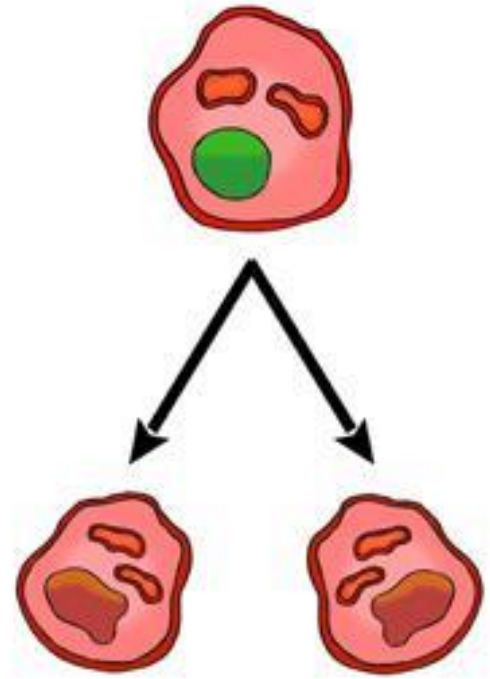
Tumor Cells

3. Normal Cytoplasm + Tumor Nucleus

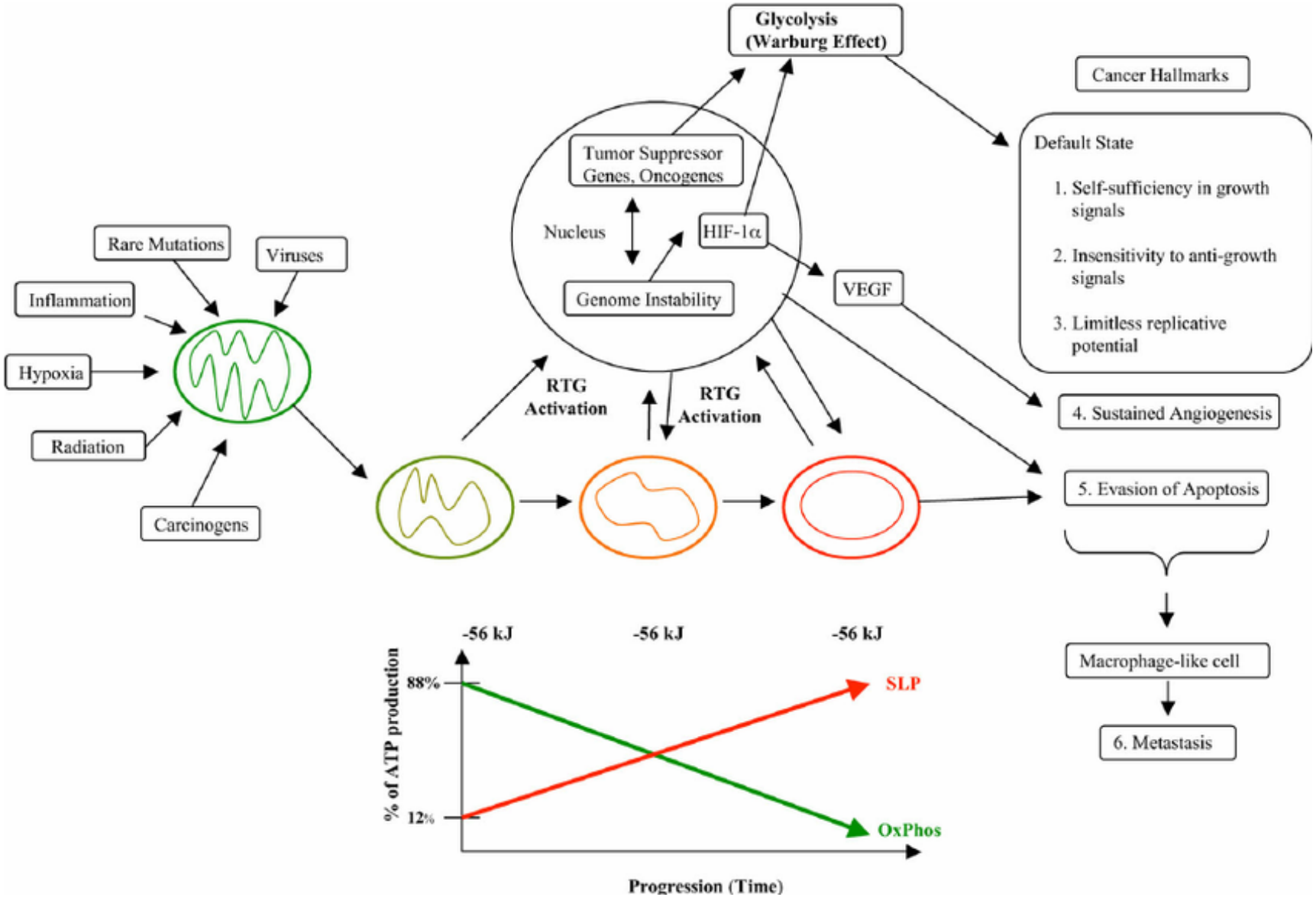


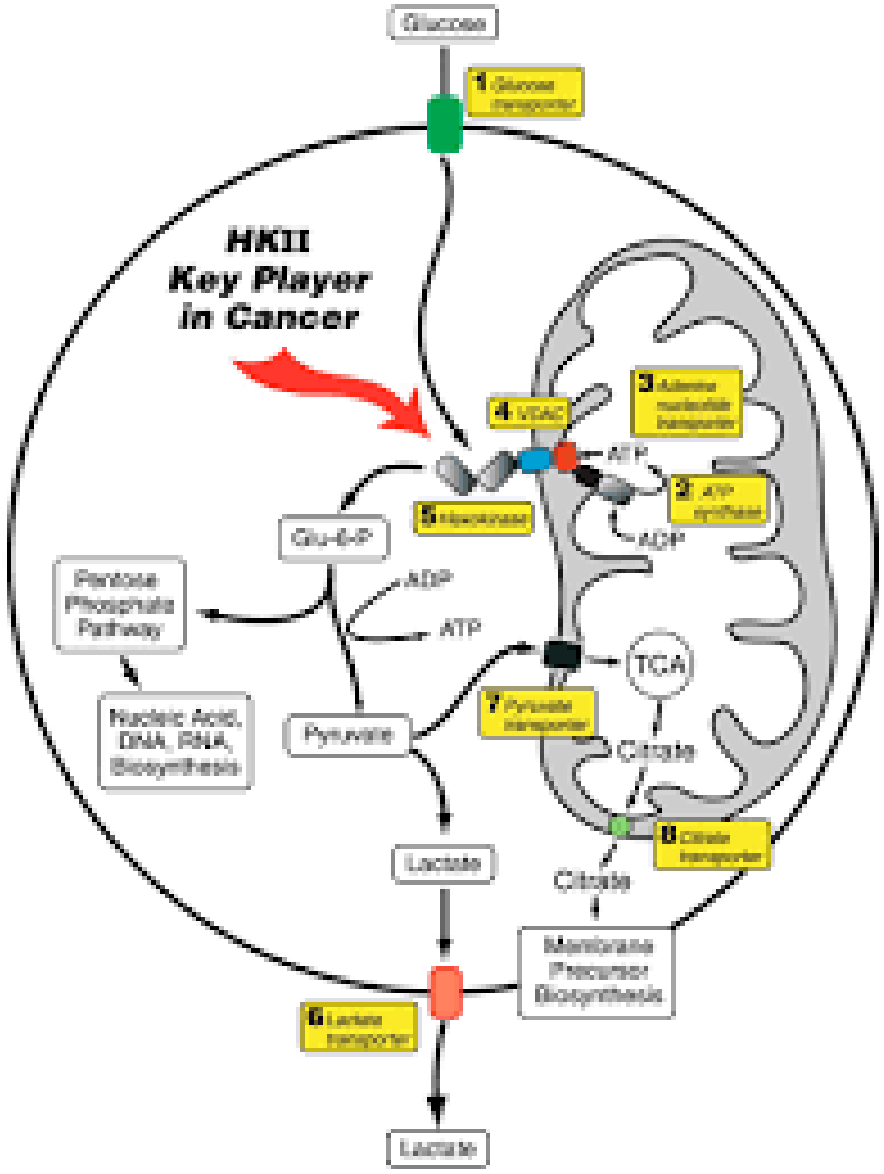
Normal Cells

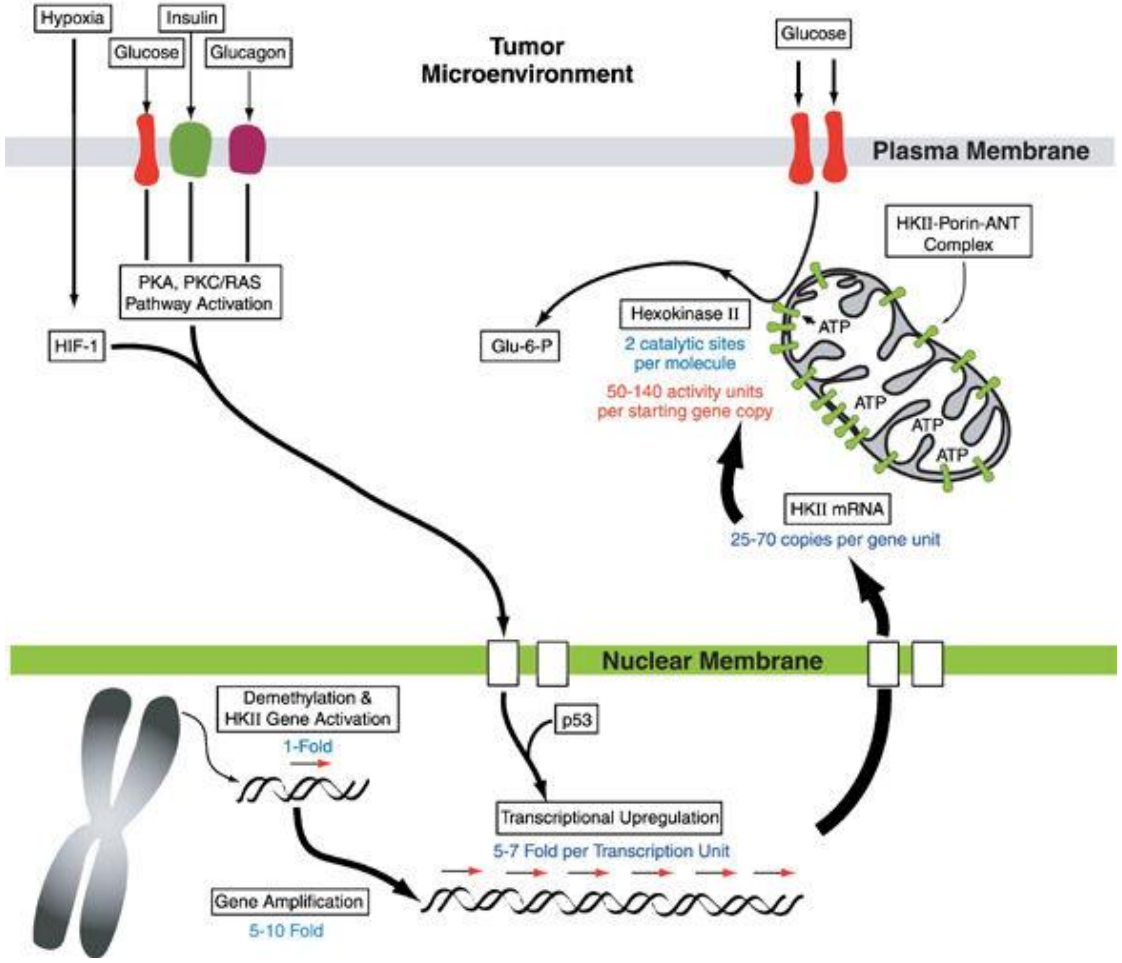
4. Tumor Cytoplasm + Normal Nucleus



Tumor Cells/Death


Glycolysis
(Warburg Effect)
Cancer Hallmarks
Default State
1. Self-sufficiency in growth signals
2. Insensitivity to anti-growth signals
3. Limitless replicative potential
Tumor Suppressor Genes, Oncogenes
Nucleus
HIF-1α
Genome Instability
VEGF
Rare Mutations
Viruses
Inflammation
Hypoxia
Radiation
Carcinogens
RTG Activation
RTG Activation
4. Sustained Angiogenesis
5. Evasion of Apoptosis
Macrophage-like cell
6. Metastasis
-56 kJ
-56 kJ
-56 kJ
% of ATP production
88%
12%
SLP
OxPhos
Progression (Time)


Glucose
HKII
Key Player
in Cancer
4 VDAC
3
2
5
ATP
ADP
Glu-6-P
Pentose Phosphate Pathway
ADP
ATP
Nucleic Acid, DNA, RNA, Biosynthesis
Pyruvate
TCA
7
Citrate
8
Lactate
Citrate
Membrane Precursor Biosynthesis
6
Lactate


Hypoxia
Insulin
Glucose
Glucagon
Tumor Microenvironment
Glucose
Plasma Membrane
HKII-Porin-ANT Complex
PKA, PKC/RAS Pathway Activation
Hexokinase II
2 catalytic sites per molecule
50-140 activity units per starting gene copy
Glu-6-P
ATP
ATP
ATP
ATP
HIF-1
HKII mRNA
25-70 copies per gene unit
Nuclear Membrane
Demethylation & HKII Gene Activation
1-Fold
p53
Transcriptional Upregulation
5-7 Fold per Transcription Unit
Gene Amplification
5-10 Fold

“At this date, we are not limited by the science; we are limited by our ability to make good use of the information and treatments we already have.”

—Vincent DeVita, MD, Former director of the National Cancer Institute, pioneer of MOPP chemotherapy, author or co-author of more than 450 scientific articles, editor-in-chief of The Cancer Journal and co-author of *Cancer: Principles and Practice of Oncology* and *The Death of Cancer*

INDEPENDENT

CANCER DRUG TRIAL FOR WHEN STANDARD TREATMENT IS NOT VIABLE SHOWS ‘INCREDIBLE’ SIGNS OF SUCCESS

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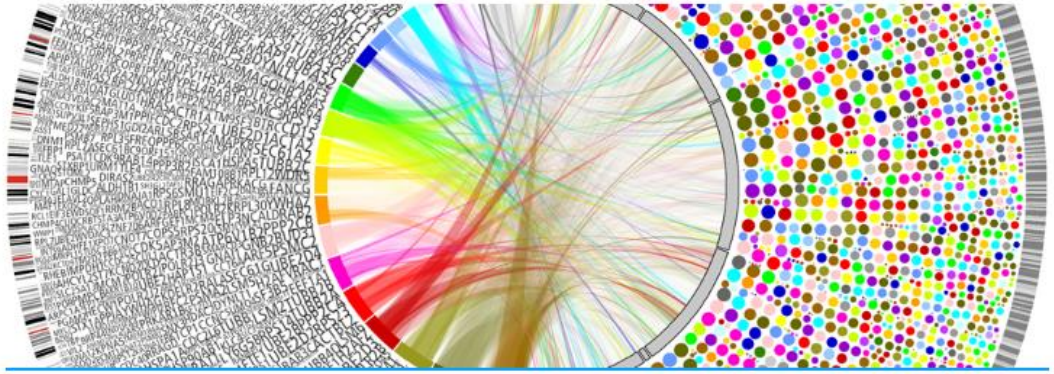

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The Care Oncology Clinic is undertaking a study into and providing cancer treatments that may complement and enhance standard of care therapy. Treating your cancer in combination with your existing treatment may increase its effect. The medications are well understood, with low side effects, offering you an acceptable quality of life.

The Telegraph

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Lifestyle › Health and Fitness › Body

Could these cheap drugs hold a cure for cancer?

share

9 Comments

Rosie Garrett was given 12-15 months to live CREDIT: ANDREW CROWLEY

By **Lois Rogers**

23 JANUARY 2017 • 7:00AM

Almost three years ago, just weeks after her wedding, Rosie Garrett, a 31 year-old children's nanny, was told she would soon

ecancermedicalscience
The open access cancer journal from the European Institute of Oncology and the OECI

Policy

The Repurposing Drugs in Oncology (ReDO) Project

