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ORIGINAL ARTICLE

A retrospective observational study on cases of anaplastic brain tumors treated with the Di Bella Method: A rationale and effectiveness

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Abstract

Despite all the new developments in cancer therapy, the life expectancy of patients with malignant anaplastic brain tumors and glioblastoma multiform (GBM) remains short. Since the establishment of the Di Bella Method (DBM) in cancer therapy, DBM was able to increase the survival rate and life quality, without overt toxicity, in comparison to what is described in the literature related to the analogous brain tumors, with the same immunohistochemical, histologic and clinical features. Therefore, we treated seven patients with malignant anaplastic brain tumors using the DBM protocol. DBM therapy consists of somatostatin and analogous (octreotide) all trans-retinoic acid (ATRA), β-Carotene, axerophthol dissolved in vitamin E, vitamin D, vitamin C, melatonin (MLT), proteoglycans-glycosaminoglycans, valproic acid, acetazolamide, diethyldithiocarbamate, hydroxyurea, and temozolomide. These molecules have either antiproliferative, antiangiogenic, cytostatic, antioxidant, antimetastatic (differentiative), and immunomodulating features. Moreover, the inclusion of ATRA, MLT, and glucosamine with sodium valproate, diethyldithiocarbamate and acetazolamide has reinforced antitumor properties of the therapy by extending them to cancer stem cells. Furthermore, the non-cytolytic and non-cytotoxic metronomic dosage of hydroxyurea and temozolomide had increased the DBM therapy outcome by strengthening anti-tumor capability. The results of such treatment revealed that all seven patients were still alive after 5 to 8 years of starting DBM. In conclusion, the multi-strategic objectives of DBM are inhibiting the proliferative-invasiveness and neoplastic angiogenesis, silencing the survival system of cancer stem cells, enhancing the immunomodulatory and antioxidant activities, improving vitality and efficiency of normal cells, and depressing the efficiency and vitality of neoplastic ones.

Abbreviations:

AAAZ	- Acetazolamide	C.M.	- GH-induced chemotaxis of Monocytes
ATRA	- All Trans Retinoic Acid	CSC	- Cancer Stem Cells
ALDH	- Aldehyde Dehydrogenase	DBM	- Di Bella Method
Ca 9	- Isoenzyme of CAH	EGF	- Epidermal Growth Factor
CAH	- Carbonic Anhydrase	EGFR	- Epidermal Growth Factor Receptor
CCK	- Cholecystokinin	FGF	- Fibroblastic Growth Factor

GBM - Glioblastoma Multiforme
gCSC - Glioblastoma Cancer Stem Cells
GF - Growth Factor
GH - Growth Hormone
GHR - Growth Hormone Receptor
HDAT - Histone deacetylase
HGF - Hepatocyte Growth Factor
HIF-1α - Hypoxia-Induced Oncogenic Factor
IGF1-2 - Insulin-like Growth Factor 1-2
IGFR - Insulin-like Growth Factor Receptor
IL8 - Interleukin 8
MRI - Magnetic Resonance Imaging
MLT - Melatonin
NGF - Nerve Growth Factor
NHL - Non-Hodgkin's Lymphoma
NOSe - Endothelial nitric oxide synthase
PDGF - Platelet-Derived Growth Factor
PET - Positron Emission Tomography
PG2 - Prostaglandin 2
PRL - Prolactin
PRLR - Prolactin Receptor
RMN - Magnetic Resonance Imaging
SSN - National Health Service
SST - Somatostatin
SSTR - Somatostatin Receptor
TGF - Transforming Growth Factor
TRK - Tyrosine-kinase
VEGF - Vascular Endothelial Growth Factor
VIP - Vasoactive Intestinal Peptide
VPA - Valproic Acid

INTRODUCTION

Malignant anaplastic brain tumors and glioblastoma multiform (GBM) remain an unresolved clinical problem. Furthermore, GBM is the most frequent and aggressive type of cancer affecting different glial cells of an adult brain. Although there are advancements in the treatment of cancer, malignant brain tumors and GBM treatments fall short. For instance, Stupp's regimen consists of the main course for treating anaplastic astrocytoma and GBM patients. The regimen consists of surgery followed by radiotherapy. However, the overall median survival remains 15-18 months after diagnosis and has not significantly improved in the last decade (Delgado-López & Corrales-García 2016; Lakomy *et al.* 2020). In addition, total resection (above 98% of tumor volume) increases survival compared to subtotal or partial resection. On the contrary, "extended" subtotal resection does not confer any advantage compared with partial resection or biopsy (Laws *et al.* 2003). Generally, the one-year survival is 57%, decreasing to 16% at two years, and to 7% at three years (Filippini *et al.* 2008). However, GBM patient who lives more than three years is described as "long survivor", and this condition is often limited to subtotal resection surgery.

Since cancer cells development is a multistep process involving multiple abnormal signaling and genetic pathways, treatment should be performed similarly. Also, cancer stem cells (CSC) should be targeted to halt the re-progression of cancer. Thus, the Di Bella Method (DBM) was established (Di Bella *et al.* 1979a; Di Bella *et al.* 1979b). The DBM consists of administrating several specific molecules where each molecule is chosen based on its mechanism of action against tumor cells, CSC, proliferation and apoptosis, oncogenes, angiogenesis, molecular analysis, and genetic mutation. Besides, some molecules were chosen for their preservative mechanisms on healthy cells, including cell membrane integrity, DNA preservation, and mitochondrial function (Di Bella 2010).

For several years, we have been using the DBM for treating several types of cancer including breast, head and neck, and several others with success (Di Bella *et al.* 1979a; Di Bella *et al.* 1979b; Di Bella 1997; Di Bella & Di Bella 1998; Di Bella 2005; Di Bella & Gualano 2006; Di Bella 2010; Di Bella *et al.* 2013a; Di Bella *et al.* 2013b; Di Bella & Di Bella 2015; Di Bella *et al.* 2017; Di Bella *et al.* 2018; Di Bella 2019). In brain cancer, the percentage of CSC is associated with chemo and radiotherapy resistance, and thus rapid re-progression of the disease occurs. Since DBM protocol targets many steps of cancer development as well as CSC, we treated seven patients with malignant anaplastic brain tumors and GBM. In addition, we mentioned how DBM components halt tumor growth and enhance patients' survival with a brain tumor.

DBM TREATMENT RATIONAL FOR MALIGNANT BRAIN TUMORS

The DBM therapy for brain tumors consisted of administrating multiple drugs, vitamins and molecules as outlined in Table 1. Each of the drugs or vitamins or supplements used was based on our previous clinical results on different types of cancer (Di Bella *et al.* 1979a; Di Bella *et al.* 1979b; Di Bella 1997; Di Bella & Di Bella 1998; Di Bella 2005; Di Bella & Gualano 2006; Di Bella 2010; Di Bella *et al.* 2013a; Di Bella *et al.* 2013b; Di Bella & Di Bella 2015; Di Bella *et al.* 2017; Di Bella *et al.* 2018; Di Bella 2019).

Somatostatin and somatostatin analogues

In the DBM method, several molecules were used to halt cancer proliferation and growth. These molecules were chosen based on scientific research. For instance, cell proliferation, physiological or pathological, and protein synthesis is closely dependent on the interaction between prolactin (PRL) and growth hormone (GH). GH is the primary inducer of growth (De Souza *et al.* 1974; Lincoln *et al.* 1998; Friend 2000; Barnett 2003; Anthony & Freda 2009). GH is also the principal mediator of postnatal cell growth and differentiation in somatic cells following binding to its receptor, GHR (Le Roith *et al.* 2001; Zhu *et al.* 2001). This binding activates pivotal pathways of cell growth and survival, such as the JAK-2/STAT signaling pathway, p44/42 family of mitogen-activated protein kinases (MAPKs), and phosphoinositide 3-kinases (PI3Ks) family (Le Roith *et al.* 2001; Zhu *et al.* 2001). On the other hand, GHRs

Tab. 1. DBM therapy for GBM

DRUG	CHEMICAL COMPOSITION	DOSAGE	ROUTE OF ADMINISTRATION	FREQUENCY
Somatostatin	Peptide hormone (14 years)	4 mg	subcutaneous or into a vein	daily (automatic infuser during night)
Octreotide LAR	Octreotide Acetate (8 years)	20 mg	intramuscular	Every 20 days
Retinoid solution	All-Trans-Retinoic acid Axerophthol Palmitate β-carotene α-Tocopherol acetate	0.5 g 0.5 g 2 g 1000 g	Per os	daily (3 times per day)
Vitamin C	L-Ascorbic Acid	4 g	Per os	Daily (lunch and dinner)
Vitamin D3	1,25-diOh-Tachysterol	30 drops=1 ml around=1 mg	Per os	Daily (3 administrations)
Synachthen®	Tetracosactide acetate	0.25 mg	Subcutaneous	3 administrations per week with infuser
Parlodel®	Bromocriptine	2.5 mg	Per os	½ tab 2 times a day
Dostinex®	Cabergoline	0.5 mg	Per os	½ tab 2 times a week
Chondroitin sulfate	D-Glucuronic Acid (GlcA) N-Acetyl-D-Galactosamine (GalNAc)	500 mg	Per os	2 times a day
Glucosamine	D-Glucosamine	500 mg	Per os	3 times a day
Deursil®	Ursodeoxycholic Acid	300-450 mg	Per os	Daily
Melatonin	Melatonin 12% Adenosine 51% Glycine 37%	100 mg	Per os	Daily
Temodal®	Temozolomide	20 mg	Per os	2 times a day
Oncocarbide®	Hydroxyurea	500 mg	Per os	Daily
Depakin Chrono®	Sodium Valproate (NaVP)	500 mg	Per os	2 times a day
Diamox®	Acetazolamide	250 mg	Per os	½ tab 2 times a day
Disulfiram	Diethyldithiocarbamate	200 mg	Per os	Daily

are widely distributed with varying concentrations in different cell types, normal as well as neoplastic ones. The fact remains - the more GHRs are expressed in tumor cells, the more tumor cells possess invasive and metastatic capabilities (Lincoln *et al.* 1994).

Besides, there are several GH-dependent mitogenic molecules, such as EGF, FGF, HGF, IGF1, VEGF, PDGF (Hagemeister & Sheridan 2008; Murray *et al.* 2004; Sall *et al.* 2004; Szepesházi *et al.* 1999; Taslipinar *et al.* 2009), and gastrointestinal (GI) specific growth factors, such as VIP, CCK, G (Kath & Höffken 2000) that are involved in many types of cancer. Furthermore, prolactin receptor (PRLR) and GH receptor (GHR) are co-expressed on cellular membranes, and through heterodimerization they can physically and functionally interact, amplifying proliferative pathways (Kelly *et al.* 1993). It has been found that GH and PRL have a key role in the development and in the progression of human tumors, especially in brain (De Souza *et al.*1974; Ben-Jonathan *et al.* 2002; Batra *et al.* 1997; Cameron *et al.* 1979).

Tumor induction and progression are positively related to GHR-PRLR expression, as demonstrated by immunohistochemistry, Western blot, in situ hybridization and qPCR analyses. It's well documented that in tumor tissues GHR levels are higher than in physiological or peritumoral ones, confirming the mitogenic key role (Di Bella *et al.* 2018; Friend 2000; Gruszka *et al.* 2001; Lincoln *et al.* 1998; Zeitler & Siriwardana 2000). Although the exact timing of etiopathogenesis is not completely understood, it's conceivable that autocrine and/or paracrine signaling could be accountable for local production of GH, GHR, PRL, PRLR, and IGFI in many tumors, including central nervous system ones.

IGF-1 is strongly dependent on GH (Daughaday & Trivedi 1987). Moreover, it's well known that GH administration causes an increase of IGF-1 in human tumor cells. A large amount of GHR could be observed in cell lines during exponential cell growth and GH/IGF-1 axes is the principal mediator of somatic growth and has a crucial role in oncogenesis (Laban *et al.* 2003),

inhibiting apoptosis (Kusano *et al.* 2014; Perry *et al.* 2006), and stimulating the production EGF, FGF and VEGF-A (Cattaneo *et al.* 1999; Brunet-Dunand *et al.* 2009; Vacas *et al.* 2016).

Furthermore, GH promotes migration and invasiveness of tumor cells via the endothelial to mesenchymal transition (EMT) in tumor cells and down-regulating plakoglobin, the cytoplasmic relocation of E-cadherin and the activation of metalloproteinases 2 and 9 (MMP2 and MMP9) (Mukhina *et al.* 2004; Sommers *et al.* 1994; Thiery 2002). Also, GH transduction leads to a significant induction of several angiogenic genes, such as the endothelial nitric oxide synthase (eNOS), the vascular endothelial growth factor (VEGF), the basic fibroblast growth factor (bFGF). Additionally, using immunohistochemistry analyses, GH displays an increase in capillary density and cellular proliferation (Kusano *et al.* 2007).

According to some studies, mRNA of GHR was found in healthy brain cells and glioblastoma (Castro *et al.* 2000). Overexpression of GH and GHRH in cancer tissues such as glioblastoma, breast, lungs and others is well documented (Lincoln *et al.* 1998). Several studies confirmed the antitumor efficacy of somatostatin analogues in glioblastoma, mainly by inhibiting GH and GHRH release (Jaeckle *et al.* 2003; Kovács *et al.* 2010).

Somatostatin and its analogues downregulate GH and GH-dependent growth factors, making their use suitable for treatment of different kinds of cancer (Arena *et al.* 2007; Di Bella 2010; Di Bella *et al.* 1979; Friend 2000; Lachowicz-Ochedalska *et al.* 2000; Lee *et al.* 2008; Pawlikowski *et al.* 1999; Pollak 1997; Verhoef *et al.* 2008; Vieira Neto *et al.* 2008). In different kinds of cancer, not only in neuroendocrine ones, an expression of somatostatin receptor is well documented (Albérini *et al.* 2000; Borgström *et al.* 1999; Briganti *et al.* 1997; Cattaneo *et al.* 1999; Corleto *et al.* 2009; Edelman *et al.* 2009; Faggiano *et al.* 2008; Florio *et al.* 2000; Florio 2008; Friend 2000; Fusco *et al.* 2008; Hassaneen *et al.* 2010; He *et al.* 2009; Hubalewska-Dydejczyk *et al.* 2008; Ioannou *et al.* 2008; Khanna *et al.* 2008; Kogner *et al.* 1997; Kwekkeboom *et al.* 2008; Laklai *et al.* 2009; Li *et al.* 2008; Luboldt *et al.* 2010; Moertel *et al.* 1994; Orlando *et al.* 2001; Pisarek *et al.* 2009; Ruscica *et al.* 2010; Sestini *et al.* 1996; Steták *et al.* 2001; van Eijck *et al.* 1998; Watt *et al.* 2008).

Furthermore, the antiproliferative effect of somatostatin and somatostatin analogues takes place by inhibiting IGH pathways (Kiaris *et al.* 2005). Regression and long survival with somatostatin in a primary gliosarcoma, a type of GBM but rare and has poor prognosis, confirmed the efficacy of somatostatin in this type of pathology (Anthony & Freda 2009; Barnett 2003; De Souza *et al.* 1974; Friend 2000; Lincoln *et al.* 1998; Trignani *et al.* 2013).

In conclusion, the PRL/GH/IGF axis has a prominent role in malignant growth, providing a rationale for the use of anti-dopamine D2 receptor agonists in combination with biological GH antagonists, such as somatostatin and its analogues. Inhibiting such axis downregulates GH-related mitogenic growth factor, including IGF1 and 2 (Arena *et al.* 2007; Buckley & Buckley 2000), EGF (Barrie *et al.* 1993; Watt *et al.* 2008), FGF (Bonneterre *et al.* 1990), VEGF (Albini *et al.* 1999; Ashino *et al.* 2003; Cascinu *et al.* 2001) PDGF (Cattaneo *et al.* 1999) and their relative pathways, resulting in antiproliferative and pro-apoptotic signals for recipient cells (Watt *et al.* 2008). This emerging way of viewing is well documented in basic research, but it's not yet translated in clinical applications.

