Human Cytomegalovirus: The Cause Of Glioblastoma Multiforme

Ilija Barukčić[1]

[1] Internist, Horandstrasse, DE-26441 Jever, Germany

[2] Correspondence: Ilija Barukčić, Horandstrasse, DE-26441 Jever, Germany.
Tel: 0049-(0)4466-333. Email: Barukcic@t-online.de

Received: May 18, 2018; Accepted: May 18, 2018; Published: May 18, 2018

Abstract

Objective: The relationship between Human cytomegalovirus (HCMV) and glioblastoma multiforme (GBM) is investigated.

Methods: A systematic review and re-analysis of some impressive key studies was conducted aimed to answer the following question. Is there a cause-effect relationship between HCMV and GBM? The method of the conditio sine qua non relationship was used to proof the hypothesis whether the presence of HCMV guarantees the presence of GBM. In other words, *without* HCMV *no* GBM. The mathematical formula of the causal relationship k was used to proof the hypothesis, whether there is a cause-effect relationship between HCMV and GBM. Significance was indicated by a p-value of less than 0.05.

Results: The studies analysed were able to provide strict evidence that HCMV is a necessary condition (a conditio sine qua non) of GBM. Furthermore, the cause-effect relationship between HCMV and GBM ($k = +1$, p value < 0.0001) was highly significant.

Conclusion: Without a human cytomegalovirus infection no glioblastoma multiforme. Human cytomegalovirus is the cause of glioblastoma multiforme.

Keywords: Cytomegalovirus, Glioblastoma multiforme,

Causal relationship

1. Introduction

Glioblastoma multiforme (GBM), affecting children and adults and equivalent to a grade IV diffuse astrocytoma, is a highly lethal brain (Zhu et al., 2002) tumour to such an extent that to date the majority of affected patients are dying from their disease by 2,5 years following diagnosis (Smoll et al., 2013). Glioblastoma multiforme consist primarily of neoplastic astrocytes but includes also other non-neoplastic cell types (Yuan et al., 2004) like neural stem cells, macrophages et cetera. In point of fact, even if Glioblastoma multiforme progresses rapidly and is fatal within a very short time despite current therapies, to date the aetiology of glioblastoma multiforme is completely unknown. Among several risk factors supposed to be involved in glioblastoma including exposure to electrical or magnetic fields or ionizing radiation (Ohgaki, 2009) cytomegalovirus too has been proposed as a contributing agent of glioblastoma multiforme. Human cytomegalovirus (HCMV) is a beta herpes virus which more or less asymptomatically (Priel et al., 2015) infects 50% to 90% of the adult (Yi et al., 2013; Najafi et al., 2016) human population. Even a foetus itself is not protected against a vertical transmission. During maternal primary infection, and to a lesser extent during recurrent infection, human cytomegalovirus can translocate the placental barrier and can cause infection of the developing foetus too. Human cytomegalovirus is occurring in 0.5–2% of pregnancies in Europe and the United States (Kenneson et al., 2007; Wang et al., 2011) and neonatal infections (Fowler et al., 2018) caused by human cytomegalovirus have been reported too. In particular, many breast milk-acquired infections in premature infants are asymptomatic. Several studies demonstrated the presence of human cytomegalovirus in glioblastoma tissues suggesting that HCMV may participate in tumour pathogenesis. But the relationship between GBM and HCMV is controversial because many other studies were unable to detect HCMV in Glioblastoma multiforme tissues.

2. Material and methods

2.1. Material

2.1.1. Search strategy

To answer the questions addressed in this paper, the electronic database PubMed was searched for appropriate studies conducted in any country which investigated the relationship between human cytomegalovirus and glioblastoma multiforme i. e. sero-epidemiologically or by polymerase chain reaction (PCR) et cetera. The search in Pubmed was performed while using some medical key words like "case control study" and "cytomegalovirus" and "glioblastoma multiforme" et cetera. The articles found where saved as a *.txt file while using the support of Pubmed (Menu: Send to, Choose Radio Button: File, Choose Format: Abstract (text). Click buttom "create file"). The created *.txt file was converted into a *.pdf file. The abstracts where studied within the *.pdf file. Those articles were considered for a re-view which provided access to data without any data access barrier. Additionally the reference list of identified articles was used as a potential source of articles appropriate for this study.

2.1.2. The 2x2 table

The meaning of the abbreviations a_t, b_t, c_t, d_t, N_t of the data table used are explained by a 2 by 2-table **Table 1**.

Table 1. The sample space of a contingency table.