Pan Pantziarka[1,2], Gauthier Bouche[1], Lydie Meheus[1], Vidula Sukhatme[3], Vikas P. Sukhatme[3,4]

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[2]The George Pantziarka TP53 Trust, London KT1 2JP, UK

[3]GlobalCures, Inc, Newton, MA 02459, USA

[4]Beth Israel Deaconess Medical Centre and Harvard Medical School, Boston, MA 02215, USA

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Abstract

The Repurposing Drugs in Oncology (ReDO) Project seeks to repurpose well-known and well-characterised non-cancer drugs for new uses in oncology. The rationale for this project is presented, examining current issues in oncological drug development, challenges for health systems, and existing and future patient needs. In addition to discussing the advantages of repurposing, the paper also outlines some of the characteristics used in the selection of drug candidates by this project. Challenges in moving candidate drugs into clinical trial and subsequent practice are also discussed.

Advantages of Repurposing

- Need for new treatments: “Indeed, some observers have described the situation as a ‘productivity crisis,’” [2]
- “The crisis is particularly acute in oncology, where the success rate for new drugs from Phase I trial to US Food and Drug Administration (FDA) approval in the period 2003 to 2011 was around 6.7%, a figure that is about half the rate for non-oncological drugs [5].”
- Safety: “In contrast to the de novo development of new molecules, drug repurposing begins with known pharmaceutical agents with a history of clinical use. There is, therefore, a wealth of data that is accessible to the clinician and researcher, including published data on pharmokinetics, bioavailability, toxicities (common and uncommon), established protocols, and dosing.”
- Economics: Most repurposed drugs are generics.

“The value of drug repurposing is underappreciated. If you can find a new use for something that’s been out there for 5, 20, or 50 years, that’s very powerful.” –Pankaj Agarwal, director of computational biology and bioinformatics at GlaxoSmithKline

“Generic drugs found to work for a new disease are in a state of purgatory.” —Craig Wegner, AstraZeneca

- Bloom notes that one hurdle to overcome in repurposing inexpensive generic drugs—rather than those still under patent—is persuading pharmaceutical companies to finance the clinical trials needed to get the drugs approved for new uses. On the surface, such a move wouldn't seem to reap big profits for drug makers. **"Because most of these are generic drugs and no one will make a profit if they actually help, it's hard to find the money to do a double-blind randomized clinical trial," he says.**

AN ONCOLOGY CLINIC FROM THE U.K.

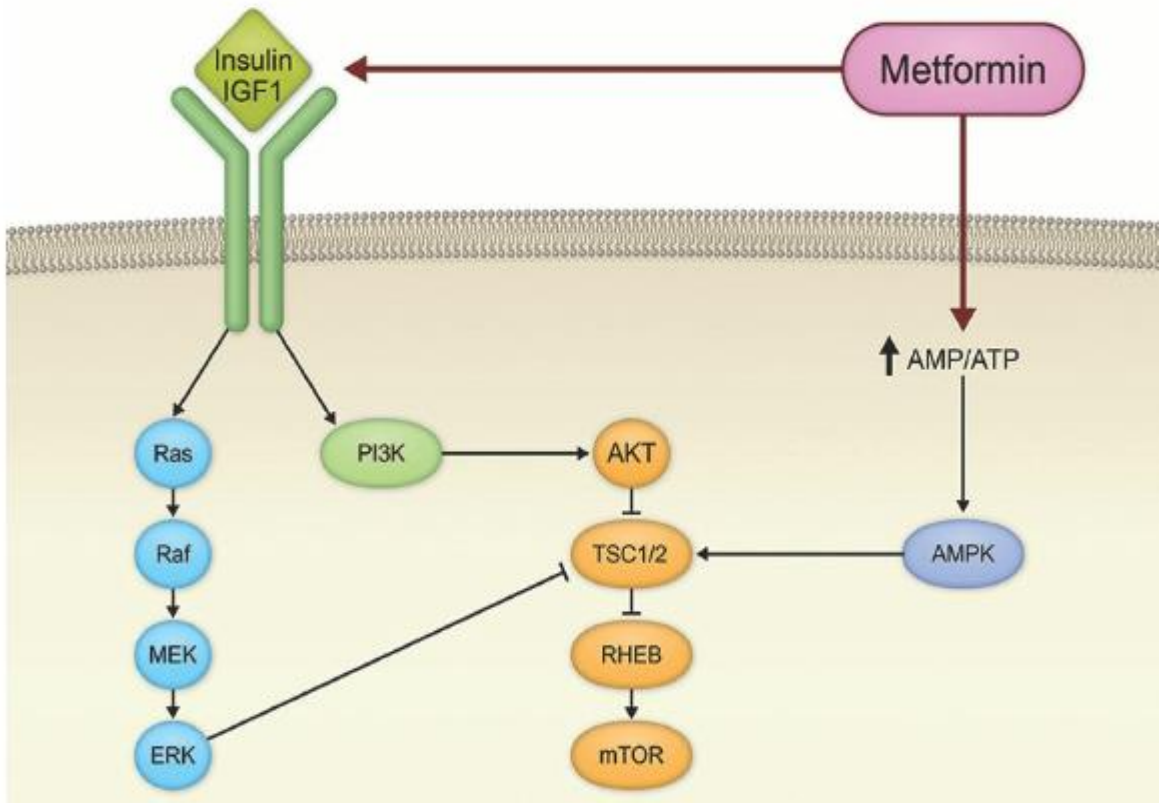
- Enough preclinical and population level data to start treating patients now (2013).
- Designed a “cocktail” therapy that synergistically exploits the dysregulated metabolism and signaling pathways in cancer cells.
- Make sure the drugs have minimal side-effects
- Make sure there are minimal drug interactions with standard-of-care therapies.
- Collect retrospective survival data.