Disulfiram (Aldehyde dehydrogenase inhibitor)

We have integrated DBM with Disulfiram, an aldehyde dehydrogenase (ALDH) inhibitor, known as a marker of glioblastoma CSCs (Toledo-Guzmán *et al.* 2019; Moreb 2008), that is involved in the renewal, differentiation and auto-protection (Marcato P *et al.* 2011; Marcato P *et al.* 2011). Glioblastoma CSCs (gCSC) represent the chemical-resistant population responsible for recurrence, with a relevant percentage in glioblastoma cellular population. The temozolomide (TMZ), an alkylating agent, is a first line chemotherapy drug, able to ameliorate patient survival, and the resistance to it leads to treatment failure (Schäfer A *et al.* 2012). It has been highlighted that "long noncoding RNAs" (lncRNAs)" are related to a significant positive regulation of TP73-AS1 in gCSC, related to overexpression of ALDH1A1, one of the predominant ALDH isozymes, protein (Nikhil *et al.* 2019), hallmark of ill-fated prognosis in GBM and in other cancer disease (Mazor *et al.* 2019). ALDH1A1 was found regularly in gCSC and it is associated with chemoresistance to TMZ (Moreb 2008). Biomolecular mechanisms involving ALDH1A1 were highlighted. In gCSC, overexpression of ALDH1A1 increases their aggressiveness and resistance, making them a target for therapeutic strategies (Safa *et al.* 2016; Xu *et al.* 2015).

gCSCs characterized by mesenchymal phenotype exhibit high intracellular of ALDH 1 Family Member A3 (ALDH1A3) and are considered more aggressive and more resistant to therapy (Chen *et al.* 2019). In a lot of cancer types, such as breast and ovarian carcinomas, neuroblastomas, retinoblastomas, etc., the presence of CSC was demonstrated and related to overexpression of their specific marker ALDH1, leading to a poor prognosis, enhanced aggressiveness and chemoresistance (Flahaut *et al.* 2016; Kim *et al.* 2018; Marcato *et al.* 2011; Marcato *et al.* 2011; Seigel *et al.* 2015). In this context, the introduction in DBM of disulfiram, a negative regulator of ALDH is a rational choice. Moreover, Disulfiram is well tolerated without any toxicity at the dosage of 200 mg per day.

Valproic Acid

VPA, an anti-convulsion medication, has been shown to have antineoplastic activities by inhibiting histone deacetylase and chromatin condensation (Krauze *et al.* 2018), and allowing access to all transcription,

differentiation and cytostatic factors (Rudà *et al.* 2016). Moreover, VPA activates tumor suppressor genes (Garcia *et al.* 2018), and inhibits glioma proliferation *in vitro* and *in vivo*, by increasing apoptosis and inducing cell cycle arrest (Pan *et al.* 2017). Therefore, VPA was considered a valid therapeutic option for GBM treatment (Ishiguro *et al.* 2018).

Furthermore, VPA acts on downregulation of O6-alkylguanine DNA alkyltransferase, inducing expression of BMP2, BMP4, ACVR, and DLX2 mRNAs and a simultaneous increase of Smad1/5 phosphorylation (Raja *et al.* 2017). VPA modifies the expression of genes involved in differentiation, DNA repair and apoptosis. In particular, VPA induces p21 expression, blocks cell cycle in G2/S phase, and activates at the same time an apoptotic cascade, through downregulation of antiapoptotic protein Bcl-2 / Bcl-XL. Indeed, as reported in recent studies, a reduction of the mitotic index emerged after VPA treatment, confirming the induction of the G1 block. Commonly, cell arrested in G1 phase move toward differentiation and subsequent apoptosis (Riva *et al.* 2014). Clinically, VPA administration with temozolomide led to an increase in survival of GBM patients (Kerkhof *et al.* 2013).

VPA has been shown to counteract the proliferation and mobility of gCSCs (Gefroh-Grimes & Gidal 2016) and potentiates the antitumor response with a lot of mechanisms, including differentiation in different types of tumor cells (Rudà *et al.* 2016). In gCSCs, VPA induces a dose-dependent reduction of metabolic activity. The efficacy of this drug is revealed, evaluating the classification of gCSCs lines, from the more sensible to less responsive: G166, G179 and G144, GBM2, GBM7, GliNS2 (Riva *et al.* 2014).

Carboanhydrase inhibitors

The carbonic anhydrases (CAH), zinc metalloproteins, are enzymes that can have a clinical relevance in cancer therapy, because of their isoform specific for cell surface. The Ca9, an isoform of CAH, is almost exclusively associated to cancers, and it is involved in tumorigenesis. Ca9 is overexpressed in many types of cancer, and it is infrequently present in healthy tissues. Ca9 expression is induced by hypoxia and acidification, both of which present in neoplastic areas of solid tumors (Winum *et al.* 2008; Said *et al.* 2010; Said *et al.* 2013; Supuran & Winum 2015). Furthermore, overexpression of Ca9 represents a significant indicator of disease prognosis, associated with increased aggressiveness, malignant progression, metastasis and poor response to treatment documented in various tumors (McDonald *et al.* 2019). Therefore, the inhibition of Ca9, mediated by acetazolamide (AAZ), counteracts its carcinogenic role (Pastorekova *et al.* 2008).

Melatonin

Melatonin (MLT) is a natural hormone produced from the pineal gland and is associated with the control of sleep-awake cycle (Auld *et al.* 2017). Furthermore, MLT has antioxidant, anti-aging and immunomodulatory properties. MLT has a relevant role in the hematopoiesis, mainly thrombogenesis, leukocytes regulation, and synthesis of hemoglobin. Besides, MLT has a prominent role in perfusion and in gaseous haemato-tissue exchanges, preventing tissue ischemia's, acidosis, and hypoxia in neoplastic environment, with a consequent over-expression of oncogenic genes, such as HIF-1α. The relevant and non-toxic apoptotic, oncostatic, anti-angiogenetic, antiproliferative properties of this indole on all neoplastic pathologies are documented (Heldin & Westermark 1991; Cos *et al.* 1996; Lissoni *et al.* 1996; Bartsch & Bartsch 1997; Blask *et al.* 1997; Pawlikowski *et al.* 1999; Lissoni *et al.* 2000; Czeczuga-Semeniuk *et al.* 2002; Reiter & Korkmaz 2008; Sánchez-Barceló *et al.* 2005; Skwarlo-Sonta 2002; Trubiani *et al.* 2005; Vijayalaxmi *et al.* 2004; Watanabe *et al.* 2008; Fischer *et al.* 2008; Bejarano *et al.* 2009; Matt *et al.* 2009; Ferreira Cda *et al.* 2010;; Kim *et al.* 2013; Moradkhani *et al.* 2020). Clinically, MLT showed potential in treating solid tumors (Di Bella 2005; Di Bella & Gualano 2006; Di Bella *et al.* 2013a; Di Bella *et al.* 2013b; Nooshinfar *et al.* 2017; Talib 2018; Di Bella 2019; Gil-Martín *et al.* 2019).

Retinoid solution

Retinoids are chemical compounds related to vitamin A. Early studies had shown that retinoids regulate cell proliferation and differentiation. Then, several studies demonstrated that retinoids play a crucial role both in prevention and therapy of cancer, limiting consequences induced by cancer and usual anticancer therapies (Abe *et al.* 2003; Adachi *et al.* 2001; Di Masi *et al.* 2015; Anthony & Freda 2009; Arany *et al.* 2003; Baroni *et al.* 2003; Basu *et al.* 2000; Chambaut-Guérin *et al.* 2000; Chou *et al.* 2000; Dufner-Beattie *et al.* 2001; Kim *et al.* 2009; Kini *et al.* 2001; Lee *et al.* 2008; Sharow *et al.* 2012; Song & Xu 2001; Wu *et al.* 2009; Ni *et al.* 2019; Ying *et al.* 2011).

For instance, the all-trans retinoic acid (ATRA) has been shown to help in differentiating blast cells in haemtological malignancies (Hassan HT & Rees J 1990), decreasing the potential for neoplastic proliferation and playing an important role in cell differentiation, apoptosis and adhesion (Herreros-Villanueva *et al.* 2015; Voigt *et al.* 2000). Furthermore, it has been shown that retinoic acid can suppress the gene transcription of oncogenic factors and promote the antiproliferative effect (Arnold *et al.* 1994), has anti-angiogenic action (Majewski *et al.* 1994). Besides, retinoic acid and temozolomide arrested cell cycle progression in the G0/G1 phase and significantly induced apoptosis of human glioma cells (Shi *et al.* 2017).

Furthermore, the effect of retinoic acid on gCSCs has been established. gCSCs are known to be the tumor initiator and tumor propagator (Wang & Liu 2019; Songthaveesin *et al.* 2018). It has been established

that glioma stem cells divide symmetrically, resulting in the poor therapeutic effect of current glioma treatments. If gCSCs are divided asymmetrically, the proliferative capacity of the tumor containing such cells is decreased, and if asymmetry is decreased in normal stem cells, the neoplastic transformation increases (Wang & Liu 2019). In that sense, it has been shown that ATRA induce asymmetric gCSCs cell division in U87MG glioblastoma cell line. These results suggest a therapeutic effect of ATRA on glioma stem cells (Wang & Liu 2019; Songthaveesin *et al.* 2018).

As presented in Table 1, retinoid solution contains not only ATRA, but also axerophthol palmitate (vitamin A), β-carotene, and α-tocopherol acetate. These constituents also enhanced the anti-cancer activities of ATRA. For instance, it has been shown that vitamin A caused death to of the neoplastic cell by apoptosis, through the activation of caspases and the degradation of the general transcription factor Sp-1 (Piedrafita & Pfahl 1997; Kanungo 2017). On the other hand, α-tocopherol (vitamin E) has a high antioxidant and anti-free radical activity and directly affects a key step in energy exchange and life itself: the transport of electrons in the respiratory chain. Furthermore, α-tocopherol inhibited the growth of various tumor cell lines (Dalen & Neuzil 2003; Elattar & Virji 1999; Fariss *et al.* 1994; Heisler *et al.* 2000; Inokuchi *et al.* 2003; Israel *et al.* 2000; Malafa *et al.* 2002; Malafa & Neitzel 2000; Kerkhof *et al.* 2013; Neuzil *et al.* 2002; Neuzil *et al.* 2001; Prasad *et al.* 1990; Prasad *et al.* 1994; Prasad *et al.* 2003; Prasad & Kumar 1996; Pussinen *et al.* 2000; Ripoll *et al.* 1986; Rose & McFadden 2001; Sarna *et al.* 2000; Shklar & Schwartz 1996; Tang & Meydani 2001; Turley *et al.* 1995; Wu *et al.* 2002; Yamamoto *et al.* 2000; Yu *et al.* 2002; Yu *et al.* 1997; Yu *et al.* 1997; Zhang *et al.* 2002). Besides, α-tocopherol enhanced the anticancer action of various chemotherapy drugs such as adriamycin, cisplatin and tamoxifen (Prasad *et al.* 1994; Ripoll *et al.* 1986) and protected bone marrow cells from the lethal effects of doxorubicin (Fariss *et al.* 1994).

Vitamin C

Ascorbic acid, or vitamin C, has a great antioxidant activities by reacting directly with single atomic oxygen, hydroxides and superoxide radicals (Padh 1991; Sauberlich 1994). Biologically, vitamin C acts as a hydrogen carrier in intermediary metabolism, including cellular respiration processes (Ngo *et al.* 2019; Pawlowska *et al.* 2019). Besides, vitamin C possess anticancer therapeutic activities (Cameron *et al.* 1979; Head 1998; Bendich & Langseth 1995; Aidoo *et al.* 1994; Lee *et al.* 2002; Blaszczak *et al.* 2019; Di Bella & Di Bella 1998; Ohno *et al.* 2009; van Gorkom *et al.* 2019), including anti-angiogenic activity (Ashino *et al.* 2003), and anti-metastatic activities (Peterkofsky 1991; Pinnel *et al.* 1987; Cameron & Pauling 1973; Utoguchi *et al.* 1995).

Vitamin D

Vitamin D is a fat-soluble molecule that is mainly responsible for increasing intestinal calcium absorption and for calcium homeostasis. However, vitamin D has many biological functions. Of these, vitamin D is an important molecule to for differentiation of cells (Marcinkowska 2001; Consolini *et al.* 2001). Also, vitamin D induces phenotypic maturation of tumor cells into functionally mature, differentiated, physiologically normal cells (Barroga EF *et al.* 2000; Majewski *et al.* 1994). Vitamin D3 was found to inhibit proliferation, and promoted differentiation of various types of tumor cells, and prevented adhesion of cellular migration from basal membrane. The latter phenomenon was due to a downregulation of alpha-6 and beta-4 integrins, laminin receptors associated with greatest cellular migration and invasiveness of prostatic cancer cells in vivo (Yudoh *et al.* 1999; Sung & Feldman 2000). Furthermore, vitamin D inhibited angiogenesis through inhibiting VEGF in a dose dependent manner (Mantell *et al.* 2000).

Proteoglicans and glycosaminoglicans

Chondroitin sulfate

Chondroitin sulfate is a sulfated glycosaminoglycan (GAG) composed of a chain of alternating sugars (N-acetylgalactosamine and glucuronic acid). It is used with glucosamine as a supplement for osteoarthritis. However, there are several studies that showed chondroitin sulfate has anti-tumor and antimetastatic activities (Fthenou *et al.* 2009; Kasten *et al.* 2018; Shi *et al.* 2021). It has been found that chondroitin sulfate inhibited the growth of a bladder cancer cell line by the activation of caspases 3 and 9 and thereby inducing apoptosis (Ferro *et al.* 2012). Besides, it has been shown that combining chondroitin sulfate with the gene of murine granulocyte macrophage-colony-stimulating enhanced the survival of mice bearing ovarian cancer (Hamada *et al.* 2012).

Glucosamine sulfate

Similar to chondroitin sulfate, glucosamine is used as a supplement for osteoarthritis. Besides, several studies have shown the potential of glucosamine sulfate in cancer treatment mainly by inhibiting CSC (Hosea *et al.* 2018; Hong *et al.* 2020). Furthermore, it has been reported that glucosamine induced autophagic cell death through stress stimulation of the endoplasmic reticulum (ER) in human glioma cells. ER stress induced by glucosamine was manifested by the induction of the expression of BiP, IRE1alpha and phospho-eIF2alpha (Hwang & Baek 2010). Besides, glucosamine suppressed the proliferation of the DU145 human prostate cancer cell line through inhibition of STAT3 signaling. In DU145 cells, glucosamine reduced the N-glycosylation of gp130, decreased the binding of IL-6 to cells, and altered the phosphorylation of JAK2, SHP2 and STAT3 (Chesnokov *et al.* 2014).

Furthermore, glucosamine has been documented that glucosamine has anti-inflammatory activity via regulating inhibiting nuclear factor κB (NF-κB) action and therefore suppresses inflammatory cytokines production (Dalirfardouei *et al.* 2016). Hence, it may be used in treating inflammatory-induced tumors (Al-Hanbali *et al.* 2009; Mansour *et al.* 2018).

Although D-glucosamine is safe, some studies have presented the toxic effect of its conjugates on cancer cells and have highlighted its application in targeting glioma. The study revealed a significant effect on cytotoxicity and apoptosis in vitro as assessed on resistant grade IV glioma cell lines. Furthermore, this effect was not observed on normal human erythrocytes in the haemolysis test. GC liposomes were not toxic to normal brain tissues of healthy Sprague-Dawley rats tested. The absence of histological and behavioral changes together with the absence of caspase-3 in the brain tissue confirmed the suitability of the system for direct infusion into the brain (Yadav *et al.* 2019).

The expression of vitamin D receptors in glioma tumors is associated with increased survival (Cataldi *et al.* 2020; Norlin 2020). The 1,25-hydroxyvitamin D3 has direct effects on nervous systems, influencing steroidogenic pathways. In the human glioma, Vitamin D3 stimulates the expression of aromatase and the 3β-hydroxysteroid dehydrogenase as well as the 17-hydroxylase/steroid lyase in the astrocytes, in addition to providing neuroprotection. The expression of vitamin D receptors in glioma is associated with a higher survival, and 1,25 hydroxyvitamin D3 and its analogous suppress the proliferation and the migration in glioma cellular lines, expressing human vitamin D receptors (Norlin 2020).

THE IMPORTANCE OF COMBINATIONS

Although there are rationales for using each molecule in DBM, the synergistic effect of the combination makes it more powerful. For instance, the synergic effect of MLT and VPA enhances the cytotoxic effect of TMX in GBM cells through the reduction of MGMT expression (Di Bella *et al.* 2013a; Di Bella *et al.* 2013b; Lissoni *et al.* 1996; Rudà *et al.* 2016), and therefore increasing life expectancy as seen in our patients (Zhang *et al.* 2016). Furthermore, the combination of CAH inhibitors with chemotherapeutic treatments for glioblastoma increased survival.

We noticed that the integration of AAZ in a multitherapeutic context contributed to reducing cortisone administration due to its diuretic and anti-edema properties. Besides, administrating AAZ and VPA reduced epileptic episodes and improved the prognosis.