		Conditioned B_t (Outcome)		
		Yes = +1	**Not = +0**	**Total**
Condition A_t (risk factor)	**Yes =+1**	a_t	b_t	$\mathbf{A_t}$
	Not = +0	c_t	d_t	$\underline{A}_t$
	Total	$\mathbf{B_t}$	$\underline{B}_t$	$\mathbf{N_t}$

In general it is $(a_t+b_t) = A_t$, $(c_t+d_t) = \underline{A}_t$, $(a_t+c_t) = B_t$, $(b_t+d_t) = \underline{B}_t$ and $a_t+b_t+c_t+d_t=N_t$. Equally, it is $B_t+\underline{B}_t = A_t + \underline{A}_t = N_t$. In this context, it is $p(a_t)=p(A_t \cap B_t)$, $p(A_t) = p(a_t)+p(b_t)$ or $p(A_t)= p(A_t \cap B_t)+ p(b_t) =p(A_t \cap B_t)+p(A_t \cap \underline{B}_t)$ while $p(A_t)$ is not defined as $p(a_t)$. In the same context, it is $p(B_t) = p(a_t)+p(c_t) = p(A_t \cap B_t) +p(c_t)$ and equally that $p(\underline{B}_t) = 1- p(B_t) =p(b_t)+p(d_t)$. Furthermore, the joint probability of A_t and B_t is denoted by $p(A_t \cap B_t)$. Thus far, it is $p(A_t \cap B_t) = p(A_t) - p(b_t) = p(B_t) - p(c_t)$ or in other words it follows that $p(B_t) + p(b_t) - p(c_t) = p(A_t)$. Thus far, define $\Lambda = p(b_t) - p(c_t)$, Einstein's term Λ under conditions of probability theory and we obtain $p(B_t) + \Lambda = p(A_t)$. In general, it is $p(a_t)+p(c_t)+p(b_t)+p(d_t) = 1$.

2.1.3. The studies analyzed

The studies analyzed are viewed by the **Table 2**.

Table 2. *Without* human cytalomegalovirus infection *no* glioblastoma multiforme.

Study Id	Country	N	Case Positive	Case Total	Control positive	Control Total	X^2(Sine)
Rahbar et al. 2013	SE	80	79	**80**	-	-	0,003125
Rahbar et al. , 2013	SE	75	74	**75**	-	-	0,003333333
Cobbs et al. , 2002	USA	45	22	**22**	0	**23**	0,011363636
Scheuer et al., 2008	USA	21	21	**21**	-	-	0,011904762
Slinger E, et al. 2010	NL	21	20	**21**	-	-	0,011904762
Straat K, et al. 2009	USA	10	10	**10**	-	-	0,025
Dziurzynski et al., 2011	USA	5	5	**5**	-	-	0,05
Mitchell et al., 2008	USA	45	42	**45**	-	-	0,138888889
Holdhoff et al., 2017	USA	15	8	**15**	-	-	2,816666667

2.1.3. The study of Cobbs et al.

Cobbs et al. (Cobbs et al. , 2002) performed immunohistochemistry investigations (IHC) on paraffin sections from 22 malignant glioma surgical specimens obtained from non-immunocompromised patients to determine whether HCMV was present in malignant glioma. Cobbs et al. detected IE1–72 immunoreactivity in 27 of 27 malignant glioma biopsy specimens but in none of the 23 controls. The data as obtained by Cobbs et al. are view by the **Table 3**.

Table 3. The Study of Cobbs et al. , 2002

		Glioblastoma multiforme (GBM) <B>		
		Yes	No	Total
HCMV infection <A>	Yes	**22**	0	22
	No	0	**23**	23
	Total	22	23	45

k = **1**
p value (k) = **1,9703E-11**

WITHOUT <A> NO <B>.
p (SINE) = 1
X^2(SINE) = **0,01136364**

IF <A> THEN <B>
p (IMP)= 1
X^2 (IMP)= **0,01136364**

<A> is SINE and IMP of <B>
p(SINE ^ IMP) = 1
X^2(SINE ^ IMP) = **0,02272727**

2.1.4. The control group of infants

Several of the studies presented are missing an own control group. Even if this has no influence on the correct calculation of the chi square value of the data, it has influence on the validity of the causal relationship. In order to be able to perform causal relationship calculations, it is possible to construct a theoretical or *fictive control group of infants*. In this context, Fowler et al. (Fowler et al., 2018) evaluated from 2007 to 2012 the prevalence of a congenital cytomegalovirus infection (HCMV) in a cohort of 100332 infants screened for HCMV while in the hospital. The overall prevalence of HCMV in the cohort of infants investigated was in the range between 1.0 per 1000 live births and 9.5 per 1000 live births. In other words, a cytomegalovirus infection can be found in less than 1% of infants while glioblastoma multiforme cases in infants have not been reported so far which is the reason to use infants as a control group. The data of the study of Fowler et al. (Fowler et al., 2018) are of use while constructing a factitive control group of infants. Such a factitive control group of infants can be used as a substitute for the missed control group in the studies presented.