Metformin May Have Broad Utility in Cancer

Diabetes drug shows promise in cancer treatment, prevention

BY SUNITA PATTERSON

52 3 92



- Researchers at MD Anderson found that among 2,529 women with early-stage breast cancer, the pathological complete response rate after chemotherapy was higher (24%) in diabetic patients who had received metformin than in diabetic patients who had not received metformin (8%) and in nondiabetic patients (16%). In the second study, a group in the Department of Gastrointestinal Medical Oncology found that among 255 diabetic patients, the risk of developing pancreatic cancer was 62% lower in those who received metformin than in those who did not.

- A study at the University of Pennsylvania reported dramatic improvement in local recurrence in 16 lung cancer patients who received chemoradiation while taking metformin.

- A study followed 87,344 men diagnosed with prostate cancer between 2000 and 2008. The median overall survival for non-diabetics (not taking metformin), diabetics on metformin, and diabetics not on metformin was 7.1, 9.1, and 7.4 years, respectively. The study concluded that both overall survival and cancer-specific survival were significantly prolonged among the diabetics on metformin.

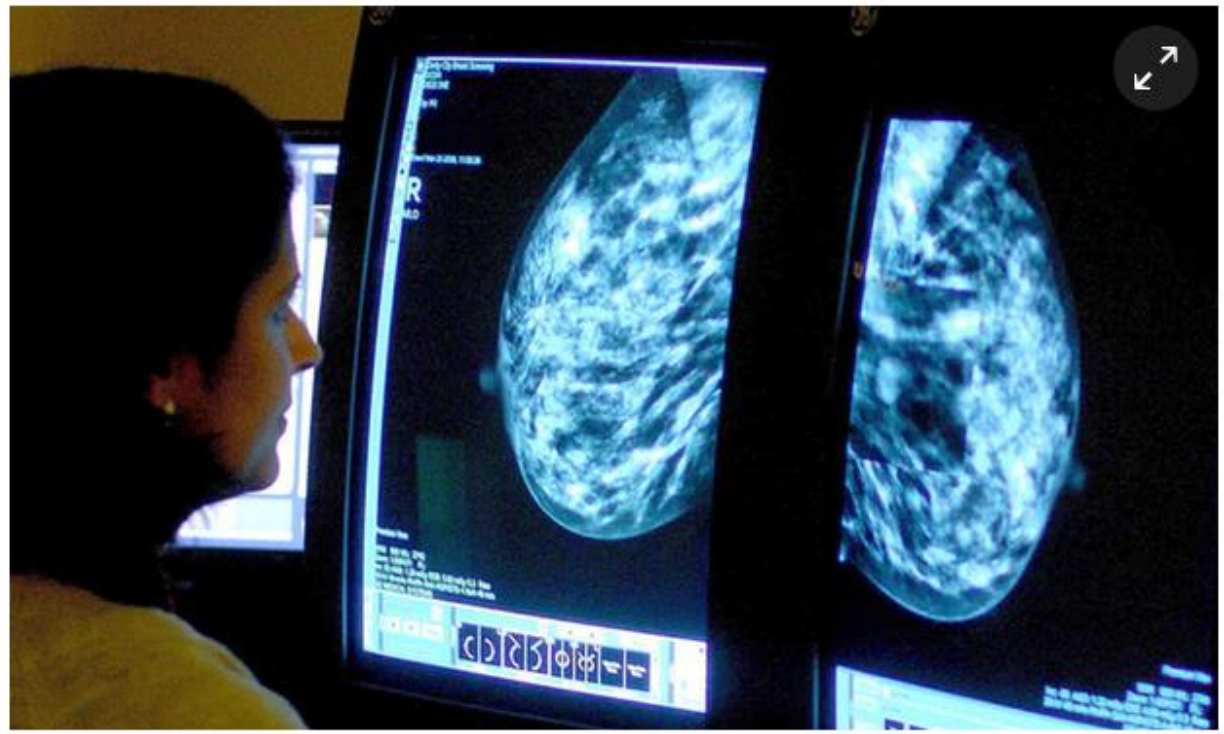
WJCO World Journal of Clinical Oncology

Abstract

In addition to cholesterol reduction, statins, currently the most commonly prescribed drug in the world, have been shown to have anti-neoplastic and immunomodulatory effects. Several observational studies and meta-analyses have shown reduction in risk of multiple cancers. More recently there has been an increasing interest in the potential role of statins as adjuvant therapy after cancer diagnosis and in modifying cancer mortality. Although post-hoc analyses of randomized controlled trials of statins for cardiovascular outcomes have not shown reduction in the risk of cancer mortality with statin use, these studies lack sufficient power to detect a significant difference in cancer outcomes. Recently, in a Danish nationwide population-based cohort study, Nielsen et al showed a 15% reduction in all-cause and cancer-specific mortality in statin users as compared to non-users. Improved survival with statin exposure was seen in 13/27 cancer subtypes, including the 4 most common cancers - lung, prostate, colorectal and breast. In this commentary, we examine this important study, review its implications and limitations, and briefly discuss impact of other drugs like metformin and aspirin that also exhibit anti-neoplastic effects.

Statins could reduce risk of breast cancer death by 38%, research shows

- Chinese research shows statins associated with reduction in death
- Analysis prompts calls for further clinical trials of cholesterol-reducing drugs



Experts and charities said the evidence presented a 'high promise avenue of investigation' for a clinical trial. Photograph: Rui Vieira/PA

“The new analysis of seven previous observational studies was presented at the American Society of Clinical Oncology in Chicago, by Dr Binliang Liu, of the National Cancer Center in Beijing. ***It examined the protective factors linked to the cholesterol-lowering lipophilic statins,*** and comes after research in April found breast cancer patients who took them were less likely to see their cancer come back.

The analysis found that taking statins after a breast cancer diagnosis was associated with an overall reduction in mortality, ***especially in patients who took the drugs for less than four years.*** In the group of women who had breast cancer, the risk of death from cancer and all other causes was reduced by 38%. Overall statin use was associated with a 27% reduction in both cancer-specific and overall mortality.

However, those who took the same drugs for more than four years did not appear to show the same protective association, with only a 16% reduction in cancer-specific death, or death from all others causes.”

Statins Reduce the Risk of Lung Cancer in Humans - A Large Case-Control Study Of US Veterans

Vikas Khurana, MD; Hanmanth R. Bejjanki, MD; Gloria Caldito, PhD; Michael W. Owens, MD

DISCLOSURES | CHEST. 2007;131(5):1282-1288.

Methods: We studied the association of lung cancer and the use of statins in patients enrolled in the Veterans Affairs (VA) Health Care System. A retrospective case-control study nested in a cohort study was conducted using prospectively collected data from the Veterans Integrated Service Networks 16 VA database from 1998 to 2004. We analyzed data on 483,733 patients from eight states located in south central United States. The primary variables of interest were lung cancer and the use of statins prior to the diagnosis of lung cancer. Multiple logistic regression analysis was done to adjust for covariates including age, sex, body mass index, smoking, diabetes, and race. Statistical software was used for statistical computing.

Results: Of the 483,733 patients in the study, 163,662 patients (33.8%) were receiving statins and 7,280 patients (1.5%) had a primary diagnosis of lung cancer. Statin use > 6 months was associated with a risk reduction of lung cancer of 55% (adjusted odds ratio, 0.45; 95% confidence interval, 0.42 to 0.48; $p < 0.01$). Furthermore, the protective effect of statin was seen across different age and racial groups and was irrespective of the presence of diabetes, smoking, or alcohol use.

Conclusions: Statins appear to be protective against the development of lung cancer, and further studies need to be done to define the clinical utility of statins as chemo protective agents.

Statin Use and Survival in Patients with Metastatic Castration-resistant Prostate Cancer Treated with Abiraterone Acetate.

Di Lorenzo G[1], Sonpavde G[2], Pond G[3], Lucarelli G[4], Rossetti S[5], Facchini G[5], Scagliarini S[6], Cartenì G[6], Federico P[7], Daniele B[8], Morelli F[9], Bellelli T[10], Ferro M[11], De Placido S[11], Buonerba C[12].

Author information

Abstract

BACKGROUND: Although statin use has been associated with favorable effects in various solid malignancies, no conclusive evidence is available at present. Statins are safe and inexpensive, and may synergize with novel antiandrogen agents abiraterone via pharmacokinetic interactions and decrease substrate availability for de novo androgen biosynthesis.

OBJECTIVE: To determine whether statin use affects survival in patients with metastatic castration-resistant prostate cancer (mCRPC) treate with abiraterone.

DESIGN, SETTING, AND PARTICIPANTS: Medical records of patients with documented mCRPC between September 2011 and August 2016 were reviewed at multiple participating centers. This research was conducted in ten institutions, including both referral centers and local hospitals. A total of 187 patients receiving abiraterone for mCRPC between September 2011 and August 2016 were eligible for inclusion in this retrospective study.

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Patients were assessed for overall survival (OS), statin use at the time of treatment initiation, prostate-specific antigen (PSA) variations, and other variables of interest. Univariable and multivariable analysis was use to explore the association of variables of interest with OS and PSA declines.