Interaction between MLT and other DBM molecules opposes several processes characterizing neoplastic phenotype, mutation and proliferation, progression and/or dissemination. All these features suggest the use of this molecule as a treatment for cancer (Di Bella *et al.* 2017; Gil-Martín *et al.* 2019; Nooshinfar *et al.* 2017; Talib 2018).

Many research papers confirm the preventive and therapeutic activity of vitamin D in neoplastic pathologies (Jeon & Shin 2018). Various synthetic analogues of Vitamin D, called deltanoids, are designed specifically to potentiate antiblastic activity, and at the same time reducing several collateral effects (Negri *et al.* 2020). Synergism of Vitamin D, Vitamin C, Vitamin E, and MLT was found in several clinical studies, showing their antiproliferative, antiangiogenic, and differentiative properties.

Furthermore, we hypothesize that the combination of Calcitriol and ATRA (All-Trans Retinoic Acid) and Temozolomide could be a safer approach to benefit from vitamin D in high degree glioma cancer management. The addition of acetazolamide to this protocol can reduce the risk of brain pseudotumors, because of vitamin D and a surplus of vitamin A can lead to intracranial hypertension; this approach can provide benefits due to antitumoral activity of acetazolamide (Elmaci *et al.* 2019).

TREATED PATIENTS WITH MALIGNANT BRAIN TUMORS

The Patient's age, diagnosis, and initial treatment used before DBM are summarized in Table 2. Below is a briefing about each case and the follow-up results after DBM.

Patient ID: 5833

Date of birth: 29/07/1989
DIAGNOSIS 20/06/2012 (23 years old) **ANAPLASTIC ASTROCYTOMA (WHO III)**
unmethylated-**MGMT**; mutated **IDH1**; **EGFRvIII** negative; overexpressed **VEGF**.

20/06/2012 – **SURGICAL RESECTION** (bilobed space-occupying lesion, around 4 cm)
26/07/2012 – **Brain MRI:** *"...small residue of the most caudal part of the left parietal glial lesion..."*
30/07/2012 – **RT + TMZ 135 mg** (up to 06/11/2012)
21/11/2012 – **TEM 370 mg**/12 courses
27/12/2012 – **PET:** *"…hypodense nodular area, caudally to the surgical cavity, in the left parietal region..."*
05/03/2013 – **Brain MRI:** *"...disease residue along the edges of the seemingly stable surgical cavity, even though the rCBV values are increased compared to the previous scan..."*
05/10/2013 – **Brain MRI:** *"...further signal alteration located in the left parietal corona radiata, suspected to be mild infiltrative disease progression..."*
05/11/2013 – **START DBM**
20/06/2014 – **Brain MRI:** *"...morphology and extension of the infiltrative disease residue along the lower edge of the surgical cavity are unaltered... the small area of signal alteration located in the left parietal corona radiata is also unaltered"*

Tab. 2. Patient's age, diagnosis, and treatments before initiation of DBM

Patient ID	Age (y) at the time of diagnosis	Time of diagnosis	Diagnosis	Mutation/ Expression	Therapy after diagnosis	Initiation of DBM	Survival after DBM
5833	23	Jun 2012	Anaplastic astrocytoma, (WHO III)	unmethylated-MGMT; mutated IDH1; EGFRvIII negative; overexpressed VEGF	Surgery + Chemotherapy +Radiotherapy	Nov 2013	>7 years
6245	23	May 2007	Oligoastrocytoma (II)	unmutated IDH1; mutated IDH2; methylated-MGMT; 1p/19q codeletion	Surgeries + Chemotherapy +Radiotherapy	Nov 2014	> 6 years
6572	27	Feb 2015	Anaplastic astrocytoma (III)	Mutated-IDH1; methylated-MGMT; GFAP positive	Surgery + Chemotherapy	Mar 2015	> 5 years
9691	19	Nov 2010	Oligoastrocytoma (II)	unmutated IDH1; IP53 negative; GFAP positive; NOGO-A positive	Surgeries	Aug 2014	> 6 years
4835	40	Nov 2012	GBM (IV)	mutated IDH1	Surgery	Dec 2012	> 8 years
5371	49	May 2013	Anaplastic glioma (III)	ND	-	Sept 2013	> 7 years
5251	43	Nov 2012	Oligodendroglioma (?)	ND	-	Apr 2013	> 7 years

25/06/2014 – **PET:** *"...reduction in radio-compound uptake at the hypodense nodular area, previously reported caudally to the surgical cavity in the left parietal region..."*
29/12/2017 – **PET:** *"...the PET-CT scan has not shown any amino acid tracer distribution abnormalities that could be related with certainty to a neoplastic disease..."*
23/03/2018 – **Brain MRI:** *"...morphology and size of the surgical cavity are unaltered... the areas of signal alteration are also unaltered, T2/FLAIR hyperintensities on the edges of the cavity, without contrast agent uptake. No documented increase in rCBV values at these alterations..."*
18/10/2018 – **MRI:** Unaltered diagnosis
10/06/2019 – **MRI:** Stable disease diagnosis with unaltered main MRI findings
10/01/2020 – **PET-CT:** *"...has not shown any amino acid tracer distribution abnormalities that could be related to a neoplastic disease, particularly at the edges of the surgical resection in the left parietal region. No further areas of focal uptake of 11C-Methionine at cortical and subcortical regions and in the cerebral hemispheres."*
26/06/2020 – **Brain MRI:** Stable disease diagnosis with unaltered main MRI reports.
26/06/2020 – **Brain MRI with Contrast Agent:** *"... shows non-significant increase in perfusion in some ROIs and choline peaks in some voxels on spectroscopy. No significant enhancement after contrast agent. Ended due to the absence of recurrent disease."*
10/10/2020 – **Histological exam:** *"Fragment of squamous epithelioma in situ (pTis UICC 2017)"*

<u>*Patient ID: 6245*</u>

Date of birth: 04/12/1982
DIAGNOSIS 21/05/2007 (25 years old) **OLIGOASTROCYTOMA (WHO II)**
unmutated **IDH1**; mutated **IDH2**; methylated-**MGMT**; **1p/19q** codeletion

21/05/2007 – **1st SURGICAL RESECTION**
31/05/2013 - **2nd SURGICAL RESECTION** (1st recurrence)
21/10/2014 - **3rd SURGICAL RESECTION** (2nd recurrence) – **RX + TEM 75 mg**
25/11/2014 – **START DBM**
20/07/2015 – **Brain MRI:** *"...no pathological alterations shown in the sequences performed after Gadolinium administration..."*
30/03/2016 – **Brain MRI:** *"...findings essentially unaltered..."*
21/11/2017 – **Brain MRI:** *"...findings essentially unaltered..."*
02/05/2018 – **Brain MRI:** *"...findings essentially unaltered..."*

27/11/2018 – **Brain MRI:** *"...findings essentially unaltered..."*
22/05/2019 – **Brain MRI:** *"stable neuroradiological diagnosis compared to previous"*
12/05/2020 – **Brain and brain stem MRI:** Stable diagnosis
13/05/2020 – **Oncology Visit:** *"In light of the recent instrumental reassessment that documented significant disease stability, and optimal and stable general clinical conditions, it is recommended to keep monitoring the patient"*
18/11/2020 – **Brain and brain stem MRI:** *"Today's findings appear completely unaltered. [...] All the remaining findings are essentially unaltered."*

Patient ID: 6572

Date of birth: 21/02/1988
DIAGNOSIS 02/02/2015 (27 years old) **ANAPLASTIC ASTROCYTOMA (WHO III)**
Mutated-**IDH1**; methylated-**MGMT**; **GFAP** positive

16/01/2015 – **SURGICAL RESECTION** (no **CT/2 RT** sessions)
27/02/2015 – **Brain MRI:** *"...centimetric residual area of T1 hyperintensities and T2 hypointensities is observed with a diffuse oedema. Adjacent to the previous finding, millimetric area of T1 hyperintensities as well as the enhanced area after contrast agent..."*
Subsequently SEIZURES – PROGRESSIVELY WORSENING HEADACHE – PARTIAL STATUS EPILEPTICUS
NEW SURGERY PROPOSED followed by RT – TMZ
16/03/2015 – **START DBM**
20/04/2016 – **Brain MRI:** *"...slightly less evident, the small area of signal alteration refers to the residual lesion after contrast agent..."*
03/10/2017 – **Brain MRI:** *"...no pathological enhancement after administration of the contrast agent..."*
02/07/2018 – **Brain MRI:** *"...No areas of pathological enhancement attributed to residues/recurrences are shown..."*
06/02/2019 – **Brain MRI:** *"The findings are essentially unaltered... no significant areas of pathological enhancement are observed"*
09/10/2019 – **Brain MRI:** *"compared to the previous scan on 30/01/19: findings unaltered; left frontal region with an area of T2 hyperintensities. Frontal horn of left lateral ventricle remains wide. Diffusion and perfusion imaging do not show areas of ADC reduction and rCBV increase at the aforementioned area of T2 hyperintensities. Remaining findings are unaltered, particularly in the malacic area affecting the right cerebral hemisphere and left thalamic ischaemic cavity, as well as the likely nodule of grey matter heterotopia along the wall of the right lateral ventricle chamber. No areas of pathological enhancement after contrast agent."*
15/07/2020 – **Brain MRI:** *"Compared to the exam observed on 09/10/2019, the baseline and post-contrast enhancement MRI findings are perfectly comparable. Currently no images are observed that are consistent with neoplastic recurrence."*

Patient ID: 9691

Date of birth: 20/11/1991
DIAGNOSIS: 30/11/2010 (19 years old) **OLIGOASTROCYTOMA (WHO II)**
unmutated **IDH1**; **IP53** negative; **GFAP** positive; **NOGO-A** positive

16/11/2010 - **1st SURGICAL RESECTION** (5 cm mass)
15/02/2013 – **2nd SURGICAL RESECTION** (recurrence) – diagnosis: OLIGODENDROGLIOMA WHO II
10/06/2013 – **Brain MRI:** *"...residual lesion..."*
08/07/2014 – **Brain MRI:** *"...extension of the residual lesion is unaltered, but diffusion imaging shows a 2-fold ADC increase compared to the white matter, and perfusion also shows an rCBV value that is 5 times that of the reference white matter..."*
JUDGED TO BE INOPERABLE (RIGHT FOOT PARALYSIS – DEPRESSION – CLONUS)
08/08/2014 – **First revision:** Prof. Giangasparo – Umberto I – Policlinico di Roma [Umberto I Polyclinic of Rome]: GRADE 3 ANAPLASTIC ASTROCYTOMA
18/08/2014 – **START DBM**
28/08/2014 **Brain MRI:** *"...slight increase in extension of the area of signal alteration, hyperintense on T2-weighted sequences, affecting the nervous tissue surrounding the surgical wound, that seems to contralaterally infiltrate through the trunk of the corpus callosum..."*
11/09/2014 – **Second Revision** Ist. Besta di Milano [Besta Institute of Milan] of histological findings from 2010 and 2013
DIAGNOSIS: (2010) **OLIGOASTROCYTOMA** – (2013) **Grade 3 ANAPLASTIC ASTROCYTOMA**
16/09/2014 – 31/10/2014 – **RT** (33 sessions): Refused chemotherapy treatment.
03/12/2014 – **Brain MRI:** *"...size and characteristics of the signal in the area of T2 hyperintensities are essentially unaltered..."*
03/06/2015 – **Brain MRI:** *"...the area of T2 hyperintensities is essentially comparable... diffusion imaging shows this at the area of signal alteration. Increased ADC values (2.6) compared to white matter (1); perfusion imaging does not detect significantly increased rCBV values"*
09/09/2015 – **Brain MRI:** *"...no areas of pathological contrast enhancement are observed after administration of the contrast agent..."*
22/11/2016 – **Brain MRI:** *"...findings unaltered... diffusion and perfusion imaging do not show areas of ADC reduction or rCBV increase..."*
28/03/2017 – **Brain MRI:** *"...the diagnosis remains stable..."*
01/09/2017 – **PET:** *"no areas of significant uptake at the known lesion, outlined in the MRI scan on 29/03/2017,*

in the left parasagittal posterior frontal hemisphere...the scan did not show the presence of areas of pathological radiopharmaceutical uptake that could be related to the primary disease..."
The patient reduced the doses of the medicinal product on their own initiative, followed by some seizures and worsening of general conditions.
31/07/2018 – **Brain MRI:** *"...stable radiological findings...no apparent recurrence of the known space-occupying lesion from their medical history..."*
Resumption of somatostatin intravenous infusion treatment at full doses, resolution of seizures
Improvement in quality of life.
09/07/2020 – **Brain MRI:** *"Compared to the previous MRI on 20/02/2020, the onset of an area of pathological contrast enhancement in the left parietal intra-axial region is observed, likely neoplastic with irregular morphology and around 20 mm in diameter. Perfusion imaging shows rCBV values that are increased 3-fold at this area of pathological enhancement compared to those of the contralateral white matter, likely in relation to signs of neoangiogenesis. A small perilesional oedema is associated with this area of pathological enhancement. Increased extension of the known area of left high-frontal signal alteration [...]posterosuperiorly to the known surgical cavity, rCBV values that are increased 2/3-fold are observed compared to those of the contralateral white matter. Compared to the abovementioned previous MRI scan, the onset of multiple small and markedly hypointense areas are observed at the same area on the T2*-weighted GE images, such as the presence of haemosiderin, suspected to be multiple small radiation-induced cavernomas. The morphovolumetrics of the ventricular system and the size of the subarachnoid spaces of the convexity and the base are essentially unaltered."*
21/10/2020 – **Brain MRI with Contrast Agent:** *"... slight size reduction in the known area of pathological contrast enhancement, of irregular morphology and in the left parietal region, is observed with a decrease in the associated perilesional oedema. Perfusion imaging shows rCBV values that are persisting and currently increased 5-fold at this area of pathological enhancement compared to those of the contralateral harmless white matter, such as neoangiogenesis. The spectroscopy documents a slight increase in choline compounds in this region and a moderate reduction in NAA compared to the homologous sampling collected from the contralateral region, without signal alteration. The extension of the left superior frontal area of signal alteration is essentially unaltered, with T2/FLAIR hyperintensities, surrounding the surgical cavity and extending to the underlying centrum semiovale and corona radiata: at the latter, rCBV values remain significantly poorly-defined, more apparent alongside the lateral ventricle. The ventricular morphovolumetrics and remaining finding are stable, in the absence of new areas of pathological contrast enhancement."*
The patient-initiated suspension of essential components of the cure these days has resulted in severe disease progression.