2.2. Methods

2.2.1. Statistical analysis

All statistical analyses (Barukčić, 1989; Barukčić, 2017a; Barukčić, 2017b; Barukčić, 2017c; Barukčić, 2018a; Barukčić, 2018b; Barukčić, 2018c) were performed with Microsoft Excel version 14.0.7166.5000 (32-Bit) Software (Microsoft GmbH, Munich, Germany). The level of significance was set to 0.05. The probabilities of the contingency table are viewed by the following table (**Table 4**).

Table 4. The probabitlities of a contingency table

		Conditioned B_t		
		Yes = +1	**No = +0**	**Total**
Condition A_t	**Yes =+1**	$p(a_t) = p(A_t \cap B_t)$	$p(b_t)$	$p(A_t)$
	No = +0	**$p(c_t)$**	$p(d_t)$	$p(\underline{A}_t)$
	Total	$p(B_t)$	$p(\underline{B}_t)$	**1**

2.2.2. Independence

In the case of independence of A_t and B_t it is generally valid that

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{1}$$

2.2.3. Exclusion (A_t excludes B_t and vice versa relationship)

The mathematical formula of the *exclusion* relationship (A_t excludes B_t and vice versa) of a population was defined as

$$p(A_t \mid B_t) \equiv \frac{b_t + c_t + d_t}{N_t} \equiv 1 - p(a_t) \equiv p(b_t) + p(c_t) + p(d_t) \equiv p(c_t) + (1 - p(B_t)) \equiv p(b_t) + (1 - p(A_t)) \equiv +1 \tag{2}$$

and used to proof the hypothesis: A_t *excludes* B_t and vice versa.

2.2.4. Necessary condition (conditio sine qua non)

The mathematical formula of the *necessary* condition relationship (conditio sine quam non) of a population was defined as

$$p(A_t \leftarrow B_t) \equiv \frac{a_t + b_t + d_t}{N_t} \equiv p(a_t) + p(b_t) + p(d_t) \equiv p(a_t) + (1 - p(B_t)) \equiv +1 \tag{3}$$

and used to proof the hypothesis: *without* A_t *no* B_t .

2.2.5. Sufficient condition (conditio per quam)

The mathematical formula of the *sufficient* condition relationship (conditio per quam) of a population was defined as

$$p(A_t \rightarrow B_t) \equiv \frac{a_t + c_t + d_t}{N_t} \equiv p(a_t) + p(c_t) + p(d_t) \equiv p(d_t) + p(B_t) \equiv +1 \tag{4}$$

and used to proof the hypothesis: *if* A_t *then* B_t .

2.2.6. The X² goodness of fit test of a necessary condition

Under conditions where the chi-square goodness of fit test (Pearson, 1900) cannot be used it is possible to use an approximate and conservative (one sided) confidence interval known as *the rule of three* (Rumke, 1975; Hanley et al. 1983; Louis, 1981; Jovanovic et al., 1997). According to the definition of the conditio sine qua non relationship it is

$$p\left(A_t \cap B_t\right) + \left(1 - p\left(B_t\right)\right) \equiv +1 \tag{5}$$

or

$$p\left(A_t \cap B_t\right) + 1 - p\left(B_t\right) \equiv +1 \tag{6}$$

Rearranging this equation, we obtain the essential foundation of the conditio sine qua non relationship as

$$p\left(A_t \cap B_t\right) = p\left(B_t\right) \tag{7}$$

and equally our starting point of the derivation of chi-square value of the conditio sine qua non relationship. Multiplying equation before by the population or sample/population size N, it is

$$N \times p\left(A_t \cap B_t\right) \equiv N \times p\left(B_t\right) \tag{8}$$

or

$$N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right) = 0 \tag{9}$$

The square operation yields

$$\left(N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right)\right) \times \left(N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right)\right) = 0 \times 0 \tag{10}$$