RESULTS AND LIMITATIONS: Statin use was a significant prognostic factor for longer OS in univariable (hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.37-0.72; p<0.001) and multivariable analysis (HR 0.40, 95% CI 0.27-0.59; p<0.001) and was significantly associate with PSA declines (>50% decline at 12 wk: 72.1% in statin users vs 38.5% in non-users; p<0.001).

CONCLUSIONS: Our study suggests a prognostic impact of statin use in patients receiving abiraterone for mCRPC. The mechanism of this interaction warrants elucidation, but may include enhancement of the antitumor activity of abiraterone as well as cardioprotective effects.

PATIENT SUMMARY: We assessed the effects of statin use in patients with advanced prostate cancer receiving abiraterone. Patients treatec with a statin plus abiraterone appeared to live longer than those treated with abiraterone only. Since no negative drug-drug interaction is known and statins are widely used and inexpensive, further studies assessing the use of abiraterone plus statins are warranted.

PLoS One. 2011; 6(12): e28813.
Published online 2011 Dec 22. doi: 10.1371/journal.pone.0028813
PMCID: PMC3245236
PMID: 22216116

Differential Effects of Pravastatin and Simvastatin on the Growth of Tumor Cells from Different Organ Sites

David G. Menter,[1] Victoria P. Ramsauer,[2,6] Sam Harirforoosh,[2] Kanishka Chakraborty,[6] Peiying Yang,[3] Linda Hsi,[4,5] Robert A. Newman,[3] and Koyamangalath Krishnan[6,*]

Joseph Alan Bauer, Editor

Author information ▶ Article notes ▶ Copyright and License information ▶ Disclaimer

"Poorly-differentiated and well-differentiated cancer cell lines were selected from various tissues and examined for their response to these two statins. Simvastatin inhibited the growth of most tumor cell lines more effectively than pravastatin in a dose dependent manner."

Br J Cancer. 2001 Apr 6;84(7):886-91.

Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial.

Kawata S[1], Yamasaki E, Nagase T, Inui Y, Ito N, Matsuda Y, Inada M, Tamura S, Noda S, Imai Y, Matsuzawa Y.

Author information

Abstract

Chemotherapy is not effective for hepatocellular carcinoma (HCC). HMG-CoA redutase inhibitors have cytostatic activity for cancer cells, but their clinical usefulness is unknown. To investigate whether pravastatin, a potent HMG-CoA reductase inhibitor, prolongs survival in patients with advanced HCC, this randomized controlled trial was conducted between February 1990 and February 1998 at Osaka University Hospital. 91 consecutive patients <71 years old (mean age 62) with unresectable HCC were enroled in this study. 8 patients were withdrawn because of progressive liver dysfunction; 83 patients were randomized to standard treatment with or without pravastatin. All patients underwent transcatheter arterial embolization (TAE) followed by oral 5-FU 200 mg(-1)d for 2 months. Patients were then randomly assigned to control (n = 42) and pravastatin (n = 41) groups. Pravastatin was administered at a daily dose of 40 mg. The effect of pravastatin on tumour growth was assessed by ultrasonography. Primary endpoint was death due to progression of HCC. The duration of pravastatin administration was 16.5 +/- 9.8 months (mean +/- SD). No patients in either group were lost to follow-up. Median survival was 18 months in the pravastatin group versus 9 months in controls (P = 0.006). The Cox proportional hazards model showed that pravastatin was a significant factor contributing to survival. Pravastatin prolonged the survival of patients with advanced HCC, suggesting its value for adjuvant treatment.

PMID: 11286466 PMCID: PMC2363838 DOI: 10.1054/bjoc.2000.1716

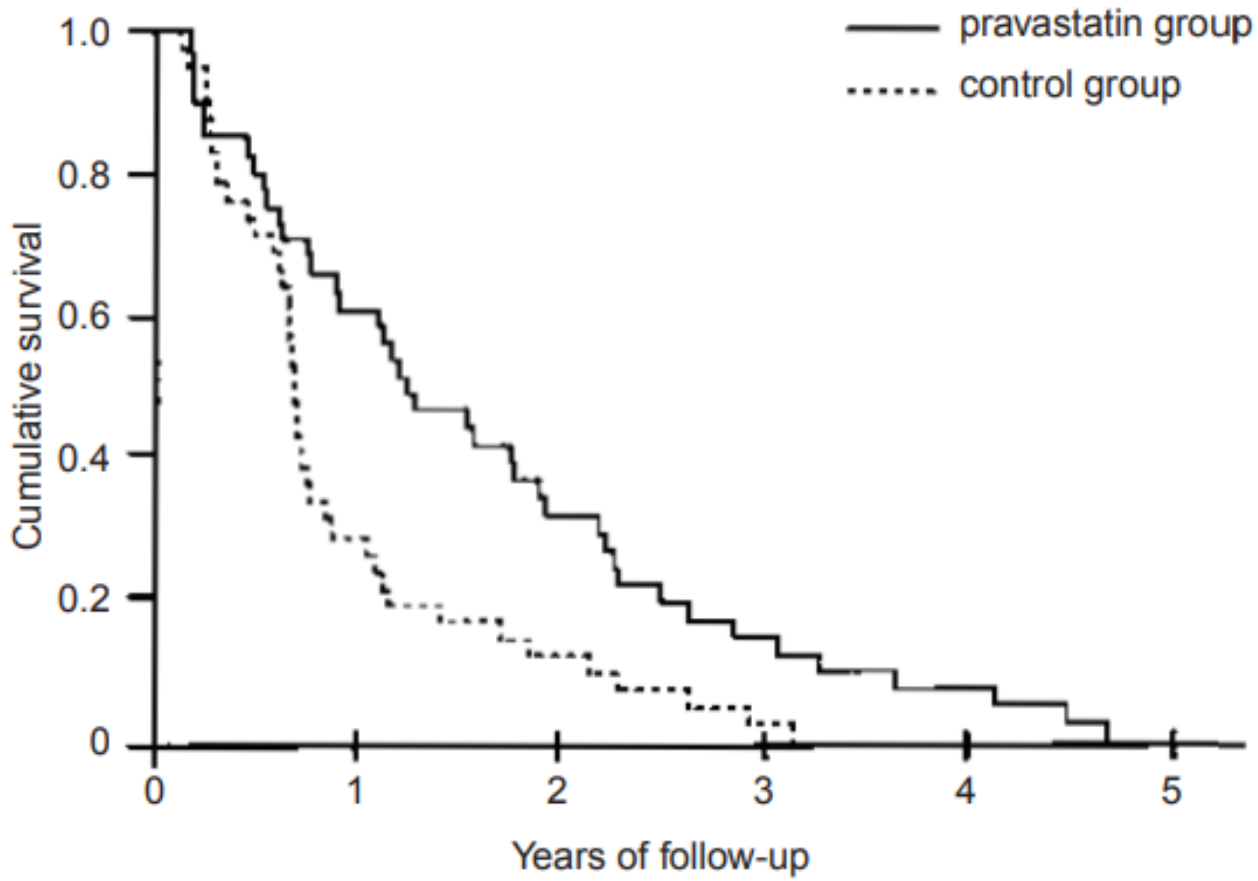


Figure 2 Kaplan–Meier survival curves in pravastatin (n = 41) and control (n = 42) groups. The median survival was 18 months in the pravastatin group and 9 months in the control group (P = 0.006 by the log-rank test)

Tumour Biol. 2015 Jul;36(7):4889-904. doi: 10.1007/s13277-015-3551-7. Epub 2015 May 23.

The effect of statins on cancer cells--review.

Matusewicz L[1], Meissner J, Toporkiewicz M, Sikorski AF.

Author information

Abstract

Statins [3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase, abbreviated HMGCR) inhibitors], are well-known cholesterol-depleting agents. Since the early 1990 s, it has been known that statins could be successfully used in cancer therapy, but the exact mechanism(s) of statin activity remains unclear and is now an extensive focus of investigation. So far, it was proven that there are several mechanisms that are activated by statins in cancer cells; some of them are leading to cell death. Statins exert different effects depending on cell line, statin concentration, duration of exposure of cells to statins, and the type of statin being used. It was shown that statins may inhibit the cell cycle by influence on both expression and activity of proteins involved in cell-cycle progression such as cyclins, cyclin-dependent kinases (CDK), and/or inhibitors of CDK. Also, statins may induce apoptosis by both intrinsic and extrinsic pathways. Statin treatment may lead to changes in molecular pathways dependent on the EGF receptor, mainly via inhibition of isoprenoid synthesis. By inhibition of the synthesis of cholesterol, statins may destabilize the cell membrane. Moreover, statins may change the arrangement of transporter OATP1, the localization of HMGCR, and could induce conformational changes in GLUT proteins. In this review, we have tried to gather and compare most of the recent outcomes of the research in this field. We have also attempted to explain why hydrophilic statins are less effective than hydrophobic statins. Finally, we have gathered results from in vivo experiments, presenting the use of statins in combined therapies and discussed a number of molecular targets that could serve as biomarkers predisposing to statin therapy.

PMID: 26002574 DOI: 10.1007/s13277-015-3551-7

TABLE 2

Risk of Overall and Individual Cancer With Statin or Metformin Use in HBV Patients

		Nonuser (n = 53,037)	Only-Metformin (n = 4774)	Only-Statin (n = 8861)	M + S (n = 5152)
All Group (n = 71,824)	No. of Patients	Adjusted HR[†] (95% CI)	Adjusted HR[†] (95% CI)	Adjusted HR[†] (95% CI)	Adjusted HR[†] (95% CI)
Total cancer	5434	1.00	1.03 (0.94–1.14)	0.60 (0.55–0.66)***	0.46 (0.40–0.52)***
Liver cancer	1735	1.00	1.25 (1.06–1.47)**	0.34 (0.27–0.42)***	0.35 (0.27–0.45)***
Nonliver cancer	3699	1.00	0.94 (0.83–1.06)	0.72 (0.65–0.80)***	0.50 (0.44–0.58)***
Lung cancer	439	1.00	0.91 (0.66–1.26)	0.51 (0.37–0.70)***	0.49 (0.34–0.71)***
Stomach cancer	144	1.00	0.77 (0.42–1.42)	0.59 (0.35–1.00)*	0.31 (0.14–0.69)**
Colorectal cancer	572	1.00	1.14 (0.85–1.53)	0.84 (0.65–1.09)	0.51 (0.35–0.75)***
Esophagus cancer	93	1.00	1.19 (0.61–2.31)	0.38 (0.17–0.86)*	0.30 (0.11–0.87)*
Pancreatic cancer	127	1.00	1.33 (0.74–2.41)	0.73 (0.40–1.31)	0.70 (0.34–1.43)
Prostate cancer[‡]	225	1.00	0.94 (0.59–1.50)	0.77 (0.51–1.15)	0.63 (0.37–1.05)
Breast cancer[§]	288	1.00	0.80 (0.47–1.32)	0.91 (0.63–1.33)	0.56 (0.33–0.95)*
Cervical cancer[§]	105	1.00	0.70 (0.31–1.58)	0.67 (0.35–1.25)	0.28 (0.10–0.79)*
Other cancers	1706	1.00	0.91 (0.76–1.09)	0.51 (0.42–0.64)***	0.75 (0.65–0.88)***

CI = confidence interval, HBV = hepatitis B virus, HR = hazard ratio, M = metformin, S = statin.