Patient ID: 4835
Date of birth: 26/05/1972
DIAGNOSIS: 15/11/2012 (40 years old)
GLIOBLASTOMA (WHO IV) (with a peripheral part of diffuse astrocytoma) mutated **IDH1**

15/11/2012 – **INCOMPLETE SURGICAL RESECTION** (70/80%): *"...the large lateral and anterior parts are removed. The neoplastic part infiltrating the premotor–motor and contralateral regions is left in situ. 70/80% of tumor removal is estimated..."*
18/12/2012 – **START DBM**
04/01/2013 – **MRI:** *"...known residual lesion in the left frontal paramedian region whose signal, area of infiltration and contrast enhancement characteristics do not appear to be substantially altered compared to the previous scan..."*
09/11/2015 – **MRI:** *"...the radiological findings appear to be essentially unaltered... in particular, the known space-occupying lesion located at the cingulate gyrus, which affects both hemispheres, is still significant..." "... no areas of intra- or extraparenchymal pathological enhancement are observed at either the lesion or the remaining sub- and supratentorial parenchyma after administration of the contrast agent..."*
29/04/2016 – **MRI:** *"...the sizes and signal characteristics of the known space-occupying lesion located at the cingulate gyrus, which affects both hemispheres, remains essentially unaltered..."*
02/11/2016 – **MRI:** *"...during today's scan, after administration of the contrast agent, the abovementioned poorly-defined area of contrast enhancement at the lesion in the right paramedian region, appears to be less apparent..."*
15/02/2018 – **MRI:** *"...no signs of locoregional recurrence are detected as a result of removing the glioblastoma that was previously located at the cingulate gyrus with bihemispheric involvement..."*
29/05/2019- **MRI:** *"...the onset of signs of locoregional disease recurrence are not observed...Remaining findings are unaltered..."*
19/03/2020 – **Brain MRI:** *"absence of enhancement attributed to signs of disease recurrence. Diffuse leukomalacia persists at the centra semiovale and in the periventricular region, unaltered compared to the previous scan. Sub- and supratentorial ventricular system of normal morphology, volume and location. Slight enlargement of the vault fluid spaces. Developmental venous anomaly in the left cerebellar region. No intra- and extra-axial pathological enhancement detected after contrast agent. Mucosal thickening of left maxillary sinus. Turbinate hypertrophy."*

Patient ID: 5371
Date of birth: 22/06/1964

DIAGNOSIS: 06/05/2013 (49 years old) **PROGRESSIVE ANAPLASTIC GLIAL TUMOUR, GRADE III INFILTRATING GLIOMA**
MOLECULAR ANALYSIS ON MUTATIONS HAS NEVER BEEN PERFORMED

06/05/2013 – **MRI:** *"...extensive cerebral tumor involving the entire bulbo-medullary junction with diffusion to the inferior cerebellar peduncles, right middle cerebellar peduncle, and infiltration of the 4th ventricle on which it already determines the mass effect..."*
10/09/2013 – **START DBM**
"Progressive anaplastic glial tumor, grade III infiltrating glioma" DIAGNOSIS, *exacerbated by the highest functional dignity of the affected area, crossed by 10 cranial nerves, from the 3rd to 12th (excluding the optic and olfactory nerves) and the 4th ventricle, site of the vital nerve, respiratory and cardiovascular centres that can be easily made inactive by compression (for tumor progression, and/or postoperative or post-therapeutic cerebral oedema). The location and extension caused paresis and disability. A court-appointed Technical Advisor, who the patient had asked to get DBM, excluded radiotherapy, operation, and confirmed the possibility of palliative treatment with a prognosis of less than a year.*
DBM achieved remission in the majority of the tumor and stability, blocking progression of the residual tumor cells that are no longer proliferating, finally enabling functional recovery and self-sufficiency in a patient that was previously known for disability and assistance.
29/01/2019 – **Brain MRI:** *"the extension of the neoplastic infiltration detected at the bulbocervical region remains stable, bilaterally with an increase in volume of the anatomic structures in question and inhomogeneous signal alteration".*
17/04/2019 – **FDG-PET:** *"compared to the MRI on 29/01/2019: the presence of inhomogeneous metabolic tracer uptake is detected, with various degrees of mild to moderate uptake at the alteration detected on the MRI. The uptake is reported to be more accentuated on the right-hand side. Moreover, moderate-severe uptake is detected at the right column, of uncertain significance (aspecific? Other?); useful assessment in characterized field. There is nothing else to report in the remaining examined body regions, particularly in the lung parenchyma and the liver. The PET findings suggest the presence of heteroplastic tissue with moderate carbohydrate metabolism at the bulbocervical junction and proximal segment of the cervical cord. N.B. in the hypermetabolic region, the activity is defined as mild-moderate-severe compared to the hepatic metabolic activity, pursuant to EANM guidelines."*

Patient ID: 5251

Date of birth: 06/03/1969
DIAGNOSIS: November 2012 (43 years old)
MOLECULAR ANALYSIS ON MUTATIONS HAS NEVER BEEN PERFORMED

17/12/2012 – **CT ANGIOGRAM and MRI:** show a tumor with *"progressive tendency" (compared with an MRI from 2006 in which it is barely noticeable, so much so that it was not taken into account at the time), with severe vascularization and sticking closely to the sylvian artery, therefore "surgery is not recommended". Considering the progressive characteristics and the spectroscopy and perfusion imaging findings, the diagnostic hypothesis puts* ***GANGLIOGLIOMA*** *or* ***OLIGODENDROGLIOMA*** *or* ***OLIGOASTROCYTOMA****.*
19/04/2013 – **START DBM**
20/03/2014 – **MRI:** *"...the presence of a space-occupying lesion, 1.95 x 1.59 cm in size, is confirmed... with mild enhancement after contrast agent..."*
20/03/2014 – **PET:** *"...the lesion, composed of solid and calcified portions, has no substantive changes compared to what was previously documented..."*
09/11/2015 – **PET:** *"...the scan does not show areas of pathological tracer uptake and, in particular, the previously reported lesion, which appears to be characterized by a coarse shell-like calcification and without a perilesional oedema that could be related to calcified meningioma"*
17/10/2017 – **MRI:** *"...the scan has not shown the evolution of the left temporosylvian lesion..."*
22/11/2018 – **MRI:** *"...lesion completely stable..."*
27/10/2020 – **Brain MRI, perfusion imaging and spectroscopy:** *"The left temporosylvian lesion remains completely unaltered, with extensive calcified parts and a smaller parenchymatous part."*

OUTCOMES OF DBM PROTOCOL

Three of the seven patients treated with DBM are still alive after 5 to 6 years, and the other four patients are still alive after seven years of starting DBM (Table 2). In 3 cases (IDs **5833, 6245, 6572**), DBM began after the failure of Stupp protocol, i.e., when disease recurrence was detected. After DBM treatment, disease progression was arrested.

The patient with GBM (ID 4835) had incomplete surgical resection then adapted DBM as first-line therapy a month later. After eight years of DBM, the patient is still alive and has neither symptoms nor disease progression. Furthermore, patient 5371, who had inoperable aplastic glial neoplasm received neither surgery nor Stupp protocol, started DBM as first-line therapy during tumor progression. After seven years, the patient did not develop recrudescence and is cancer-free. Also, patient 5251, with inoperable oligoastrocytoma, didn't start Stupp therapy and didn't have surgery. Eight years following DBM, the patient is still alive after eight years with free-tumor progression and living a normal life.

DISCUSSION

In malignant brain tumors and GBM, the prognosis remains poor despite surgery, chemo- and radiotherapy, with a median survival of 14-18 months after diagnosis

(Delgado-López & Corrales-García 2016). In our study, DBM improved life expectancy and quality of life and avoided relevant toxicity (Di Bella *et al.* 2017; Di Bella *et al.* 2013a; Di Bella *et al.* 2013b; Di Bella 2005; Di Bella 2019; Di Bella 2010; Di Bella *et al.* 2018; Di Bella *et al.* 1979a; Di Bella *et al.* 1979b; Di Bella 1997; Di Bella & Di Bella 2015; Di Bella & Gualano 2006; Di Bella & Di Bella 1998).

During most tumors' progression, with more evidence in brain ones, the percentage of CSCs compared with other cellular components of the neoplastic population is high, and it's associated with chemo and radiotherapy resistance and the rapid progression of the disease. For this reason, we have gradually increased the dosage of molecules that negatively affect CSCs and reprograms CSCs.

Unlike Stupp's protocol, the metronomic administration in DBM of temozolomide (20 mg in the morning and the evening) and hydroxyurea (500 mg at lunch) has enhanced proliferation control and invasiveness of cancer cells. Besides, the daily administration of MLT (100mg) with the retinoid solution in vitamin E reduced the myelotoxicity of temozolomide and hydroxyurea (Di Bella *et al.* 2013a; Di Bella *et al.* 2013b; Di Bella & Di Bella 2015; Di Bella & Gualano 2006).

The DBM, in contrast with a classical oncological point of view, moves the therapeutic axis from cytolytic, toxic, and immunosuppressive mechanisms to the contrast of negatively regulating oncogenesis through different mechanisms (Di Bella *et al.* 2018; Perry *et al.* 2008). Furthermore,

differentiating components of DBM, such as a retinoid solution in vitamin E, vitamins C, D, and MLT, counteract the mutagenic capability of tumor cells, based on a defense system and a survival program that allows efficient and rapid repair of DNA damages induced by chemo- and radiotherapy. For instance, the prokaryotes, the first forms of life, are still surviving until the present day. Thanks to a defense system developed during evolution based on a mutational program, DNA repair in case of adverse events. The prokaryotes survival program termed the state of emergency, "SOS program," has been passed to the somatic cells (Radman 1975). In addition, it has been shown that the SOS program is activated in tumor cells, and many homologies in neoplastic cell genes and bacterial ones have been identified (Israel 1996).

Cancer cells in acute stress implement DNA repair systems and express or silence genes according to their needs, selecting and retaining for each mutation a whole series of advantages with speed and efficiency far superior to bacterial cells. The SOS system allows the neoplastic population to progressively become insusceptible to different oncotherapeutic drugs through DNA repair and recombination.

The SOS system is silenced and inactivated in stable biological conditions, transcriptionally stopped by a repressor, the LEX-A protein. When severe damages occur in a somatic cell DNA, the transcriptional repressor LEX-A is turned off by the positive regulator REC-A. The SOS activation carries along with a series of mutations that repair but, at the same time, modify the DNA, leading to carcinogenesis. The mutating cells start a progression of the SOS program, in which a continuous selection and retention of mutations confers a series of advantages, as confirmed by (Lambert *et al.* 2011) and recently by (Russo *et al.* 2019).

In conclusion, the multi-strategic objectives of DBM are inhibiting the proliferative-invasiveness and neoplastic angiogenesis, and silencing the SOS survival system through differentiated components, like the retinoid solution in vitamin E, MLT, vitamin C, and D, etc. Besides, the differentiative components of DBM display trophic, immunomodulatory, and antioxidant activities, improve vitality and efficiency of normal cells and depress the efficiency and vitality of neoplastic ones.

The DBM is expanding its activity to numerous vital responses typical of neoplastic biology. DBM moves the therapeutic axis from a merely cytotoxic and cytolytic activity that expected a utopian and elusive lifelong eradication of all tumor cells in the body to an immuno-neuro-endocrine homeostasis recovery. A more physiologic strategy thought the reconversion of vital functions that deviate in cancer cells, the differentiation of tumor cells, and the reprogramming of cancer stem cells.

REFERENCES

1 Abe M, Shibata K, Urata H, Sakata N, Katsuragi T (2003). Induction of leukotriene C4 synthase after the differentiation of rat basophilic leukemia cells with retinoic acid and a low dose of actinomycin D and its suppression with methylprednisolone. J Cell Physiol. **196**(1): 154–64. doi: 10.1002/jcp.10285.

2 Adachi Y, Itoh F, Yamamoto H, Iku S, Matsuno K, Arimura Y, Imai K (2001). Retinoic acids reduce matrilysin (matrix metalloproteinase 7) and inhibit tumor cell invasion in human colon cancer. Tumour Biol. **22**(4): 247–53. doi: 10.1159/000050623.

3 Aidoo A, Lyn-Cook LE, Lensing S, Wamer W (1994). Ascorbic acid (vitamin C) modulates the mutagenic effects produced by an alkylating agent in vivo. Environ Mol Mutagen. **24**(3): 220–8. doi: 10.1002/em.2850240311.

4 Albérini JL, Meunier B, Denzler B, Devillers A, Tass P, Dazord L et al.. (2000). Somatostatin receptor in breast cancer and axillary nodes: study with scintigraphy, histopathology and receptor autoradiography. Breast Cancer Res Treat. **61**(1): 21–32. doi: 10.1023/a:1006447325077.

5 Albini A, Florio T, Giunciuglio D, Masiello L, Carlone S, Corsaro A et al.. (1999). Somatostatin controls Kaposi's sarcoma tumor growth through inhibition of angiogenesis. FASEB J. **13**(6): 647–55. doi: 10.1096/fasebj.13.6.647.

6 Al-Hanbali M, Ali D, Bustami M, Abdel-Malek S, Al-Hanbali R, Alhussainy T, Qadan F, Matalka KZ. Epicatechin suppresses IL-6, IL-8 and enhances IL-10 production with NF-□B nuclear translocation in whole blood stimulated system. Neuroendocrinol Lett. **30**(1): 131–138, 2009. PubMed PMID: 19300393.

7 Anthony L, Freda PU (2009). From somatostatin to octreotide LAR: evolution of a somatostatin analogue. Curr Med Res Opin. **25**(12): 2989–99.

8 Arany I, Whitehead WE, Ember IA, Tyring SK (2003). Dose-dependent activation of p21WAF1 transcription by all-trans-acid in cervical squamous carcinoma cells. Anticancer Res. **23**(1A): 495–7.

9 Arena S, Pattarozzi A, Massa A, Esteve JP, Iuliano R, Fusco A et al.. (2007). An intracellular multi-effector complex mediates somatostatin receptor 1 activation of phospho-tyrosine phosphatase eta. Mol Endocrinol. **21**(1): 229–46. doi: 10.1210/me.2006-0081.

10 Arnold A, Ayoub J, Douglas L, Hoogendoorn P, Skingley L, Gelmon K et al. (1994). Phase II trial of 13-cis-retinoic acid plus interferon alpha in non-small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Natl Cancer Inst. **16;86**(4): 306–9. doi: 10.1093/jnci/86.4.306.

11 Ashino H, Shimamura M, Nakajima H, Dombou M, Kawanaka S, Oikawa T et al. (2003). Novel function of ascorbic acid as an angiostatic factor. Angiogenesis. **6**(4): 259–69. doi: 10.1023/B:AGEN.0000029390.09354.f8.

12 Auld F, Maschauer EL, Morrison I, Skene DJ, Riha RL. Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders. Sleep Medicine Reviews. 2017; **34**: 10–22.

13 Barnett P (2003) Somatostatin and somatostatin receptor physiology. Endocrine. **20**(3): 255–64. doi: 10.1385/ENDO:20:3:255.

14 Baroni A, Paoletti I, Silvestri I, Buommino E, Carriero MV (2003). Early vitronectin receptor downregulation in a melanoma cell line during all-trans retinoic acid-induced apoptosis. Br J Dermatol. **148**(3): 424–33. doi: 10.1046/j.1365-2133.2003.05165.x.

15 Barrie R, Woltering EA, Hajarizadeh H, Mueller C, Ure T, Fletcher WS (1993). Inhibition of angiogenesis by somatostatin and somatostatin-like compounds is structurally dependent. J Surg Res. **55**(4): 446–50. doi: 10.1006/jsre.1993.1167.

16 Barroga EF, Kadosawa T, Okumura M, Fujinaga T (2000). Inhibitory effects of 22-oxa-calcitriol and all- trans retinoic acid on the growth of a canine osteosarcoma derived cell-line in vivo and its pulmonary metastasis in vivo. Res Vet Sci. **68**(1): 79–87. doi: 10.1053/rvsc.1999.0360.

17 Basu M, Banerjee A, Bhattacharya UK, Bishayee A, Chatterjee M (2000). Beta-carotene prolongs survival, decreases lipid peroxidation and enhances glutathione status in transplantable murine lymphoma. Phytomedicine. **7**(2): 151–9. doi: 10.1016/S0944-7113(00)80088-4.

18 Batra RK, Olsen JC, Hoganson DK, Caterson B, Boucher RC (1997). Retroviral gene transfer is inhibited by chondroitin sulfate proteoglycans/glycosaminoglycans in malignant pleural effusions. J Biol Chem. **272**(18): 11736–43. doi: 10.1074/jbc.272.18.11736.

19 Bejarano I, Redondo PC, Espino J, Rosado JA, Paredes SD, Barriga C et al. (2009). Melatonin induces mitochondrial-mediated apoptosis in human myeloid HL-60 cells. J Pineal Res. **46**(4): 392–400. doi: 10.1111/j.1600-079X.2009.00675.x..

20 Bendich A, Langseth L (1995). The health effects of vitamin C supplementation: a review. J Am Coll Nutr. **14**(2): 124–36. doi: 10.1080/07315724.1995.10718484.

21 Ben-Jonathan N, Liby K, McFarland M, Zinger M (2002). Prolactin as an autocrine/paracrine growth factor in human cancer. Trends Endocrinol Metab. **13**(6): 245–50. doi: 10.1016/s1043-2760(02)00603-3.

22 Bhatti P, Doody DR, Mckean-Cowdin R, Mueller BA (2015). Neonatal vitamin D and childhood brain tumor risk. Int J Cancer. **136**(10): 2481–5. doi: 10.1002/ijc.29291.

23 Blask DE, Wilson ST, Zalatan F (1997). Physiological melatonin inhibition of human breast cancer cell growth in vitro: evidence for a glutathione-mediated pathway. Cancer Res. **57**(10): 1909–14. PMID: 9157984.

24 Blaszczak W, Barczak W, Masternak J, Kopczyński P, Zhitkovich A, Rubiś B (2019). Vitamin C as a Modulator of the Response to Cancer Therapy. Molecules. **24**(3): 453. doi: 10.3390/molecules24030453.

25 Bonneterre J, Peyrat JP, Beuscart R, Demaille A (1990). Biological and clinical aspects of prolactin receptors (PRL-R) in human breast cancer. J Steroid Biochem Mol Biol. **37**(6): 977–81. doi: 10.1016/0960-0760(90)90453-r.

26 Borgström P, Hassan M, Wassberg E, Refai E, Jonsson C, Larsson SA et al. (1999). The somatostatin analogue octreotide inhibits neuroblastoma growth in vivo. Pediatr Res. **46**(3): 328–32. doi: 10.1203/00006450-199909000-00014.