Dividing by $N \times p(B_t)$ we obtain

$$\frac{\left(N \times p\left(A_t \cap B_t\right) - N \times p\left(B_t\right)\right)^2}{N \times p\left(B_t\right)} = 0 \tag{11}$$

which is equivalent with

$$\frac{\left(a_t - \left(B_t\right)\right)^2}{\left(B_t\right)} = \frac{\left(a_t - \left(a_t + c_t\right)\right)^2}{\left(B_t\right)} = \frac{\left(c_t\right)^2}{\left(B_t\right)} = 0 \tag{12}$$

Adding $((b_t+d_t) - (\underline{B}_t))^2/\underline{B}_t = ((b_t+d_t) - (b_t+d_t))^2/\underline{B}_t = 0$ yields

$$\frac{\left(c_t\right)^2}{\left(B_t\right)} + 0 = 0 + 0 \tag{13}$$

Using *the continuity correction*, the chi-square value of a conditio sine qua non distribution before changes to

$$\chi^2\left(SINE\right) \equiv \frac{\left(c_t - \left(\frac{1}{2}\right)\right)^2}{\left(B_t\right)} + 0 = 0 \tag{14}$$

The use of the continuity correction should follow the rules of statistics as established and valid today. This definition of the X² distribution of a *conditio sine qua non* distribution (degrees of freedom = 2-1=1) is more precise than already published formulas. In this context, it is not necessary to improve the definition of the X² distribution of a *conditio per quam* distribution as already published. A statistically significant conditio sine qua non relationship demands a causal relationship k which is $k > 0$, otherwise the result of a study should be treated with cautious.

2.2.7. The X² goodness of fit test of the exclusion relationship
According to the definition of the exclusion relationship it is

$$p(b_t)+p(c_t)+p(d_t)\equiv+1 \tag{15}$$

Rearranging this equation, we obtain

$$p(b_t)=1-p(c_t)-p(d_t)=1-\left(p(c_t)+p(d_t)\right)\equiv 1-p(\underline{A}_t)=p(A_t) \tag{16}$$

and

$$p(c_t)=1-p(b_t)-p(d_t)\equiv 1-\left(p(b_t)+p(d_t)\right)=1-p(\underline{B}_t)=p(B_t) \tag{17}$$

The chi square goodness of fit test of the exclusion relationship can be derived as follows.

$$\begin{aligned} N\times p(b_t) &= N\times p(A_t) \\ \left(N\times p(b_t)-N\times p(A_t)\right) &= 0 \\ \left(N\times p(b_t)-N\times p(A_t)\right)\times\left(N\times p(b_t)-N\times p(A_t)\right) &= 0\times 0 \\ \frac{\left(N\times p(b_t)-N\times p(A_t)\right)^2}{N\times p(A_t)} &= \frac{0}{N\times p(A_t)}=0 \end{aligned} \tag{18}$$

$$\chi^2(b_t)=\frac{\left(N\times p(b_t)-N\times p(A_t)\right)^2}{N\times p(A_t)}=\frac{\left(b_t-(a_t+b_t)\right)^2}{A_t}=\frac{\left(-(a_t)\right)^2}{A_t} = 0$$

$$\chi^2(b_t)=\frac{\left(-(a_t)-0,5\right)^2}{A_t} = 0$$

and as

$$\begin{aligned} N\times p(c_t) &= N\times p(B_t) \\ \left(N\times p(c_t)-N\times p(B_t)\right) &= 0 \\ \left(N\times p(c_t)-N\times p(B_t)\right)\times\left(N\times p(c_t)-N\times p(B_t)\right) &= 0\times 0 \\ \frac{\left(N\times p(c_t)-N\times p(B_t)\right)^2}{N\times p(B_t)} &= \frac{0}{N\times p(B_t)}=0 \end{aligned}$$

$$\chi^2(b_t)=\frac{\left(N\times p(c_t)-N\times p(B_t)\right)^2}{N\times p(B_t)}=\frac{\left(c_t-(a_t+c_t)\right)^2}{B_t}=\frac{\left(-(a_t)\right)^2}{B_t} = 0 \tag{19}$$

$$\chi^2(c_t)=\frac{\left(-(a_t)-0,5\right)^2}{B_t} = 0$$

The chi square value with degree of freedom 2-1=1of the exclusion relationship with a *continuity correction* can be calculated as

$$\chi^2(\mathrm{EXCL}) = \frac{\left(-(a_t)-0,5\right)^2}{A_t} + \frac{\left(-(a_t)-0,5\right)^2}{B_t} \tag{20}$$

A statistically significant exclusion relationship demands a causal relationship k which is **k < 0** otherwise the results of a study should be interpreted with some cautious.