[†] Adjusted for baseline propensity score.

[‡] Study cohort for female patients.

[§] Study cohort for male patients.

* $P < 0.05$.

Biol Pharm Bull. 2017;40(8):1247-1254. doi: 10.1248/bpb.b17-00077.

Mechanistic Study of Inhibitory Effects of Metformin and Atorvastatin in Combination on Prostate Cancer Cells in Vitro and in Vivo.

Wang ZS[1], Huang HR[1], Zhang LY[1], Kim S[2], He Y[1], Li DL[3], Farischon C[2], Zhang K[1,2], Zheng X[2,4], Du ZY[1], Goodin S[4].

⊕ Author information

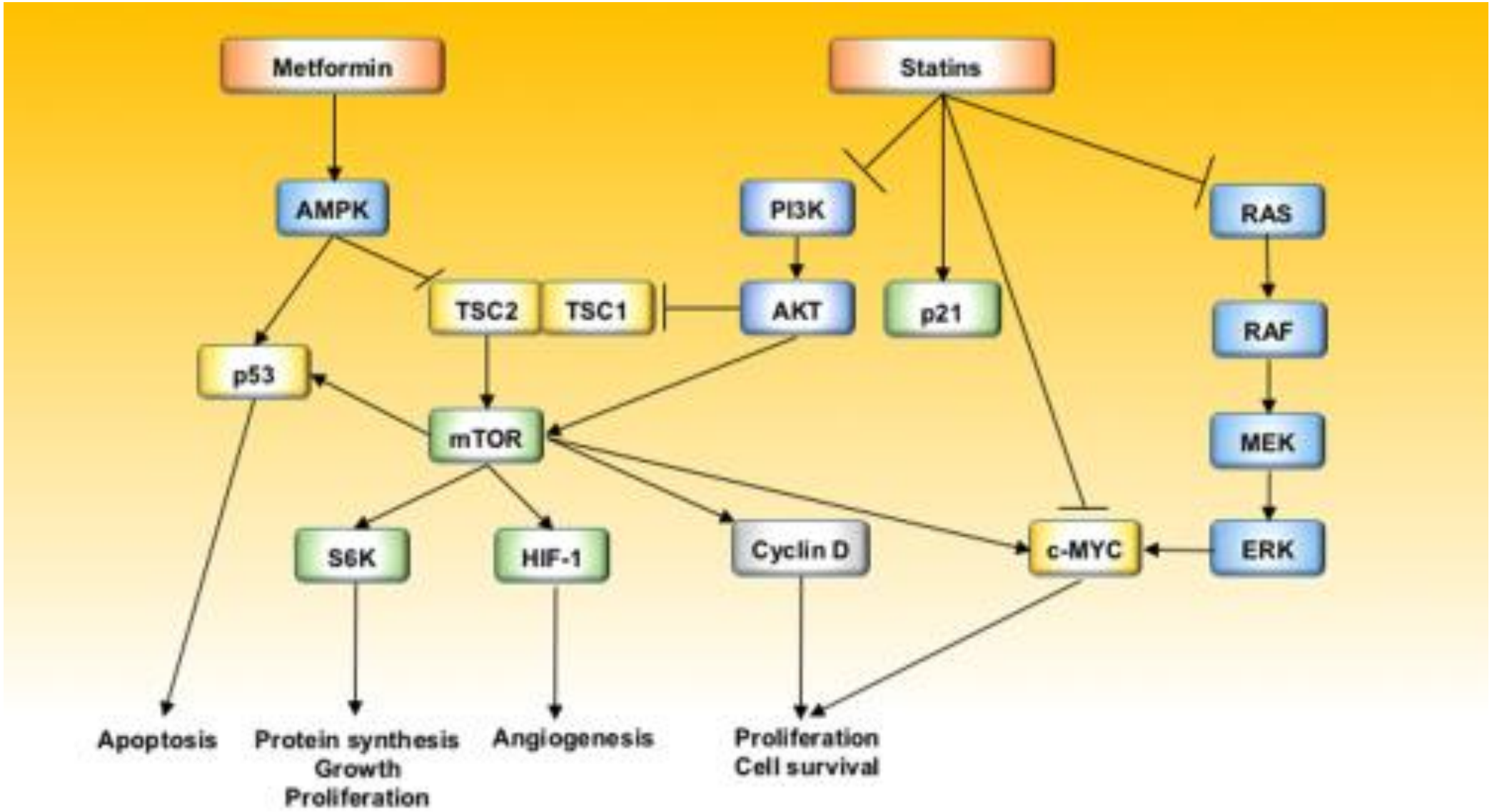
Abstract

Metformin is a commonly used drug for the treatment of type II diabetes and atorvastatin is the most prescribed cholesterol-lowering statin. The present study investigated the effects and mechanisms of metformin and atorvastatin in combination on human prostate cancer cells cultured in vitro and grown as xenograft tumor in vivo. Metformin in combination with atorvastatin had stronger effects on growth inhibition and apoptosis in PC-3 cells than either drug alone. The combination also potently inhibited cell migration and the formation of tumorspheres. Metformin and atorvastatin in combination had a potent inhibitory effect on nuclear factor-kappaB (NF-κB) activity and caused strong decreases in the expression of its downstream anti-apoptotic gene Survivin. Moreover, strong decreases in the levels of phospho-Akt and phosphor-extracellular signal-regulated kinase (Erk)1/2 were found in the cells treated with the combination. The in vivo study showed that treatment of severe combined immunodeficient (SCID) mice with metformin or atorvastatin alone resulted in moderate inhibition of tumor growth while the combination strongly inhibited the growth of the tumors. Results of the present study indicate the combination of metformin and atorvastatin may be an effective strategy for inhibiting the growth of prostate cancer and should be evaluated clinically.

KEYWORDS: apoptosis; atorvastatin; combination; metformin; prostate cancer

PMID: 28769006 DOI: 10.1248/bpb.b17-00077

Free full text


Metformin
Statins
AMPK
PI3K
RAS
TSC2
TSC1
AKT
p21
RAF
p53
mTOR
MEK
S6K
HIF-1
Cyclin D
c-MYC
ERK
Apoptosis
Protein synthesis
Growth
Proliferation
Angiogenesis
Proliferation
Cell survival

PLoS One. 2012;7(6):e39581. doi: 10.1371/journal.pone.0039581. Epub 2012 Jun 21.

Statin treatment increases lifespan and improves cardiac health in Drosophila by decreasing specific protein prenylation.

Spindler SR[1], Li R, Dhahbi JM, Yamakawa A, Mote P, Bodmer R, Ocorr K, Williams RT, Wang Y, Ablao KP.

⊕ Author information

Abstract

Statins such as simvastatin are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and standard therapy for the prevention and treatment of cardiovascular diseases in mammals. Here we show that simvastatin significantly increased the mean and maximum lifespan of Drosophila melanogaster (Drosophila) and enhanced cardiac function in aging flies by significantly reducing heart arrhythmias and increasing the contraction proportion of the contraction/relaxation cycle. These results appeared independent of internal changes in ubiquinone or juvenile hormone levels. Rather, they appeared to involve decreased protein prenylation. Simvastatin decreased the membrane association (prenylation) of specific small Ras GTPases in mice. Both farnesyl (L744832) and type 1 geranylgeranyl transferase (GGTI-298) inhibitors increased Drosophila lifespan. These data are the most direct evidence to date that decreased protein prenylation can increase cardiac health and lifespan in any metazoan species, and may explain the pleiotropic (non-cholesterol related) health effects of statins.

PMID: 22737247 PMCID: PMC3380867 DOI: 10.1371/journal.pone.0039581

[Indexed for MEDLINE] Free PMC Article

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Priority Research Papers:

Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: Treating cancer like an infectious disease

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Oncotarget. 2015; 6:4569-4584. https://doi.org/10.18632/oncotarget.3174

Metrics: PDF *17110 views* | HTML *20162 views*

ABSTRACT

Here, we propose a new strategy for the treatment of early cancerous lesions and advanced metastatic disease, via the selective targeting of cancer stem cells (CSCs), a.k.a., tumor-initiating cells (TICs). We searched for a global phenotypic characteristic that was highly conserved among cancer stem cells, across multiple tumor types, to provide a mutation-independent approach to cancer therapy. This would allow us to target cancer stem cells, effectively treating cancer as a single disease of "stemness", independently of the tumor tissue type. Using this approach, we identified a conserved phenotypic weak point – a strict dependence on mitochondrial biogenesis for the clonal expansion and survival of cancer stem cells. Interestingly, several classes of FDA-approved antibiotics inhibit mitochondrial biogenesis as a known "side-effect", which could be harnessed instead as a "therapeutic effect". Based on this analysis, we now show that 4-to-5 different classes of FDA-approved drugs can be used to eradicate cancer stem cells, in 12 different cancer cell lines, across 8 different tumor types (breast, DCIS, ovarian, prostate, lung, pancreatic, melanoma, and glioblastoma (brain)). These five classes of mitochondrially-targeted antibiotics include: the erythromycins, the tetracyclines, the glycylcyclines, an anti-parasitic drug, and chloramphenicol. Functional data are presented for one antibiotic in each drug class: azithromycin, doxycycline, tigecycline, pyrvinium pamoate, as well as chloramphenicol, as proof-of-concept. Importantly, many of these drugs are non-toxic for normal cells, likely reducing the side effects of anti-cancer therapy. Thus, we now propose to treat cancer like an infectious disease, by repurposing FDA-approved antibiotics for anti-cancer therapy, across multiple tumor types. These drug classes should also be considered for prevention studies, specifically focused on the prevention of tumor recurrence and distant metastasis. Finally, recent clinical trials with doxycycline and azithromycin (intended to target cancer-associated infections, but not cancer cells) have already shown positive therapeutic effects in cancer patients, although their ability to eradicate cancer stem cells was not yet appreciated.