27 Briganti V, Sestini R, Orlando C, Bernini G, La Cava G, Tamburini A et al. (1997). Imaging of somatostatin receptors by indium-111-pentetreotide correlates with quantitative determination of somatostatin receptor type 2 gene expression in neuroblastoma tumors. Clin Cancer Res. **3**(12 Pt 1): 2385–91.

28 Brunet-Dunand SE, Vouyovitch C, Araneda S, Pandey V, Vidal LJ, Print C et al. (2009). Autocrine human growth hormone promotes tumor angiogenesis in mammary carcinoma. Endocrinology. **150**(3): 1341–52. doi: 10.1210/en.2008-0608. .

29 Buckley AR, Buckley DJ (2000). Prolactin regulation of apoptosis-associated gene expression in T cells. Ann N Y Acad Sci. **917**: 522–33. doi: 10.1111/j.1749-6632.2000.tb05417.x.

30 Cameron E, Pauling L (1973). Ascorbic acid and the glycosaminoglycans. An orthomolecular approach to cancer and other diseases. Oncology. **27**(2): 181–92. doi: 10.1159/000224733.

31 Cameron E, Pauling L, Leibovitz B (1979). Ascorbic acid and cancer: a review. Cancer Res. **39**(3): 663–81. PMID: 371790.

32 Campbell MJ, Gombart AF, Kwok SH, Park S, Koeffler HP (2000). The anti-proliferative effects of 1alpha,25(OH)2D3 on breast and prostate cancer cells are associated with induction of BRCA1 gene expression. Oncogene. **19**(44): 5091–7. doi: 10.1038/sj.onc.1203888.

33 Carystinos GD, Alaoui-Jamali MA, Phipps J, Yen L, Batist G (2001). Upregulation of gap junctional intercellular communication and connexin 43 expression by cyclic-AMP and all-trans-retinoic acid is associated with glutathione depletion and chemosensitivity in neuroblastoma cells. Cancer Chemother Pharmacol. **47**(2): 126–32. doi: 10.1007/s002800000231.

34 Cascinu S, Del Ferro E, Ligi M, Staccioli MP, Giordani P, Catalano V et al. (2001). Inhibition of vascular endothelial growth factor by octreotide in colorectal cancer patients. Cancer Invest. **19**(1): 8–12. doi: 10.1081/cnv-100000069.

35 Castro JR, Costoya JA, Gallego R, Prieto A, Arce VM, Señarís R (2000). Expression of growth hormone receptor in the human brain. Neurosci Lett. **281**(2–3): 147–50. doi: 10.1016/s0304-3940(00)00830-2.

36 Cataldi S, Arcuri C, Lazzarini A, Nakashidze I, Ragonese F, Fioretti B et al. (2020). Effect of 1α,25(OH)2 Vitamin D3 in Mutant P53 Glioblastoma Cells: Involvement of Neutral Sphingomyelinase1. Cancers (Basel). **12**(11): 3163. doi: 10.3390/cancers12113163.

37 Cattaneo MG, Scita G, Vicentini LM (1999). Somatostatin inhibits PDGF-stimulated Ras activation in human neuroblastoma cells. FEBS Lett. **459**(1): 64–8. doi: 10.1016/s0014-5793(99)01218-1.

38 Chambaut-Guérin AM, Costa SL, Lefrançois T, Fages C, Gauthereau X, Tardy M (2000). Effects of retinoic acid and tumor necrosis factor alpha on GL-15 glioblastoma cells. Neuroreport. **11**(2): 389–93. doi: 10.1097/00001756-200002070-00033.

39 Chen Z, Wang HW, Wang S, Fan L, Feng S, Cai X et al. (2019). USP9X deubiquitinates ALDH1A3 and maintains mesenchymal identity in glioblastoma stem cells. J Clin Invest. **129**(5): 2043–2055. doi: 10.1172/JCI126414.

40 Chesnokov V, Gong B, Sun C, Itakura K (2014). Anti-cancer activity of glucosamine through inhibition of N-linked glycosylation. Cancer Cell Int. **14**: 45. doi: 10.1186/1475-2867-14-45.

41 Chokkalingam AP, McGlynn KA, Gao YT, Pollak M, Deng J, Sesterhenn IA et al. (2001). Vitamin D receptor gene polymorphisms, insulin-like growth factors, and prostate cancer risk: a population-based case-control study in China. Cancer Res. **61**(11): 4333–6. PMID: 11389055.

42 Chou HK, Chen SL, Hsu CT, Chao YC, Tsao YP (2000). Bcl-2 accelerates retinoic acid-induced growth arrest and recovery in human gastric cancer cells. Biochem J. **348** Pt 2(Pt 2): 473–9. PMID: 10816444.

43 Consolini R, Pala S, Legitimo A, Crimaldi G, Ferrari S, Ferrari S (2001). Effects of vitamin D on the growth of normal and malignant B-cell progenitors. Clin Exp Immunol. **126**(2): 214–9. doi: 10.1046/j.1365-2249.2001.01671.x.

44 Corleto VD, Falconi M, Panzuto F, Milione M, De Luca O, Perri P et al. (2009). Somatostatin receptor subtypes 2 and 5 are associated with better survival in well-differentiated endocrine carcinomas. Neuroendocrinology. **89**(2): 223–30. doi: 10.1159/000167796.

45 Cos S, Verduga R, Fernández-Viadero C, Megías M, Crespo D (1996). Effects of melatonin on the proliferation and differentiation of human neuroblastoma cells in culture. Neurosci Lett. **216**(2): 113–6. doi: 10.1016/0304-3940(96)13035-4.

46 Czeczuga-Semeniuk E, Wołczyński S, Anchim T, Dziecioł J, Dabrowska M, Pietruczuk M (2002). Effect of melatonin and all-trans retinoic acid on the proliferation and induction of the apoptotic pathway in the culture of human breast cancer cell line MCF-7. Pol J Pathol. **53**(2): 59–65.

47 Dalen H, Neuzil J (2003). Alpha-tocopheryl succinate sensitises a T lymphoma cell line to TRAIL-induced apoptosis by suppressing NF-kappaB activation. Br J Cancer. **88**(1): 153–8. doi: 10.1038/sj.bjc.6600683.

48 Dalirfardouei R, Karimi G, Jamialahmadi K (2016). Molecular mechanisms and biomedical applications of glucosamine as a potential multifunctional therapeutic agent. Life Sci. **152**: 21–9. doi: 10.1016/j.lfs.2016.03.028

49 Daughaday WH, Trivedi B (1987). Absence of serum growth hormone binding protein in patients with growth hormone receptor deficiency (Laron dwarfism). Proc Natl Acad Sci U S A. **84**(13): 4636–40. doi: 10.1073/pnas.84.13.4636

50 De Souza I, Morgan L, Lewis UL, Raggatt PR, Salih H, Hobbs JR (1974). Growth-hormone dependence among human breast cancers. Lancet. **2**(7874): 182–4. doi: 10.1016/s0140-6736(74)91482-2.

51 Delgado-López PD, Corrales-García EM (2016). Survival in glioblastoma: a review on the impact of treatment modalities. Clin Transl Oncol. **18**(11): 1062–1071. doi: 10.1007/s12094-016-1497-x.

52 Di Bella G (2005). Il Metodo Di Bella. II edizione. Mattioli editore. [(Di Bella's method. II edition) (In Italian)]. Mattioli publisher.

53 Di Bella G (2010). The Di Bella Method (DBM). Neuro Endocrinol Lett. **31 Suppl 1**: 1–42. PMID: 20881933.

54 Di Bella G (2019). La Scelta Antitumore. Prevenzione, terapia farmacologica e stile di vita. Uno editori, Macro. [(The Anti-Tumor Choice. Prevention, drug therapy and lifestyle) (In Italian)].

55 Di Bella G, Colori B, Scanferlato R (2018). The over-expression of GH/GHR in tumour tissues with respect to healthy ones confirms its oncogenic role and the consequent oncosuppressor role of its physiological inhibitor, somatostatin: a review of the literature. Neuro Endocrinol Lett. **39**(3): 179–188.

56 Di Bella G, Gualano L, Di Bella L (2017). Melatonin with adenosine solubilized in water and stabilized with glycine for oncological treatment - technical preparation, effectivity and clinical findings. Neuro Endocrinol Lett. **38**(7): 465–474. PMID: 29369596.

57 Di Bella G, Mascia F, Gualano L, Di Bella L (2013a). Melatonin anticancer effects: review. Int J Mol Sci. **14**(2): 2410–30. doi: 10.3390/ijms14022410.

58 Di Bella G, Mascia F, Ricchi A, Colori B (2013b). Evaluation of the safety and efficacy of the first-line treatment with somatostatin combined with melatonin, retinoids, vitamin D3, and low doses of cyclophosphamide in 20 cases of breast cancer: a preliminary report. Neuro Endocrinol Lett. **34**(7): 660–8. PMID: 24464005

59 Di Bella L (1997). Melatonina dalla ricerca agli interventi – Atti del convegno– Reggio Calabria.

60 Di Bella L, Di Bella G (1998). "Cancro: siamo sulla strada giusta?" Travel factory. [(Cancer: Are we on the right track?) (In Italian)].

61 Di Bella L, Di Bella G (2015). Solution of retinoids in vitamin E in the Di Bella Method biological multitherapy. Neuro Endocrinol Lett. **36**(7): 661–76

62 Di Bella L, Gualano L (2006). Key aspects of melatonin physiology: thirty years of research. Neuro Endocrinol Lett. **27**(4): 425–32. PMID: 16892002.

63 Di Bella L, Gualano L, Rossi MT, Scalera G (1979a). Azione della melatonina sulla piastrinogenesi in vitro. Casa Editrice V. Idelson.

64 Di Bella L, Rossi MT, Scalera G (1979b). Perspectives in pineal functions. Prog Brain Res. **52**: 475–8. doi: 10.1016/s0079-6123(08)62954-4.

65 Di Masi A, Leboffe L, De Marinis E, Pagano F, Cicconi L, Rochette-Egly C et al. (2015). Retinoic acid receptors: from molecular mechanisms to cancer therapy. Mol Aspects Med. **41**: 1–115. doi: 10.1016/j.mam.2014.12.003.

66 Dufner-Beattie J, Lemons RS, Thorburn A (2001). Retinoic acid-induced expression of autotaxin in N-myc-amplified neuroblastoma cells. Mol Carcinog. **30**(4): 181–9. doi: 10.1002/mc.1028.

67 Dyce PW, Tenn N, Kidder GM (2018). Retinoic acid enhances germ cell differentiation of mouse skin-derived stem cells. J Ovarian Res. **11**(1): 19. doi: 10.1186/s13048-018-0390-3.

68 Edelman MJ, Clamon G, Kahn D, Magram M, Lister-James J, Line BR (2009). Targeted radiopharmaceutical therapy for advanced lung cancer: phase I trial of rhenium Re188 P2045, a somatostatin analog. J Thorac Oncol. **4**(12): 1550–4. doi: 10.1097/JTO.0b013e3181bf1070.

69 Elattar TM, Virji AS (1999). Biphasic action of vitamin E on the growth of human oral squamous carcinoma cells. Anticancer Res. **19**(1A): 365–8. PMID: 10226568.

70 Elmaci I, Ozpinar A, Ozpinar A, Perez JL, Altinoz MA (2019). From epidemiology and neurometabolism to treatment: Vitamin D in pathogenesis of glioblastoma Multiforme (GBM) and a proposal for Vitamin D + all-trans retinoic acid + Temozolomide combination in treatment of GBM. Metab Brain Dis. **34**(3): 687–704. doi: 10.1007/s11011-019-00412-5.

71 Ewees MG, Abdelghany TM, Abdel-Aziz AA, Abdel-Bakky MS (2015). All-trans retinoic acid mitigates methotrexate-induced liver injury in rats; relevance of retinoic acid signaling pathway. Naunyn Schmiedebergs Arch Pharmacol. **388**(9): 931–8. doi: 10.1007/s00210-015-1130-5.

72 Faggiano A, Tavares LB, Tauchmanova L, Milone F, Mansueto G, Ramundo V et al. (2008). Effect of treatment with depot somatostatin analogue octreotide on primary hyperparathyroidism (PHP) in multiple endocrine neoplasia type 1 (MEN1) patients. Clin Endocrinol (Oxf). **69**(5): 756–62. doi: 10.1111/j.1365-2265.2008.03301.x

73 Fariss MW, Fortuna MB, Everett CK, Smith JD, Trent DF, Djuric Z (1994). The selective antiproliferative effects of alpha-tocopheryl hemisuccinate and cholesteryl hemisuccinate on murine leukemia cells result from the action of the intact compounds. Cancer Res. **54**(13): 3346–51. PMID: 8012947.

74 Ferreira Cda S, Maganhin CC, Simões Rdos S, Girão MJ, Baracat EC, Soares JM Jr (2010). Melatonina: modulador de morte celular [Melatonin: cell death modulator]. Rev Assoc Med Bras (1992). Nov-Dec; **56**(6): 715–8. Portuguese. doi: 10.1590/s0104-42302010000600024.

75 Ferro M, Giuberti G, Zappavigna S, Perdonà S, Facchini G, Sperlongano P et al. (2012). Chondroitin sulphate enhances the antitumor activity of gemcitabine and mitomycin-C in bladder cancer cells with different mechanisms. Oncol Rep. **27**(2): 409–15. doi: 10.3892/or.2011.1526.

76 Fischer TW, Zmijewski MA, Wortsman J, Slominski A (2008). Melatonin maintains mitochondrial membrane potential and attenuates activation of initiator (casp-9) and effector caspases (casp-3/casp-7) and PARP in UVR-exposed HaCaT keratinocytes. J Pineal Res. **44**(4): 397–407. doi: 10.1111/j.1600-079X.2007.00542.x.

77 Flahaut M, Jauquier N, Chevalier N, Nardou K, Balmas Bourloud K, Joseph JM et al. (2016). Aldehyde dehydrogenase activity plays a Key role in the aggressive phenotype of neuroblastoma. BMC Cancer. **16**(1): 781. doi: 10.1186/s12885-016-2820-1.

78 Florio T (2008). Somatostatin/somatostatin receptor signalling: phosphotyrosine phosphatases. Mol Cell Endocrinol. **286**(1–2): 40–8. doi: 10.1016/j.mce.2007.08.012.

79 Florio T, Thellung S, Arena S, Corsaro A, Bajetto A, Schettini G et al. (2000). Somatostatin receptor 1 (SSTR1)-mediated inhibition of cell proliferation correlates with the activation of the MAP kinase cascade: role of the phosphotyrosine phosphatase SHP-2. J Physiol Paris. **94**(3-4): 239–50. doi: 10.1016/s0928-4257(00)00214-x.

80 Friend KE (2000). Targeting the growth hormone axis as a therapeutic strategy in oncology. Growth Horm IGF Res. **10 Suppl A**: S45–6. doi: 10.1016/s1096-6374(00)90022-4.

81 Fritz H, Flower G, Weeks L, Cooley K, Callachan M, McGowan J et al. (2014). Intravenous Vitamin C and Cancer: A Systematic Review. Integr Cancer Ther. **13**(4): 280–300. doi: 10.1177/1534735414534463.

82 Fthenou E, Zong F, Zafiropoulos A, Dobra K, Hjerpe A, Tzanakakis GN (2009). Chondroitin sulfate A regulates fibrosarcoma cell adhesion, motility and migration through JNK and tyrosine kinase signaling pathways. In Vivo. **23**(1): 69–76. PMID: 19368127.

83 Fujita K, Shinpo K, Yamada K, Sato T, Niimi H, Shamoto M et al. (1982). Reduction of adriamycin toxicity by ascorbate in mice and guinea pigs. Cancer Res. **42**(1): 309–16. PMID: 7053858.

84 Fusco A, Gunz G, Jaquet P, Dufour H, Germanetti AL, Culler MD et al. (2008). Somatostatinergic ligands in dopamine-sensitive and -resistant prolactinomas. Eur J Endocrinol. **158**(5): 595–603. doi: 10.1530/EJE-07-0806.

85 Garcia CG, Kahn SA, Geraldo LHM, Romano I, Domith I, Silva DCLE et al. (2018). Combination Therapy with Sulfasalazine and Valproic Acid Promotes Human Glioblastoma Cell Death Through Imbalance of the Intracellular Oxidative Response. Mol Neurobiol. **55**(8): 6816–6833. doi: 10.1007/s12035-018-0895-1.