Oncotarget. 2016 Oct 18;7(42):68571-68584. doi: 10.18632/oncotarget.11851.

Mebendazole and a non-steroidal anti-inflammatory combine to reduce tumor initiation in a colon cancer preclinical model.

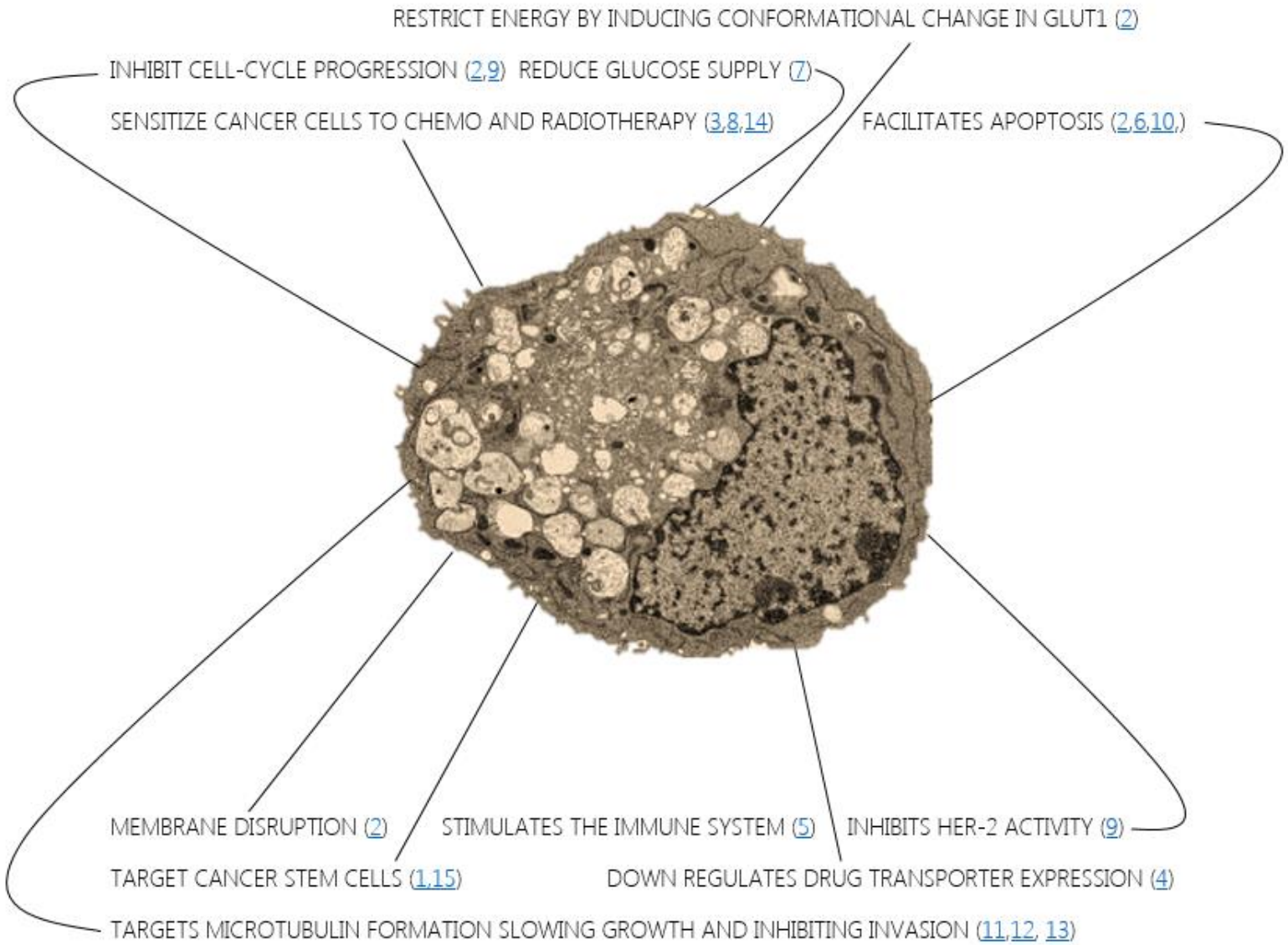
Williamson T[1], Bai RY[1], Staedtke V[2], Huso D[3], Riggins GJ[1,4].

Author information

Abstract

Inheritance of a gene mutation leads to the initiation of 5 to 10% of most cancers, including colon cancer cases. We developed a chemoprevention strategy using a novel combination of the non-steroidal anti-inflammatory (NSAID) sulindac plus the anthelminthic benzimidazole, mebendazole. This oral drug combination was effective in the ApcMin/+ mouse model of Familial Adenomatous Polyposis (FAP). Treatment with 35 mg/kg daily mebendazole reduced the number of intestinal adenomas by 56% ($P = 0.0002$), 160 ppm sulindac by 74% ($P < 0.0001$), and the combination by 90% ($P < 0.0001$). The combination significantly reduced microadenomas, polyp number and size in both the small intestines and colon when compared to untreated controls or sulindac alone. Mebendazole as a single agent decreased COX2 expression, blood vessel formation, VEGFR2 phosphorylation, and worked synergistically with sulindac to reduce overexpression of MYC, BCL2, and various pro-inflammatory cytokines. Given the low toxicity of mebendazole, these preclinical findings support the consideration of clinical trials for high risk cancer patients using mebendazole either alone or in combination. The findings have implications for populations with moderate and above risk for developing cancer.

AN ONCOLOGY CLINIC FROM THE U.K.



AN ONCOLOGY CLINIC FROM THE U.K.

COC PROTOCOL™

- METFORMIN
- ATORVASTATIN
- DOXYCYCLINE
- MEBENDAZOLE

*All Doses are within standard dose range for approved indication

United States patent ***US9622982B2***

Trial record **1 of 1** for: metformin mebendazole metrics

Previous Study | Return to List | Next Study

Study of the Safety, Tolerability and Efficacy of Metabolic Combination Treatments on Cancer (METRICS)

This study is currently recruiting participants.

See ▶ Contacts and Locations

Verified June 2017 by Health Clinics Limited

Sponsor:
Health Clinics Limited

ClinicalTrials.gov Identifier:
NCT02201381

First Posted: July 28, 2014
Last Update Posted: June 14, 2017

AN ONCOLOGY CLINIC FROM THE U.K.

- Full medical and surgical history, including thorough oncological history
- Drug history including allergies to delineate possible interactions with our medications
- Baseline serology including FBC, renal and liver profiles, tumor markers where appropriate
- Baseline clinical observations
- Baseline functional and quality of life assessment
- Assessment of any nutritional supplementation or specific dietary plans

AN ONCOLOGY CLINIC FROM THE U.K.

- Suitable patients initially identified from a data trawl from Care Oncology Clinic patient database with keyword ‘GBM’ or ‘glioblastoma’

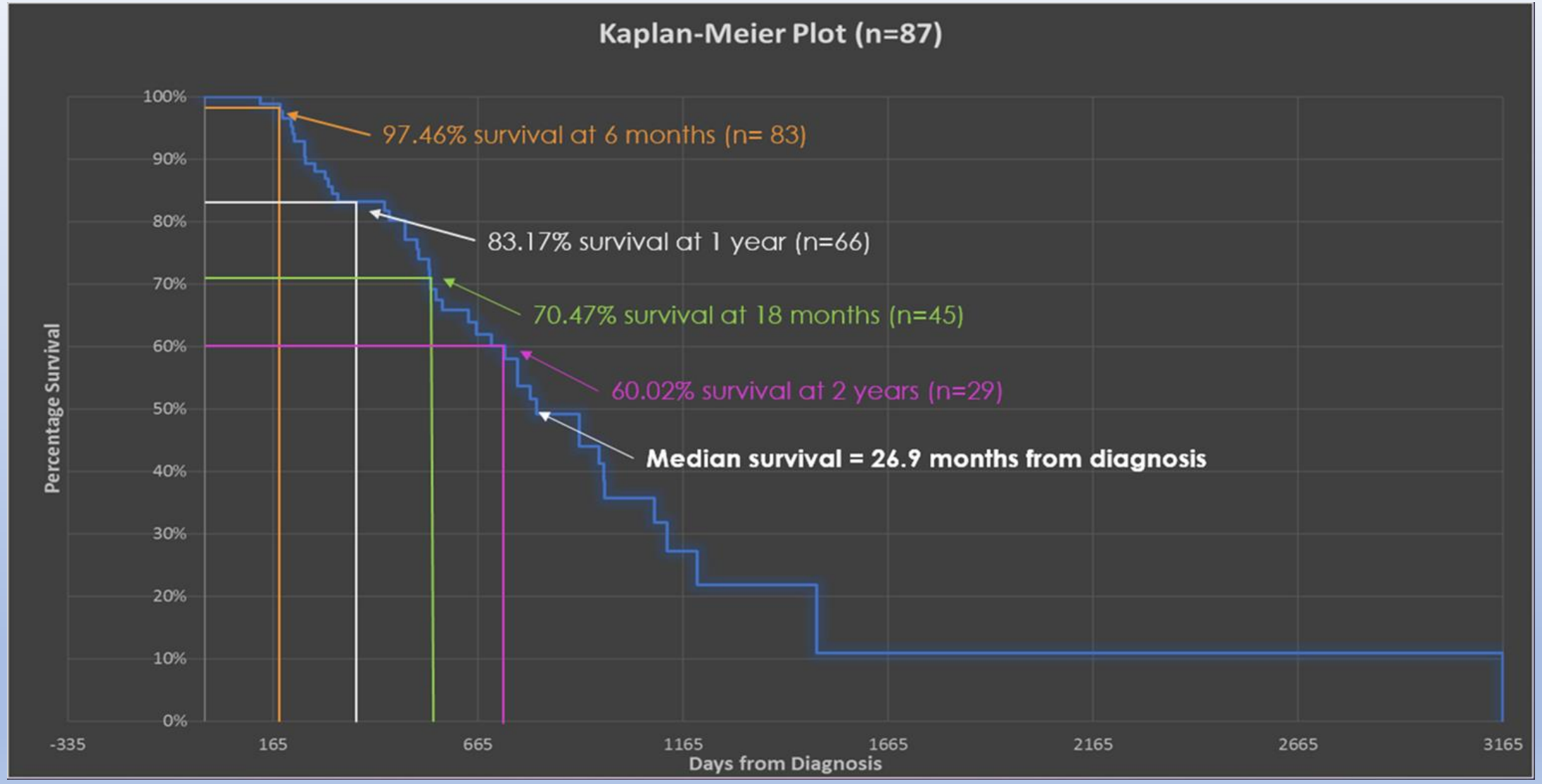
- Inclusion criteria:
- Must have a biopsy-proven diagnosis of Glioblastoma Multiforme
- Must have received 1 or more Care Oncology Clinic medications

- All patients received treatment if they consented and it was safe to prescribe. There was no control group

- Data analyzed on an Intention to Treat basis

AN ONCOLOGY CLINIC FROM THE U.K.

- 99 patients satisfied criteria
- 69 male (69.7%), 30 female
- Average age at diagnosis 49.55 years (S.D. 18.64 years)
- 77% underwent primary surgical resection
- Average length of follow-up from diagnosis 21.7 months
- Average length of follow-up from commencing COC protocol 9.97 months
- Average time from diagnosis to commencing COC protocol: 317.19 days


Kaplan-Meier Plot (n=87)
97.46% survival at 6 months (n= 83)
83.17% survival at 1 year (n=66)
70.47% survival at 18 months (n=45)
60.02% survival at 2 years (n=29)
Median survival = 26.9 months from diagnosis
Percentage Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
-335
165
665
1165
1665
2165
2665
3165
Days from Diagnosis

Results of METRICS trial on glioblastoma

TWO YEAR OVERALL SURVIVAL

55%

Standard-of-care + COC protocol™

VS

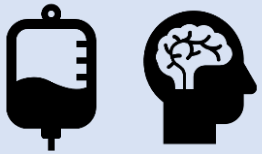
28.7%

Standard-of-care alone

Comparing adjunctive treatments for glioblastoma

Standard-of-care alone*
14.6 months OS

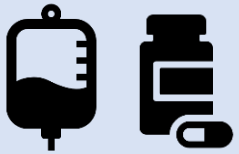
*Surgery + radiotherapy + temozolomide



Standard-of-care + Optune®
20.5 months OS

5.9 months longer

$252,000 per year



Standard-of-care + Care Protocol™
26.3 months OS

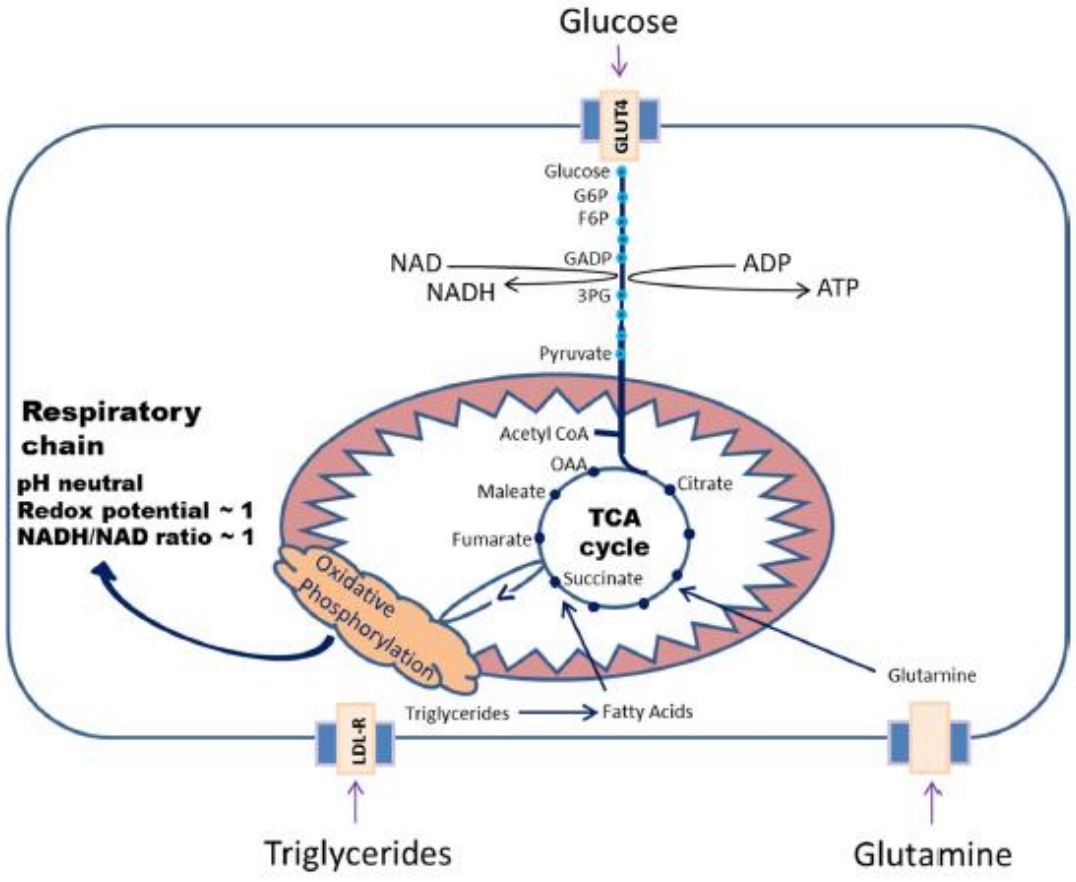
10.2 months longer

$3,600 per year

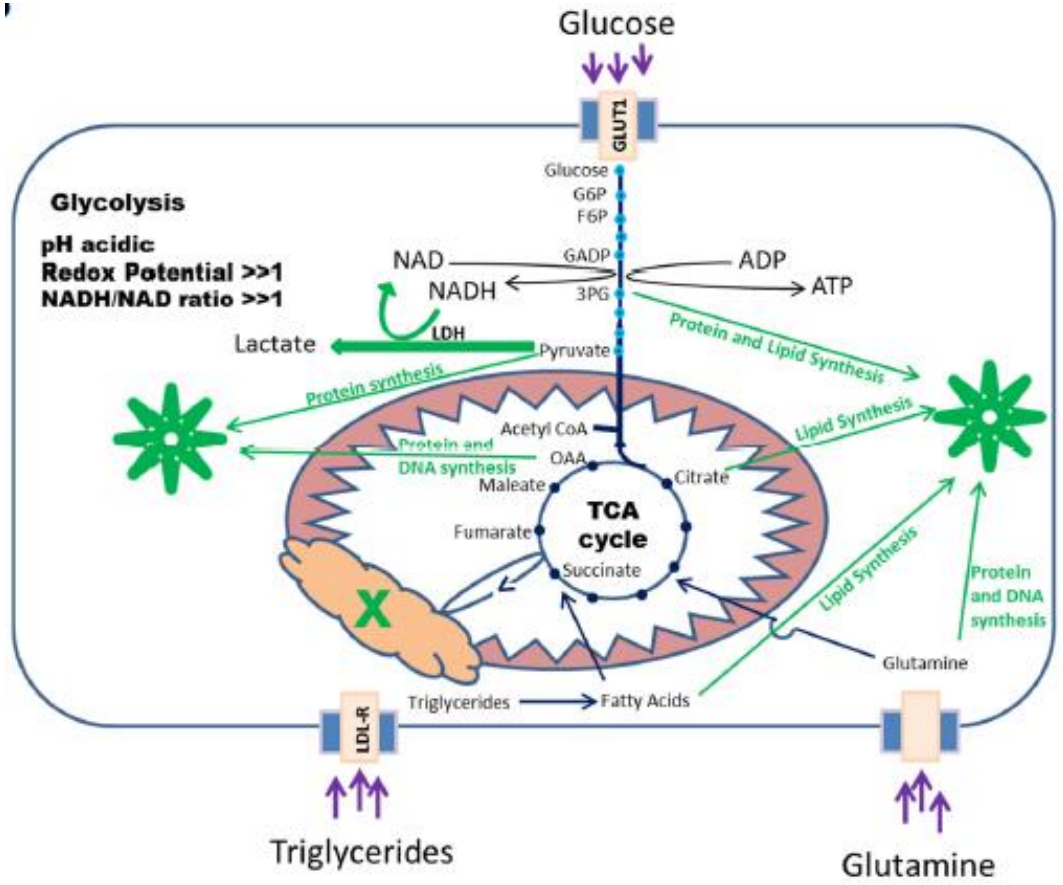
*Results of METRICS trial on glioblastoma – internal analysis reviewed by Cytel

AN ONCOLOGY CLINIC FROM THE U.K.