86 Gefroh-Grimes HA, Gidal BE (2016). Antiepileptic drugs in patients with malignant brain tumor: beyond seizures and pharmacokinetics. Acta Neurol Scand. **133**(1): 4–16. doi: 10.1111/ane.12437.

87 Gil-Martín E, Egea J, Reiter RJ, Romero A (2019). The emergence of melatonin in oncology: Focus on colorectal cancer. Med Res Rev. **39**(6): 2239–2285. doi: 10.1002/med.21582..

88 Gruszka A, Pawlikowski M, Kunert-Radek J (2001). Anti-tumoral action of octreotide and bromocriptine on the experimental rat prolactinoma: anti-proliferative and pro-apoptotic effects. Neuro Endocrinol Lett. **22**(5): 343–8. PMID: 11600876.

89 Hagemeister AL, Sheridan MA (2008). Somatostatin inhibits hepatic growth hormone receptor and insulin-like growth factor I mRNA expression by activating the ERK and PI3K signaling pathways. Am J Physiol Regul Integr Comp Physiol. **295**(2): R490–7. doi: 10.1152/ajpregu.00099.2008.

90 Hamada K, Yoshihara C, Ito T, Tani K, Tagawa M, Sakuragawa N et al. (2012). Antitumor effect of chondroitin sulfate-coated ternary granulocyte macrophage-colony-stimulating factor plasmid complex for ovarian cancer. J Gene Med. **14**(2): 120–7. doi: 10.1002/jgm.1647.

91 Hassan HT, Rees J (1990). Triple combination of retinoic acid plus actinomycin D plus dimethylformamide induces differentiation of human acute myeloid leukaemic blasts in primary culture. Cancer Chemother Pharmacol. **26**(1): 26–30. doi: 10.1007/BF02940289.

92 Hassaneen W, Cahill DP, Fuller GN, Levine NB (2010). Immunohistochemical detection of somatostatin receptor subtype 5 (SSTR-5) in cushing adenoma. J Neurooncol. **98**(1): 151–2. doi: 10.1007/s11060-009-0048-5.

93 He Y, Yuan XM, Lei P, Wu S, Xing W, Lan XL, et al. (2009). The antiproliferative effects of somatostatin receptor subtype 2 in breast cancer cells. Acta Pharmacol Sin. **30**(7): 1053–9. doi: 10.1038/aps.2009.59.9.

94 Head KA (1998). Ascorbic acid in the prevention and treatment of cancer. Altern Med Rev. Jun; **3**(3): 174–86.

95 Heisler T, Towfigh S, Simon N, Liu C, McFadden DW (2000). Peptide YY augments gross inhibition by vitamin E succinate of human pancreatic cancer cell growth. J Surg Res. Jan; **88**(1): 23–5. doi: 10.1006/jsre.1999.5775.

96 Heldin CH, Westermark B (1991). Platelet-derived growth factor and autocrine mechanisms of oncogenic processes. Crit Rev Oncog. **2**(2): 109–24.

97 Herreros-Villanueva M, Er TK, Bujanda L (2015). Retinoic Acid Reduces Stem Cell-Like Features in Pancreatic Cancer Cells. Pancreas. Aug; **44**(6): 918–24. doi: 10.1097/MPA.0000000000000373.

98 Hong Y, Park EY, Kim D, Lee H, Jung HS, Jun HS (2020). Glucosamine potentiates the differentiation of adipose-derived stem cells into glucose-responsive insulin-producing cells. Ann Transl Med. Apr; **8**(8): 561. doi: 10.21037/atm.2020.03.103.

99 Hosea R, Hardiany NS, Ohneda O, Wanandi SI (2018). Glucosamine decreases the stemness of human ALDH+ breast cancer stem cells by inactivating STAT3. Oncol Lett. Oct; **16**(4): 4737–4744. doi: 10.3892/ol.2018.9222.

100 Hubalewska-Dydejczyk A, Trofimiuk M, Sowa-Staszczak A, Gilis-Januszewska A, Wierzchowski W, Pach D, Budzyński A et al. (2008). Ekspresja receptorów somatostatynowych (SSTR1-sSTR5) w guzach chromochłonnych [Somatostatin receptors expression (SSTR1-SSTR5) in pheochromocytomas]. Przegl Lek. **65**(9): 405–7. Polish. PMID: 19140390.

101 Hwang MS, Baek WK (2010). Glucosamine induces autophagic cell death through the stimulation of ER stress in human glioma cancer cells. Biochem Biophys Res Commun. Aug 13; **399**(1): 111–6. doi: 10.1016/j.bbrc.2010.07.050.

102 Inokuchi H, Hirokane H, Tsuzuki T, Nakagawa K, Igarashi M, Miyazawa T (2003). Anti-angiogenic activity of tocotrienol. Biosci Biotechnol Biochem. Jul; **67**(7): 1623–7. doi: 10.1271/bbb.67.1623.

103 Ioannou M, Papagelopoulos PJ, Papanastassiou I, Iakovidou I, Kottakis S, Demertzis N (2008). Detection of somatostatin receptors in human osteosarcoma. World J Surg Oncol. Sep 10; **6**: 99. doi: 10.1186/1477-7819-6-99.

104 Ishiguro Y, Kobayashi M, Ideno M, Narumi K, Furugen A, Iseki K (2018). Valproate sensitizes human glioblastoma cells to 3-bromopyruvate-induced cytotoxicity. Int J Pharm. Nov 15; **551**(1–2): 97–102. doi: 10.1016/j.ijpharm.2018.08.039.

105 Israel K, Yu W, Sanders BG, Kline K (2000). Vitamin E succinate induces apoptosis in human prostate cancer cells: role for Fas in vitamin E succinate-triggered apoptosis. Nutr Cancer. **36**(1): 90–100.

106 Israel L (1996). Tumour progression: random mutations or an integrated survival response to cellular stress conserved from unicellular organisms? J Theor Biol. Feb 21;178(4):375-80. doi: 10.1006/jtbi.1996.0033.

107 Jaeckle KA, Hess KR, Yung WK, Greenberg H, Fine H, Schiff D et al. (2003); North American Brain Tumor Consortium. Phase II evaluation of temozolomide and 13-cis-retinoic acid for the treatment of recurrent and progressive malignant glioma: a North American Brain Tumor Consortium study. J Clin Oncol. Jun 15; **21**(12): 2305–11. doi: 10.1200/JCO.2003.12.097.

108 Jeon SM, Shin EA (2018). Exploring vitamin D metabolism and function in cancer. Exp Mol Med. Apr 16; **50**(4): 1–14. doi: 10.1038/s12276-018-0038-9.

109 Kanungo J (2017). Retinoic Acid Signaling in P19 Stem Cell Differentiation. Anticancer Agents Med Chem. **17**(9): 1184–1198. doi: 10.2174/1871520616666160615065000.

110 Kasten BB, Oliver PG, Kim H, Fan J, Ferrone S, Zinn KR et al. (2018). 212Pb-Labeled Antibody 225.28 Targeted to Chondroitin Sulfate Proteoglycan 4 for Triple-Negative Breast Cancer Therapy in Mouse Models. Int J Mol Sci. Mar 21; **19**(4): 925. doi: 10.3390/ijms19040925.

111 Kath R, Höffken K (2000). The significance of somatostatin analogues in the antiproliferative treatment of carcinomas. Recent Results Cancer Res. **153**: 23–43. doi: 10.1007/978-3-642-59587-5_3.

112 Kelly PA, Ali S, Rozakis M, Goujon L, Nagano M, Pellegrini I et al. (1993). The growth hormone/prolactin receptor family. Recent Prog Horm Res. **48**: 123–64. doi: 10.1016/b978-0-12-571148-7.50009-9.

113 Kerkhof M, Dielemans JC, van Breemen MS, Zwinkels H, Walchenbach R, Taphoorn MJ et al. (2013). Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme. Neuro Oncol. Jul; **15**(7): 961–7. doi: 10.1093/neuonc/not057.

114 Khanna G, Bushnell D, O'Dorisio MS (2008). Utility of radiolabeled somatostatin receptor analogues for staging/restaging and treatment of somatostatin receptor-positive pediatric tumors. Oncologist. Apr; **13**(4): 382–9. doi: 10.1634/theoncologist.2007-0175.

115 Kiaris H, Schally AV, Kalofoutis A (2005). Extrapituitary effects of the growth hormone-releasing hormone. Vitam Horm. **70**: 1–24. doi: 10.1016/S0083-6729(05)70001-7.

116 Kim D, Choi BH, Ryoo IG, Kwak MK (2018). High NRF2 level mediates cancer stem cell-like properties of aldehyde dehydrogenase (ALDH)-high ovarian cancer cells: inhibitory role of all-trans retinoic acid in ALDH/NRF2 signaling. Cell Death Dis. Aug 30; **9**(9): 896. doi: 10.1038/s41419-018-0903-4.
117 Kim KJ, Choi JS, Kang I, Kim KW, Jeong CH, Jeong JW (2013). Melatonin suppresses tumor progression by reducing angiogenesis stimulated by HIF-1 in a mouse tumor model. J Pineal Res. Apr; **54**(3): 264–70. doi: 10.1111/j.1600-079X.2012.01030.x.
118 Kim SH, Cho SS, Simkhada JR, Lee HJ, Kim SW, Kim TS et al. (2009). Enhancement of 1,25-dihydroxyvitamin D3- and all-trans retinoic acid-induced HL-60 leukemia cell differentiation by Panax ginseng. Biosci Biotechnol Biochem. May; **73**(5): 1048–53. doi: 10.1271/bbb.80823.
119 Kini AR, Peterson LA, Tallman MS, Lingen MW (2001). Angiogenesis in acute promyelocytic leukemia: induction by vascular endothelial growth factor and inhibition by all-trans retinoic acid. Blood. Jun 15; **97**(12): 3919–24. doi: 10.1182/blood.v97.12.3919.
120 Klimant E, Wright H, Rubin D, Seely D, Markman M (2018). Intravenous vitamin C in the supportive care of cancer patients: a review and rational approach. Curr Oncol. Apr; **25**(2): 139–148. doi: 10.3747/co.25.3790.
121 Kogner P, Borgström P, Bjellerup P, Schilling FH, Refai E, Jonsson C et al. (1997). Somatostatin in neuroblastoma and ganglioneuroma. Eur J Cancer. Oct; **33**(12): 2084–9. doi: 10.1016/s0959-8049(97)00212-8.
122 Kovács M, Schally AV, Hohla F, Rick FG, Pozsgai E, Szalontay L, et al. (2010) A correlation of endocrine and anticancer effects of some antagonists of GHRH. Peptides. Oct; **31**(10): 1839-46. doi: 10.1016/j.peptides.2010.07.006.
123 Krauze AV, Mackey M, Rowe L, Chang MG, Holdford DJ, Cooley T et al. (2018). Late toxicity in long-term survivors from a phase 2 study of concurrent radiation therapy, temozolomide and valproic acid for newly diagnosed glioblastoma. Neurooncol Pract. Nov; **5**(4): 246–250. doi: 10.1093/nop/npy009.
124 Kusano K, Rao VS, Cawkwell L, Drew PJ (2014). Radioresistance in carcinoma of the breast. Breast. Dec; **13**(6): 452–60. doi: 10.1016/j.breast.2004.08.004.
125 Kusano K, Tsutsumi Y, Dean J, Gavin M, Ma H, Silver M, et al. (2007). Long-term stable expression of human growth hormone by rAAV promotes myocardial protection post-myocardial infarction. J Mol Cell Cardiol. Feb; **42**(2): 390–9. doi: 10.1016/j.yjmcc.2006.10.016.
126 Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP et al. (2008). Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol. May 1; **26**(13): 2124–30. doi: 10.1200/JCO.2007.15.2553.
127 Laban C, Bustin SA, Jenkins PJ (2003). The GH-IGF-I axis and breast cancer. Trends Endocrinol Metab. Jan; **14**(1): 28–34. doi: 10.1016/s1043-2760(02)00003-6.
128 Lachowicz-Ochedalska A, Rebas E, Kunert-Radek J, Winczyk K, Pawlikowski M (2000). Effects of somatostatin and its analogues on tyrosine kinase activity in rodent tumors. Biol Signals Recept. Sep-Oct; **9**(5): 255–9. doi: 10.1159/000014647.
129 Laklai H, Laval S, Dumartin L, Rochaix P, Hagedorn M, Bikfalvi A et al. (2009). Thrombospondin-1 is a critical effector of oncosuppressive activity of sst2 somatostatin receptor on pancreatic cancer. Proc Natl Acad Sci U S A. Oct 20; **106**(42): 17769–74. doi: 10.1073/pnas.0908674106.
130 Lakomy R, Kazda T, Selingerova I, et al. Real-World Evidence in Glioblastoma: Stupp's Regimen After a Decade. Front Oncol. 2020; **10**: 840. Published 2020 Jul 3. doi:10.3389/fonc.2020.00840
131 Lambert G, Estévez-Salmeron L, Oh S, Liao D, Emerson BM, Tlsty TD et al. (2011). An analogy between the evolution of drug resistance in bacterial communities and malignant tissues. Nat Rev Cancer. May; **11**(5): 375–82. doi: 10.1038/nrc3039.
132 Le Roith D, Bondy C, Yakar S, Liu JL, Butler A (2001). The somatomedin hypothesis: 2001. Endocr Rev. Feb; **22**(1): 53–74. doi: 10.1210/edrv.22.1.0419.
133 Lee KW, Lee HJ, Kang KS, Lee CY (2002). Preventive effects of vitamin C on carcinogenesis. Lancet. Jan 12; **359**(9301): 172. doi: 10.1016/S0140-6736(02)07358-0.
134 Lee LT, Schally AV, Liebow C, Lee PP, Lee PH, Lee MT (2008). Dephosphorylation of cancer protein by tyrosine phosphatases in response to analogs of luteinizing hormone-releasing hormone and somatostatin. Anticancer Res. Sep-Oct; **28**(5A): 2599–605. PMID: 19035284.
135 Li M, Wang X, Li W, Li F, Yang H, Wang H et al. (2008). Somatostatin receptor-1 induces cell cycle arrest and inhibits tumor growth in pancreatic cancer. Cancer Sci. Nov; **99**(11): 2218–23. doi: 10.1111/j.1349-7006.2008.00940.x.
136 Lincoln DT, el-Hifnawi E, Sinowatz F, Waters MJ (1994). Immunohistochemical localization of growth hormone receptor binding protein in the mammalian cerebellum. Ann Anat. Oct; **176**(5): 419–27. doi: 10.1016/s0940-9602(11)80468-1.
137 Lincoln DT, Sinowatz F, Temmim-Baker L, Baker HI, Kölle S, Waters MJ (1998). Growth hormone receptor expression in the nucleus and cytoplasm of normal and neoplastic cells. Histochem Cell Biol. Feb; **109**(2): 141–59. doi: 10.1007/s004180050212.
138 Lissoni P, Meregalli S, Nosetto L, Barni S, Tancini G, Fossati V et al. (1996). Increased survival time in brain glioblastomas by a radioneuroendocrine strategy with radiotherapy plus melatonin compared to radiotherapy alone. Oncology. Jan-Feb; **53**(1): 43–6. doi: 10.1159/000227533.
139 Lissoni P, Rovelli F, Malugani F, Bucovec R, Conti A, Maestroni GJ (2001). Anti-angiogenic activity of melatonin in advanced cancer patients. Neuro Endocrinol Lett. **22**(1): 45–7.
140 Luboldt W, Zöphel K, Wunderlich G, Abramyuk A, Luboldt HJ, Kotzerke J (2010). Visualization of somatostatin receptors in prostate cancer and its bone metastases with Ga-68-DOTATOC PET/CT. Mol Imaging Biol. Jan-Feb; **12**(1): 78–84. doi: 10.1007/s11307-009-0230-3.
141 Majewski S, Szmurlo A, Marczak M, Jablonska S, Bollag W (1994). Synergistic effect of retinoids and interferon alpha on tumor-induced angiogenesis: anti-angiogenic effect on HPV-harboring tumor-cell lines. Int J Cancer. Apr 1; **57**(1): 81–5. doi: 10.1002/ijc.2910570115.
142 Malafa MP, Fokum FD, Smith L, Louis A (2002). Inhibition of angiogenesis and promotion of melanoma dormancy by vitamin E succinate. Ann Surg Oncol. Dec; **9**(10): 1023–32. doi: 10.1007/BF02574523.
143 Malafa MP, Neitzel LT (2000). Vitamin E succinate promotes breast cancer tumor dormancy. J Surg Res. Sep; **93**(1): 163–70. doi: 10.1006/jsre.2000.5948.
144 Mansoor KA, Qadan F, Schmidt M, Qinna NA, Badr M, Matalka KZ. A functional food mixture "Protector" reinforces the protective immune parameters against viral flu infection in mice. Nutrients 2018; **10**: 743, E743. PMID: 29890620.
145 Mantell DJ, Owens PE, Bundred NJ, Mawer EB, Canfield AE (2000). 1 alpha,25-dihydroxyvitamin D(3) inhibits angiogenesis in vitro and in vivo. Circ Res. Aug 4; **87**(3): 214–20. doi: 10.1161/01.res.87.3.214.
146 Marcato P, Dean CA, Giacomantonio CA, Lee PW (2011). Aldehyde dehydrogenase: its role as a cancer stem cell marker comes down to the specific isoform. Cell Cycle. May 1; **10**(9): 1378–84. doi: 10.4161/cc.10.9.15486.
147 Marcato P, Dean CA, Pan D, Araslanova R, Gillis M, Joshi M et al. (2011). Aldehyde dehydrogenase activity of breast cancer stem cells is primarily due to isoform ALDH1A3 and its expression is predictive of metastasis. Stem Cells. Jan; **29**(1): 32–45. doi: 10.1002/stem.563.
148 Marcinkowska E (2001). Evidence that activation of MEK1,2/erk1,2 signal transduction pathway is necessary for calcitriol-induced differentiation of HL-60 cells. Anticancer Res. Jan-Feb; **21**(1A): 499–504. PMID: 11299787.
149 Matt P, Schoenhoff F, Habashi J, Holm T, Van Erp C, Loch D et al. (2009); GenTAC Consortium. Circulating transforming growth factor-beta in Marfan syndrome. Circulation. Aug 11; **120**(6): 526–32. doi: 10.1161/CIRCULATIONAHA.108.841981.