Normal cell

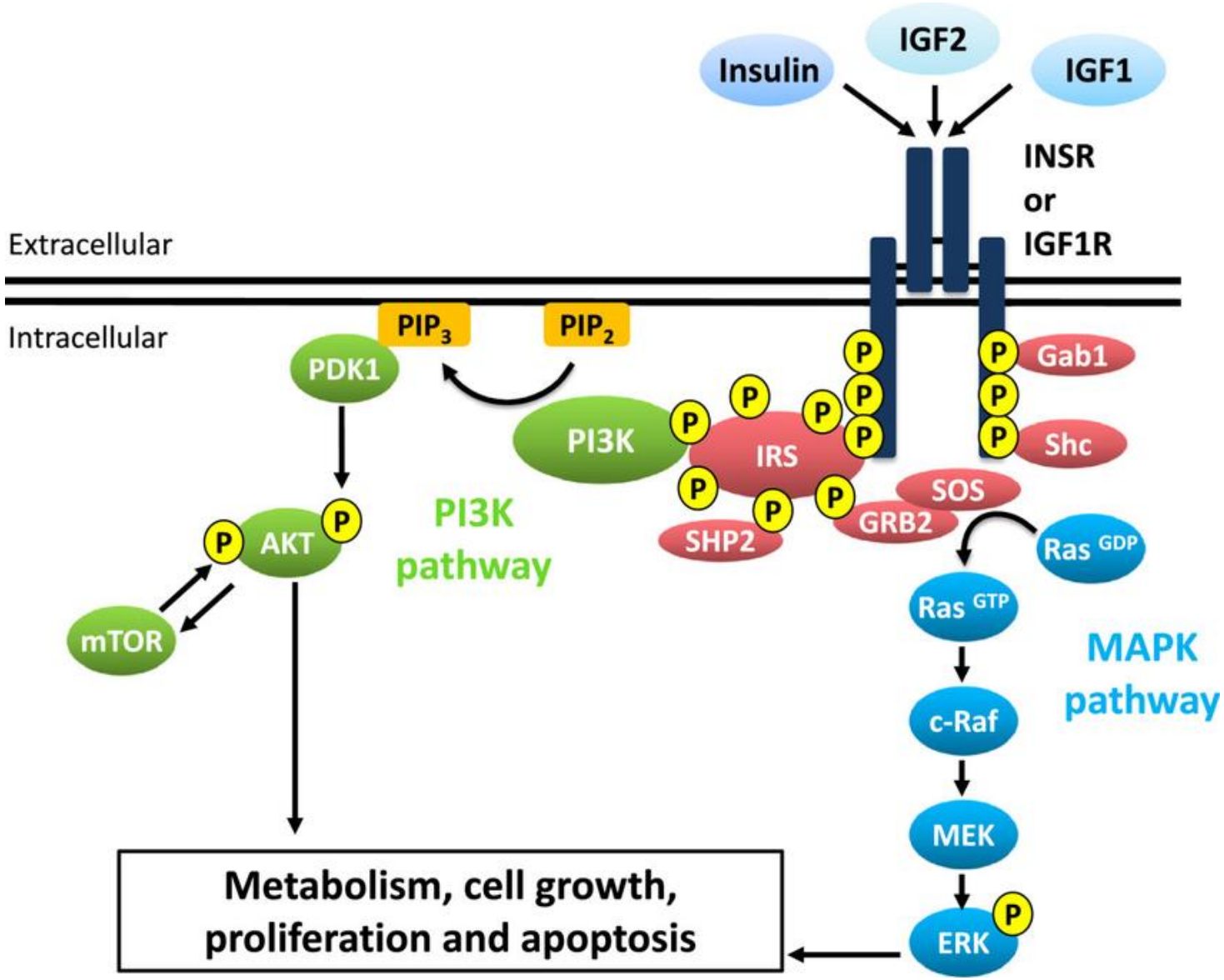


Cancer cell



"Even James Watson, one of the fathers of molecular biology, is convinced that **targeting metabolism is a more promising avenue in current cancer research than gene-centered approaches.** At his office at the Cold Spring Harbor Laboratory in Long Island, Watson, 88, sat beneath one of the original sketches of the DNA molecule and told me that **locating the genes that cause cancer has been "remarkably unhelpful" — If he were going into cancer research today, Watson said, he would study biochemistry rather than molecular biology."**

-New York Times, 2016 *An Old Idea, Revived: Starve Cancer to Death*


Insulin
IGF2
IGF1
INSR
or
IGF1R
Extracellular
Intracellular
PIP3
PIP2
PDK1
PI3K
IRS
Gab1
Shc
SOS
GRB2
SHP2
Ras GDP
Ras GTP
AKT
mTOR
PI3K
pathway
MAPK
pathway
c-Raf
MEK
ERK
Metabolism, cell growth,
proliferation and apoptosis

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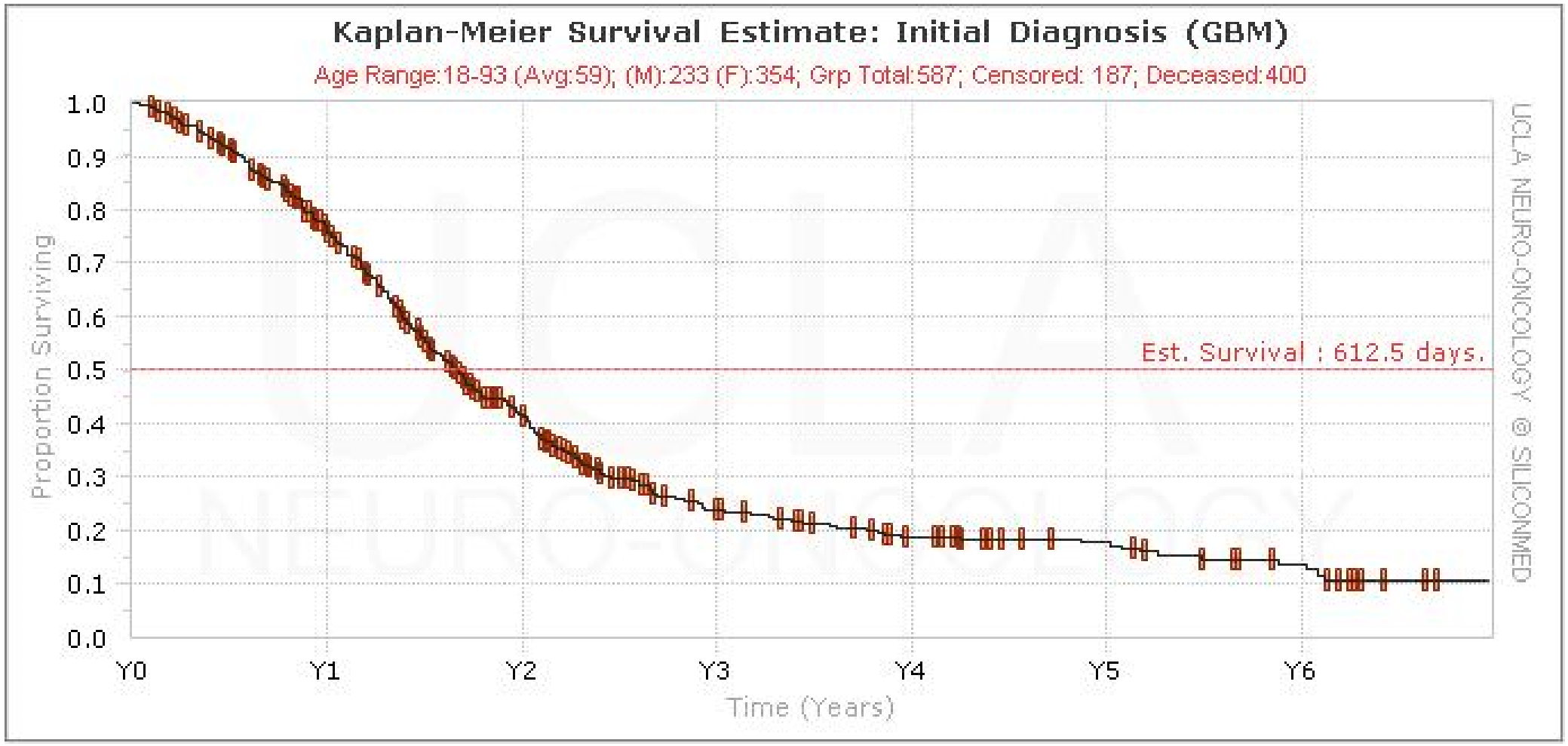
A leading comprehensive brain tumor program, using molecular diagnostic, gene expression analysis, cutting edge clinical trials and advanced medical informatics to customize treatment plans for cancer patients.



- Published median survival: 438 days*

Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, NJ of Med, Mar, 2005

What chemotherapy agents does UCLA Neuro-Oncology use to treat patients with a GBM tumor?

Because each patient's treatment plan is unique, therapy normally is dictated by several factors including a personâ€™s age, Karnofsky Score and any previous therapy they have received. Advances in our molecular diagnostics lab is enabling us to better predict what agents will benefit a particular patient group. In general, the following is an overview of agents we used to treat our GBM patients during the past 24 months. This list includes all patients treated at UCLA Neuro-Oncology between 9/19/2015 and 9/19/2017.

- 5FC
- AMG 595
- AMG-595
- AVANDIA (Rosiglitazone Maleate)
- BCNU
- Carboplatin
- CCI-779
- CDX-110
- Celecoxib (Systemic)
- Chlorquine
- CPT -11 (CAMPTOSAR, Irinotecan)
- Dasatinib (BMS-354825, Sprycel)
- Dcvax
- Etoposide (Eposin, Etopophos, Vepesid)
- GLIADEL Wafer
- IL-13
- Iressa (ZD-1839)
- Keytruda
- LY317615 (Enzastaurin)
- Mefloquine
- Methotrexate for Cancer (Systemic)
- Nivolumab
- Opdivo
- PCV
- RAD001 Novartis (mTOR inhibitor)
- RMP-7
- Sirolimus
- SU5416 Sugen
- Tagrisso
- Taxol
- Thalomid (thalidomide)
- TOCA INTRACRANIAL
- Accutane Hoffmann-La Roche
- AMG-102
- Anti Neoplaston
- Avastin
- BiCNU Carmustine
- CC-223
- CCNU
- CDX-110 (RINDOPEPIMUT)
- Celldex
- Cilengitide (EMD 121974)
- CPT-11
- DC vaccine
- Dendritic Cell Therapy
- GDC-0449
- Hydroxychloroquine
- IMC-3G3
- Irinotecan
- Lapatinib (GW572016)
- Marizomib
- Memantine
- Neo100
- Novocure TTF Therapy
- Optune
- Pembrolizumab
- Rapamycin (Rapamune, Sirolimus)
- RTA 744
- Sorafenib
- Sulfasalazine (Azulfidine)
- Tamoxifen
- TEMODAR Schering-Plough
- Toca 511
- Topotecan (Systemic)
- AEE788 Novartis
- AMG-386
- AQ4N (Banoxantrone)
- Avastin (Bevacizumab) Genetech
- BMS-CA209143 NIVOLUMAB
- CC223
- CCNU Lomustine
- Ceenu
- Chloroquine
- Cisplatin
- Cytoxan
- DC Vax
- Disulfiram
- Gleevec (imatinib mesylate)
- Hydroxyurea
- Immune Therapy
- Ketogenic Diet
- LOMUSTINE
- MEDI4736
- Metformin
- Nilotinib
- ONARTUZUMAB VS PLACEBO
- OSI-774
- Procarbazine
- Rindopepimut
- Simvastatin
- SU-101
- Sutent (Pfizer)
- TARCEVA (erlotinib HCl)
- TGF-B Anti-Sense
- TOCA FC
- Valcyte

- Published median survival (avg. age 56): 438 days
- UCLA median survival (avg. age 59): 612 days

- UCLA median survival (avg. age 45) : 633 days
- COC median survival (avg. age 49): 801 days

ADVANTAGES TO THIS PROPRIETARY OFF-LABEL PROTOCOL

- Decades of clinical use establishing safety
- Targets ubiquitous metabolic dysregulation
- Provides critical need for adjunctive therapy
- Provides a treatment option when no other exists or has been exhausted
- Provides a treatment option to prevent recurrence