150 Mazor G, Levin L, Picard D, Ahmadov U, Carén H, Borkhardt A et al. (2019). The lncRNA TP73-AS1 is linked to aggressiveness in glioblastoma and promotes temozolomide resistance in glioblastoma cancer stem cells. Cell Death Dis. **10**(3): 246. doi: 10.1038/s41419-019-1477-5.
151 McDonald PC, Chafe SC, Brown WS, Saberi S, Swayampakula M, Venkateswaran G et al. (2019). Regulation of pH by Carbonic Anhydrase 9 Mediates Survival of Pancreatic Cancer Cells With Activated KRAS in Response to Hypoxia. Gastroenterology. Sep; **157**(3): 823–837. doi: 10.1053/j.gastro.2019.05.004.
152 Mishra S, Kelly KK, Rumian NL, Siegenthaler JA (2018). Retinoic Acid Is Required for Neural Stem and Progenitor Cell Proliferation in the Adult Hippocampus. Stem Cell Reports. Jun 5; **10**(6): 1705–1720. doi: 10.1016/j.stemcr.2018.04.024.
153 Moertel CL, Reubi JC, Scheithauer BS, Schaid DJ, Kvols LK (1994). Expression of somatostatin receptors in childhood neuroblastoma. Am J Clin Pathol. Dec; **102**(6): 752–6. doi: 10.1093/ajcp/102.6.752.
154 Moradkhani F, Moloudizargari M, Fallah M, Asghari N, Heidari Khoei H, Asghari MH (2020). Immunoregulatory role of melatonin in cancer. J Cell Physiol. Feb; **235**(2): 745–757. doi: 10.1002/jcp.29036.
155 Moreb JS (2008). Aldehyde dehydrogenase as a marker for stem cells. Curr Stem Cell Res Ther. Dec; **3**(4): 237–46. doi: 10.2174/157488808786734006.
156 Mukhina S, Mertani HC, Guo K, Lee KO, Gluckman PD, Lobie PE (2004). Phenotypic conversion of human mammary carcinoma cells by autocrine human growth hormone. Proc Natl Acad Sci U S A. Oct 19; **101**(42): 15166–71. doi: 10.1073/pnas.0405881101.
157 Murphy LJ, Bell GI, Friesen HG (1987). Growth hormone stimulates sequential induction of c-myc and insulin-like growth factor I expression in vivo. Endocrinology. May; **120**(5): 1806–12. doi: 10.1210/endo-120-5-1806.
158 Murray RD, Kim K, Ren SG, Chelly M, Umehara Y, Melmed S (2004). Central and peripheral actions of somatostatin on the growth hormone-IGF-I axis. J Clin Invest. Aug; **114**(3): 349–56. doi: 10.1172/JCI19933.
159 Negri M, Gentile A, de Angelis C, Montò T, Patalano R, Colao A et al. (2020). Vitamin D-Induced Molecular Mechanisms to Potentiate Cancer Therapy and to Reverse Drug-Resistance in Cancer Cells. Nutrients. Jun 17; **12**(6): 1798. doi: 10.3390/nu12061798.
160 Neuzil J, Kågedal K, Andera L, Weber C, Brunk UT (2002). Vitamin E analogs: a new class of multiple action agents with anti-neoplastic and anti-atherogenic activity. Apoptosis. Apr; **7**(2): 179–87. doi: 10.1023/a:1014378901843.
161 Neuzil J, Weber T, Schröder A, Lu M, Ostermann G, Gellert N et al. (2001). Induction of cancer cell apoptosis by alpha-tocopheryl succinate: molecular pathways and structural requirements. FASEB J. Feb; **15**(2): 403–15. doi: 10.1096/fj.00-0251com.
162 Ngo B, Van Riper JM, Cantley LC, Yun J (2019). Targeting cancer vulnerabilities with high-dose vitamin C. Nat Rev Cancer. May; **19**(5): 271–282. doi: 10.1038/s41568-019-0135-7.
163 Ni X, Hu G, Cai X (2019). The success and the challenge of all-trans retinoic acid in the treatment of cancer. Crit Rev Food Sci Nutr. **59**(sup1): S71–S80. doi: 10.1080/10408398.2018.1509201.
164 Nikhil K, Viccaro K, Shah K (2019). Multifaceted Regulation of ALDH1A1 by Cdk5 in Alzheimer's Disease Pathogenesis. Mol Neurobiol. Feb; **56**(2): 1366–1390. doi: 10.1007/s12035-018-1114-9.
165 Nooshinfar E, Safaroghli-Azar A, Bashash D, Akbari ME (2017). Melatonin, an inhibitory agent in breast cancer. Breast Cancer. Jan; **24**(1): 42–51. doi: 10.1007/s12282-016-0690-7.
166 Norlin M (2020). Effects of vitamin D in the nervous system: Special focus on interaction with steroid hormone signalling and a possible role in the treatment of brain cancer. J Neuroendocrinol. Jan; **32**(1): e12799. doi: 10.1111/jne.12799.
167 Ohno S, Ohno Y, Suzuki N, Soma G, Inoue M (2009). High-dose vitamin C (ascorbic acid) therapy in the treatment of patients with advanced cancer. Anticancer Res. Mar; **29**(3): 809–15. PMID: 19414313.
168 Orlando C, Raggi CC, Bagnoni L, Sestini R, Briganti V, La Cava G et al. (2001). Somatostatin receptor type 2 gene expression in neuroblastoma, measured by competitive RT-PCR, is related to patient survival and to somatostatin receptor imaging by indium -111-pentetreotide. Med Pediatr Oncol. Jan; **36**(1): 224–6. doi: 10.1002/1096-911X(20010101)36:1<224::AID-MPO1054>3.0.CO;2-#.
169 Padh H (1991). Vitamin C: newer insights into its biochemical functions. Nutr Rev. Mar; **49**(3): 65–70. doi: 10.1111/j.1753-4887.1991.tb07407.x..
170 Pan H, Wang H, Jia Y, Wang Q, Li L, Wu Q et al. (2017). VPA and MEL induce apoptosis by inhibiting the Nrf2-ARE signaling pathway in TMZ-resistant U251 cells. Mol Med Rep. Jul; **16**(1): 908–914. doi: 10.3892/mmr.2017.6621.
171 Pastorekova S, Zatovicova M, Pastorek J (2008). Cancer-associated carbonic anhydrases and their inhibition. Curr Pharm Des. **14**(7): 685–98. doi: 10.2174/138161208783877893.
172 Pawlikowski M, Kunert-Radek J, Winczyk K, Melen-Mucha G, Gruszka A, Karasek M (1999). The antiproliferative effects of melatonin on experimental pituitary and colonic tumors. Possible involvement of the putative nuclear binding site? Adv Exp Med Biol. **460**: 369–72. doi: 10.1007/0-306-46814-x_41.
173 Pawlowska E, Szczepanska J, Blasiak J (2019). Pro- and Antioxidant Effects of Vitamin C in Cancer in correspondence to Its Dietary and Pharmacological Concentrations. Oxid Med Cell Longev. Dec 24; **2019**: 7286737. doi: 10.1155/2019/7286737.
174 Perry JK, Emerald BS, Mertani HC, Lobie PE (2006). The oncogenic potential of growth hormone. Growth Horm IGF Res. Oct-Dec; **16**(5–6): 277–89. doi: 10.1016/j.ghir.2006.09.006.
175 Perry JK, Mohankumar KM, Emerald BS, Mertani HC, Lobie PE (2008). The contribution of growth hormone to mammary neoplasia. J Mammary Gland Biol Neoplasia. Mar; **13**(1): 131–45. doi: 10.1007/s10911-008-9070-z.
176 Peterkofsky B (1991). Ascorbate requirement for hydroxylation and secretion of procollagen: relationship to inhibition of collagen synthesis in scurvy. Am J Clin Nutr. Dec; **54**(6 Suppl): 1135S–1140S. doi: 10.1093/ajcn/54.6.1135s.
177 Piedrafita FJ, Pfahl M (1997). Retinoid-induced apoptosis and Sp1 cleavage occur independently of transcription and require caspase activation. Mol Cell Biol. Nov; **17**(11): 6348–58. doi: 10.1128/MCB.17.11.6348.
178 Pinnel SR, Murad S, Darr D (1987). Induction of collagen synthesis by ascorbic acid. A possible mechanism. Arch Dermatol. Dec; **123**(12): 1684–6. doi: 10.1001/archderm.123.12.1684.
179 Pisarek H, Pawlikowski M, Kunert-Radek J, Radek M (2009). Expression of somatostatin receptor subtypes in human pituitary adenomas -- immunohistochemical studies. Endokrynol Pol. Jul-Aug; **60**(4): 240–51. PMID: 19753537.
180 Pollak M (1997). The potential role of somatostatin analogues in breast cancer treatment. Yale J Biol Med. Sep-Dec; **70**(5–6): 535–9. PMID: 9825480; PMCID: PMC2589265.
181 Prasad KN, Cohrs RJ, Sharma OK (1990). Decreased expressions of c-myc and H-ras oncogenes in vitamin E succinate induced morphologically differentiated murine B-16 melanoma cells in culture. Biochem Cell Biol. Nov; **68**(11): 1250–5. doi: 10.1139/o90-185.
182 Prasad KN, Hernandez C, Edwards-Prasad J, Nelson J, Borus T, Robinson WA (1994). Modification of the effect of tamoxifen, cis-platin, DTIC, and interferon-alpha 2b on human melanoma cells in culture by a mixture of vitamins. Nutr Cancer. **22**(3): 233–45. doi: 10.1080/01635589409514349.
183 Prasad KN, Kumar B, Yan XD, Hanson AJ, Cole WC (2003). Alpha-tocopheryl succinate, the most effective form of vitamin E for adjuvant cancer treatment: a review. J Am Coll Nutr. Apr; **22**(2): 108–17. doi: 10.1080/07315724.2003.10719283.
184 Prasad KN, Kumar R (1996). Effect of individual and multiple antioxidant vitamins on growth and morphology of human nontumorigenic and tumorigenic parotid acinar cells in culture. Nutr Cancer. **26**(1): 11–9. doi: 10.1080/01635589609514458.

185 Pussinen PJ, Lindner H, Glatter O, Reicher H, Kostner GM, Wintersperger A et al. (2000). Lipoprotein-associated alpha-tocopheryl-succinate inhibits cell growth and induces apoptosis in human MCF-7 and HBL-100 breast cancer cells. Biochim Biophys Acta. May 31; **1485**(2–3): 129–44. doi: 10.1016/s1388-1981(00)00035-4.

186 Radman M (1975). SOS repair hypothesis: phenomenology of an inducible DNA repair which is accompanied by mutagenesis. Basic Life Sci. **5A**: 355–67. doi: 10.1007/978-1-4684-2895-7_48.

187 Raja E, Komuro A, Tanabe R, Sakai S, Ino Y, Saito N et al. (2017). Bone morphogenetic protein signaling mediated by ALK-2 and DLX2 regulates apoptosis in glioma-initiating cells. Oncogene. Aug 31; **36**(35): 4963–4974. doi: 10.1038/onc.2017.112.

188 Reiter RJ, Korkmaz A (2008). Clinical aspects of melatonin. Saudi Med J. Nov; **29**(11): 1537–47. PMID: 18997997.

189 Rhinn M, Dollé P (2012). Retinoic acid signalling during development. Development. Mar; **139**(5): 843–58. doi: 10.1242/dev.065938.

190 Ripoll EA, Rama BN, Webber MM (1986). Vitamin E enhances the chemotherapeutic effects of adriamycin on human prostatic carcinoma cells in vitro. J Urol. Aug; **136**(2): 529–31. doi: 10.1016/s0022-5347(17)44937-8.

191 Riva G, Baronchelli S, Paoletta L, Butta V, Biunno I, Lavitrano M et al. (2014). In vitro anticancer drug test: A new method emerges from the model of glioma stem cells. Toxicol Rep. May 22; **1**: 188–199. doi: 10.1016/j.toxrep.2014.05.005. PMID: 28962238; PMCID: PMC5598297.

192 Rochette-Egly C (2015). Retinoic acid signaling and mouse embryonic stem cell differentiation: Cross talk between genomic and non-genomic effects of RA. Biochim Biophys Acta. Jan; **1851**(1): 66–75. doi: 10.1016/j.bbalip.2014.04.003.

193 Rose AT, McFadden DW (2001). Alpha-tocopherol succinate inhibits growth of gastric cancer cells in vitro. J Surg Res. Jan; **95**(1): 19–22. doi: 10.1006/jsre.2000.6022.

194 Rudà R, Pellerino A, Soffietti R (2016). Does valproic acid affect tumor growth and improve survival in glioblastomas? CNS Oncol. **5**(2): 51–3. doi: 10.2217/cns-2016-0004.

195 Ruscica M, Arvigo M, Gatto F, Dozio E, Feltrin D, Culler MD et al. (2010). Regulation of prostate cancer cell proliferation by somatostatin receptor activation. Mol Cell Endocrinol. Feb 5; **315**(1–2): 254–62. doi: 10.1016/j.mce.2009.11.006.

196 Russo M, Crisafulli G, Sogari A, Reilly NM, Arena S, Lamba S et al. (2019). Adaptive mutability of colorectal cancers in response to targeted therapies. Science. Dec 20; **366**(6472): 1473–1480. doi: 10.1126/science.aav4474.

197 Safa AR, Saadatzadeh MR, Cohen-Gadol AA, Pollok KE, Bijangi-Vishehsaraei K (2016). Emerging targets for glioblastoma stem cell therapy. J Biomed Res. Jan; **30**(1): 19–31. doi: 10.7555/JBR.30.20150100.

198 Said HM, Hagemann C, Carta F, Katzer A, Polat B, Staab A et A. (2013). Hypoxia induced CA9 inhibitory targeting by two different sulfonamide derivatives including acetazolamide in human glioblastoma. Bioorg Med Chem. **21**(13): 3949–57. doi: 10.1016/j.bmc.2013.03.068.

199 Said HM, Supuran CT, Hageman C, Staab A, Polat B, Katzer A et al. (2010). Modulation of carbonic anhydrase 9 (CA9) in human brain cancer. Curr Pharm Des. **16**(29): 3288–99. doi: 10.2174/138161210793429788.

200 Sall JW, Klisovic DD, O'Dorisio MS, Katz SE (2004). Somatostatin inhibits IGF-1 mediated induction of VEGF in human retinal pigment epithelial cells. Exp Eye Res. Oct; **79**(4): 465–76. doi: 10.1016/j.exer.2004.06.007.

201 Sánchez-Barceló EJ, Cos S, Mediavilla D, Martínez-Campa C, González A, Alonso-González C (2005). Melatonin-estrogen interactions in breast cancer. J Pineal Res. May; **38**(4): 217–22. doi: 10.1111/j.1600-079X.2004.00207.x.

202 Sarna S, Kumar A, Bhola RK (2000). alpha-Tocopherol enhances tumour growth inhibition by cis-dichlorodiammine platinum (II). Braz J Med Biol Res. Aug; **33**(8): 929–36. doi: 10.1590/s0100-879x2000000800009.

203 Sauberlich HE (1994). Pharmacology of vitamin C. Annu Rev Nutr. **14**: 371–91. doi: 10.1146/annurev.nu.14.070194.002103.

204 Schäfer A, Teufel J, Ringel F, Bettstetter M, Hoepner I, Rasper M et al. (2012). Aldehyde dehydrogenase 1A1--a new mediator of resistance to temozolomide in glioblastoma. Neuro Oncol. Dec; **14**(12): 1452–64. doi: 10.1093/neuonc/nos270.

205 Seigel GM, Campbell LM, Narayan M, Gonzalez-Fernandez F (2005). Cancer stem cell characteristics in retinoblastoma. Mol Vis. Sep 12; **11**: 729–37. PMID: 16179903.

206 Sestini R, Orlando C, Peri A, Tricarico C, Pazzagli M, Serio M et al. (1996). Quantitation of somatostatin receptor type 2 gene expression in neuroblastoma cell lines and primary tumors using competitive reverse transcription-polymerase chain reaction. Clin Cancer Res. Oct; **2**(10): 1757–65. PMID: 9816127.

207 Sharow KA, Temkin B, Asson-Batres MA (2012). Retinoic acid stability in stem cell cultures. Int J Dev Biol. **56**(4): 273–8. doi: 10.1387/ijdb.113378ks.

208 Shi L, Li H, Zhan Y (2017). All-trans retinoic acid enhances temozolomide-induced autophagy in human glioma cells U251 via targeting Keap1/Nrf2/ARE signaling pathway. Oncol Lett. Sep; **14**(3): 2709–2714. doi: 10.3892/ol.2017.6482.

209 Shi X, Yang X, Liu M, Wang R, Qiu N, Liu Y et al. (2021). Chondroitin sulfate-based nanoparticles for enhanced chemo-photodynamic therapy overcoming multidrug resistance and lung metastasis of breast cancer. Carbohydr Polym. Feb 15; **254**: 117459. doi: 10.1016/j.carbpol.2020.117459.

210 Shimpo K, Nagatsu T, Yamada K, Sato T, Niimi H, Shamoto M et al. (1991). Ascorbic acid and adriamycin toxicity. Am J Clin Nutr. Dec; **54**(6 Suppl): 1298S–1301S. doi: 10.1093/ajcn/54.6.1298s.

211 Shklar G, Schwartz JL (1996). Vitamin E inhibits experimental carcinogenesis and tumour angiogenesis. Eur J Cancer B Oral Oncol. Mar; **32B**(2): 114–9. doi: 10.1016/0964-1955(95)00077-1.

212 Skwarlo-Sonta K (2002). Melatonin in immunity: comparative aspects. Neuro Endocrinol Lett. Apr; **23 Suppl 1**: 61–6. PMID: 12019354.

213 Sommers CL, Byers SW, Thompson EW, Torri JA, Gelmann EP (1994). Differentiation state and invasiveness of human breast cancer cell lines. Breast Cancer Res Treat. **31**(2–3): 325–35. doi: 10.1007/BF00666165.

214 Song S, Xu XC (2001). Effect of benzo[a]pyrene diol epoxide on expression of retinoic acid receptor-beta in immortalized esophageal epithelial cells and esophageal cancer cells. Biochem Biophys Res Commun. Mar 9; **281**(4): 872–7. doi: 10.1006/bbrc.2001.4433.

215 Songthaveesin C, Sa-Nongdej W, Limboonreung T, Chongthammakun S (2018). Combination of metformin and 9-cis retinoic acid increases apoptosis in C6 glioma stem-like cells. Heliyon. May 31; **4**(5): e00638. doi: 10.1016/j.heliyon.2018.e00638

216 Steták A, Lankenau A, Vántus T, Csermely P, Ullrich A, Kéri G (2001). The antitumor somatostatin analogue TT-232 induces cell cycle arrest through PKCdelta and c-Src. Biochem Biophys Res Commun. Jul 13; **285**(2): 483–8. doi: 10.1006/bbrc.2001.5199.

217 Sung V, Feldman D (2000). 1,25-Dihydroxyvitamin D3 decreases human prostate cancer cell adhesion and migration. Mol Cell Endocrinol. Jun; **164**(1–2): 133–43. doi: 10.1016/s0303-7207(00)00226-4.

218 Supuran CT, Winum JY (2015). Carbonic anhydrase IX inhibitors in cancer therapy: an update. Future Med Chem. **7**(11): 1407–14. doi: 10.4155/fmc.15.71.

219 Szepesházi K, Halmos G, Schally AV, Arencibia JM, Groot K, Vadillo-Buenfil M et al. (1999). Growth inhibition of experimental pancreatic cancers and sustained reduction in epidermal growth factor receptors during therapy with hormonal peptide analogs. J Cancer Res Clin Oncol. Aug-Sep; **125**(8–9): 444–52. doi: 10.1007/s004320050301.

220 Talib WH (2018). Melatonin and Cancer Hallmarks. Molecules. Feb 26; **23**(3): 518. doi: 10.3390/molecules23030518.

221 Tang FY, Meydani M (2001). Green tea catechins and vitamin E inhibit angiogenesis of human microvascular endothelial cells through suppression of IL-8 production. Nutr Cancer. **41**(1–2): 119–25. doi: 10.1080/01635581.2001.9680622.

222 Taslipinar A, Bolu E, Kebapcilar L, Sahin M, Uckaya G, Kutlu M (2009). Insulin-like growth factor-1 is essential to the increased mortality caused by excess growth hormone: a case of thyroid cancer and non-Hodgkin's lymphoma in a patient with pituitary acromegaly. Med Oncol. **26**(1): 62–6. doi: 10.1007/s12032-008-9084-9.

223 Thiery JP (2002). Epithelial-mesenchymal transitions in tumour progression. Nat Rev Cancer. Jun; **2**(6): 442–54. doi: 10.1038/nrc822.

224 Toledo-Guzmán ME, Hernández MI, Gómez-Gallegos ÁA, Ortiz-Sánchez E (2019). ALDH as a Stem Cell Marker in Solid Tumors. Curr Stem Cell Res Ther. **14**(5): 375–388. doi: 10.2174/1574888X13666180810120012.

225 Trignani M, Taraborrelli M, Ausili Cèfaro G (2013). The case of a patient affected by primary gliosarcoma and neuroendocrine pancreatic cancer with prolonged survival. Tumori. May-Jun; **99**(3): e117–9. doi: 10.1700/1334.14818.

226 Trubiani O, Recchioni R, Moroni F, Pizzicannella J, Caputi S, Di Primio R (2005). Melatonin provokes cell death in human B-lymphoma cells by mitochondrial-dependent apoptotic pathway activation. J Pineal Res. Nov; **39**(4): 425–31. doi: 10.1111/j.1600-079X.2005.00270.x.

227 Turley JM, Funakoshi S, Ruscetti FW, Kasper J, Murphy WJ, Longo DL et al. (1995). Growth inhibition and apoptosis of RL human B lymphoma cells by vitamin E succinate and retinoic acid: role for transforming growth factor beta. Cell Growth Differ. Jun; **6**(6): 655–63. PMID: 7669719.

228 Utoguchi N, Ikeda K, Saeki K, Oka N, Mizuguchi H, Kubo K et al. (1995). Ascorbic acid stimulates barrier function of cultured endothelial cell monolayer. J Cell Physiol. May; **163**(2): 393–9. doi: 10.1002/jcp.1041630219.

229 Vacas E, Muñoz-Moreno L, Valenzuela PL, Prieto JC, Schally AV, Carmena MJ et al. (2016). Growth hormone-releasing hormone induced transactivation of epidermal growth factor receptor in human triple-negative breast cancer cells. Peptides. Dec; **86**: 153–161. doi: 10.1016/j.peptides.2016.11.004.

230 Valiyaveettil D, Malik M, Joseph DM, Ahmed SF, Kothwal SA, Vijayasaradhi M (2018). Effect of valproic acid on survival in glioblastoma: A prospective single-arm study. South Asian J Cancer. Jul-Sep; **7**(3): 159–162. doi: 10.4103/sajc.sajc_188_17.

231 van Eijck CH, Kwekkeboom DJ, Krenning EP (1998). Somatostatin receptors and breast cancer. Q J Nucl Med. Mar; **42**(1): 18–25. PMID: 9646641.

232 van Gorkom GNY, Lookermans EL, Van Elssen CHMJ, Bos GMJ (2019). The Effect of Vitamin C (Ascorbic Acid) in the Treatment of Patients with Cancer: A Systematic Review. Nutrients. Apr 28; **11**(5): 977. doi: 10.3390/nu11050977.

233 Verhoef C, van Dekken H, Hofland LJ, Zondervan PE, de Wilt JH, van Marion R et al. (2008). Somatostatin receptor in human hepatocellular carcinomas: biological, patient and tumor characteristics. Dig Surg. **25**(1): 21–6. doi: 10.1159/000117819.

234 Vieira Neto L, Taboada GF, Gadelha MR (2008). Somatostatin receptors subtypes 2 and 5, dopamine receptor type 2 expression and gsp status as predictors of octreotide LAR responsiveness in acromegaly. Arq Bras Endocrinol Metabol. Nov; **52**(8): 1288–95. doi: 10.1590/s0004-27302008000800014.

235 Vijayalaxmi, Reiter RJ, Tan DX, Herman TS, Thomas CR Jr (2004). Melatonin as a radioprotective agent: a review. Int J Radiat Oncol Biol Phys. Jul 1; **59**(3): 639–53. doi: 10.1016/j.ijrobp.2004.02.006.

236 Voigt A, Hartmann P, Zintl F (2000). Differentiation, proliferation and adhesion of human neuroblastoma cells after treatment with retinoic acid. Cell Adhes Commun. May; **7**(5): 423–40. doi: 10.3109/15419060009109023.

237 Wang R, Liu C (2019). All-trans retinoic acid therapy induces asymmetric division of glioma stem cells from the U87MG cell line. Oncol Lett. Oct; **18**(4): 3646–3654. doi: 10.3892/ol.2019.10691.

238 Watanabe M, Kobayashi Y, Takahashi N, Kiguchi K, Ishizuka B (2008). Expression of melatonin receptor (MT1) and interaction between melatonin and estrogen in endometrial cancer cell line. J Obstet Gynaecol Res. Aug; **34**(4): 567–73. doi: 10.1111/j.1447-0756.2008.00818.x.

239 Watt HL, Kharmate G, Kumar U (2008). Biology of somatostatin in breast cancer. Mol Cell Endocrinol. May 14; **286**(1–2): 251–61. doi: 10.1016/j.mce.2008.01.006.

240 Winum JY, Rami M, Scozzafava A, Montero JL, Supuran C (2008). Carbonic anhydrase IX: a new druggable target for the design of antitumor agents. Med Res Rev. May; **28**(3): 445–63. doi: 10.1002/med.20112.

241 Wu K, Li Y, Zhao Y, Shan YJ, Xia W, Yu WP et al. (2002). Roles of Fas signaling pathway in vitamin E succinate-induced apoptosis in human gastric cancer SGC-7901 cells. World J Gastroenterol. Dec; **8**(6): 982–6. doi: 10.3748/wjg.v8.i6.982.

242 Wu XX, Kakehi Y, Jin XH, Inui M, Sugimoto M (2009). Induction of apoptosis in human renal cell carcinoma cells by vitamin E succinate in caspase-independent manner. Urology. Jan; **73**(1): 193–9. doi: 10.1016/j.urology.2008.04.055.

243 Xu SL, Liu S, Cui W, Shi Y, Liu Q, Duan JJ et al. (2015). Aldehyde dehydrogenase 1A1 circumscribes high invasive glioma cells and predicts poor prognosis. Am J Cancer Res. Mar 15; **5**(4): 1471–83. PMID: 26101711; PMCID: PMC4473324.

244 Yadav N, Rajendra J, Acharekar A, Dutt S, Vavia P (2019). Effect of Glucosamine Conjugate-Functionalized Liposomes on Glioma Cell and Healthy Brain: An Insight for Future Application in Brain Infusion. AAPS PharmSciTech. Dec 16; **21**(1): 24. doi: 10.1208/s12249-019-1567-9.

245 Yamamoto S, Tamai H, Ishisaka R, Kanno T, Arita K, Kobuchi H et al. (2000). Mechanism of alpha-tocopheryl succinate-induced apoptosis of promyelocytic leukemia cells. Free Radic Res. Oct; **33**(4): 407–18. doi: 10.1080/10715760000300941.

246 Ying M, Wang S, Sang Y, Sun P, Lal B, Goodwin CR et al. (2011). Regulation of glioblastoma stem cells by retinoic acid: role for Notch pathway inhibition. Oncogene. Aug 4; **30**(31): 3454–67. doi: 10.1038/onc.2011.58.

247 Yu A, Somasundar P, Balsubramaniam A, Rose AT, Vona-Davis L, McFadden DW (2002). Vitamin E and the Y4 agonist BA-129 decrease prostate cancer growth and production of vascular endothelial growth factor. J Surg Res. Jun 1; **105**(1): 65–8. doi: 10.1006/jsre.2002.6454.

248 Yu W, Israel K, Liao QY, Aldaz CM, Sanders BG, Kline K (1999). Vitamin E succinate (VES) induces Fas sensitivity in human breast cancer cells: role for Mr 43,000 Fas in VES-triggered apoptosis. Cancer Res. Feb 15; **59**(4): 953–61. PMID: 10029090.

249 Yu W, Sanders BG, Kline K (1997). RRR-alpha-tocopheryl succinate inhibits EL4 thymic lymphoma cell growth by inducing apoptosis and DNA synthesis arrest. Nutr Cancer. **27**(1): 92–101. doi: 10.1080/01635589709514508

250 Yudoh K, Matsuno H, Kimura T (1999). 1alpha,25-dihydroxyvitamin D3 inhibits in vitro invasiveness through the extracellular matrix and in vivo pulmonary metastasis of B16 mouse melanoma. J Lab Clin Med. Feb; **133**(2): 120–8. doi: 10.1016/s0022-2143(99)90004-5.

251 Zeitler P, Siriwardana G (2000). Stimulation of mitogen-activated protein kinase pathway in rat somatotrophs by growth hormone-releasing hormone. Endocrine. Jun; **12**(3): 257–64. doi: 10.1385/ENDO:12:3:257.

252 Zhang C, Liu S, Yuan X, Hu Z, Li H, Wu M et al (2016). Valproic Acid Promotes Human Glioma U87 Cells Apoptosis and Inhibits Glycogen Synthase Kinase-3β Through ERK/Akt Signaling. Cell Physiol Biochem. **39**(6): 2173–2185. doi: 10.1159/000447912.

253 Zhang Y, Ni J, Messing EM, Chang E, Yang CR, Yeh S (2002). Vitamin E succinate inhibits the function of androgen receptor and the expression of prostate-specific antigen in prostate cancer cells. Proc Natl Acad Sci U S A. May 28; **99**(11): 7408–13. doi: 10.1073/pnas.102014399.

254 Zhou S, Wang X, Tan Y, Qiu L, Fang H, Li W (2015). Association between vitamin C intake and glioma risk: evidence from a meta-analysis. Neuroepidemiology. **44**(1): 39–44. doi: 10.1159/000369814.

255 Zhu T, Goh EL, Graichen R, Ling L, Lobie PE (2001). Signal transduction via the growth hormone receptor. Cell Signal. Sep; **13**(9): 599–616. doi: 10.1016/s0898-6568(01)00186-3.

Documentation of the numerous and serious anomalies that have deprived the ministerial experimentation of the 1998 DBM of any scientific dignity:

Marcus Müller (1999). Di Bella's therapy the last word? BMJ: 318:208-209. "The authors also say that they could not have done randomised trials for ethical reasons, but these are not clear. Indeed some would claim that the inferior design of there studies was unethical"

Müllner M (1999). Di Bella's therapy: the last word? The evidence would be stronger if the researchers had randomised their studies. BMJ. Jan 23;318(7178):208-9. doi: 10.1136/bmj.318.7178.208

Vincenzo Brancatisano (1999). Un po' di verità sulla terapia Di Bella. Editore Travel Factory,

Di Bella G (2005). Il Metodo Di Bella. II edizione. Mattioli editore.

Di Bella G (2010). The Di Bella Method (DBM). Neuro Endocrinol Lett.;31 Suppl 1:1-42.

Di Bella G (2019). La Scelta Antitumore. Prevenzione, terapia farmacologica e stile di vita. Uno editori, Macro.