2.3.5. The mathematical formula of the causal relationship k

The mathematical formula of the causal relationship k (Barukčć, 1989; Barukčć, 2017a; Barukčć, 2017b; Barukčć, 2017c; Barukčć, 2018a; Barukčć, 2018b; Barukčć, 2018c) is defined *at every single event*, *at every single Bernoulli trial t*, as

$$k(A_t, B_t) \equiv \frac{\left(p(A_t \cap B_t) - \left(p(A_t) \times p(B_t)\right)\right)}{\sqrt[2]{\left(p(A_t) \times p(\underline{A}_t)\right) \times \left(p(B_t) \times p(\underline{B}_t)\right)}} \tag{21}$$

where A_t denotes the cause and B_t denotes the effect. The chi-square distribution can be applied to determine the significance of causal relationship k. Correlation (Pearson, 1896) is not causation, causation is not correlation. The relationship between correlation and causation is discussed already in many publications. This does not necessarily imply that repeating itself over and over again may contribute anything new to further scientific progress.

2.3.6. The chi square distribution

The following critical values of the chi square distribution as visualized by **Table 5** are used in this publication.

Table 5. The critical values of the chi square distribution (degrees of freedom: 1).

	p-Value	One sided X^2	Two sided X^2
	0,1000000000	1,642374415	2,705543454
	0,0500000000	**2,705543454**	**3,841458821**
	0,0400000000	3,06490172	4,217884588
	0,0300000000	3,537384596	4,709292247
	0,0200000000	4,217884588	5,411894431
	0,0100000000	5,411894431	6,634896601
The chi square distribution	0,0010000000	9,549535706	10,82756617
	0,0001000000	13,83108362	15,13670523
	0,0000100000	18,18929348	19,51142096
	0,0000010000	22,59504266	23,92812698
	0,0000001000	27,03311129	28,37398736
	0,0000000100	31,49455797	32,84125335
	0,0000000010	35,97368894	37,32489311
	0,0000000001	40,46665791	41,82145620

3. Results

3.1. *Without* a human cytomegalovirus infection *no* glioblastoma multiforme.

Claims.
Null hypothesis:
A cytomegalovirus infection is a necessary condition (a conditio sine qua non) of glioblastoma multiforme. In other words, the sample distribution of the study analyzed agrees with the hypothetical (theoretical) distribution of a necessary condition.
Alternative hypothesis:
A cytomegalovirus infection is not a necessary condition (a conditio sine qua non) of glioblastoma multiforme. In other words, the sample distribution of the study analyzed does not agree with the hypothetical (theoretical) distribution of a necessary condition.
The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.
Proof.
The results of the re-analyses of the data reviewed by this article (**Table 2**) which investigated the relationship between a cytomegalovirus infection and glioblastoma multiforme are viewed by the table (**Table 2**). Altogether, 9 studies were meta-analyzed while the level of significance was alpha = 0,05. In toto, 9 from 9 studies provide significant evidence of a conditio sine qua non relationship between a cytomegalovirus infection and glioblastoma multiforme. *The most studies were performed without a control group which has no effect on the calculation of the chi square value*. The study of Cobbs et al. provided evidence of a highly significant cause effect relationship (k = +1, p value = 1,9703E-11) between a cytomegalovirus infection and glioblastoma multiforme while the sample size was greater than 30. Consequently, it was possible to use the normal distribution. In other words, the data analyzed support the Null-hypothesis: *without* a cytomegalovirus infection *no* glioblastoma multiforme. Human cytomegalovirus is the cause of glioblastoma multiforme (k = +1, p value = 1,9703E-11). **Q. e. d.**

3.2. HCMV is the cause of glioblastoma multiforme.

The causal relationship between HCMV and GBM is difficult to proof due to fact of *missing control groups* in the studies presented. Because of this, some of the cases are compared with *a fictive control group* of **infants** (**Table 6**). The reason for such a procedure is that GMB has not been reported in infants so far which justifies such an undertaking. In ontrast to this, a HCVM infection has been documented in infants. Human cytomegalovirus infects the adult human population (Yi et al., 2013; Najafi et al., 2016) but infants (Fowler et al., 2018) too. HCMV is able to translocate the placental barrier and is occurring in about 0.5–2% of pregnancies in Europe and the United States (Kenneson et al., 2007; Wang et al., 2011). In point of fact, Fowler et al. (Fowler et al., 2018) were able to document a cytomegalovirus infection in less than 1% of infants. This fact is the foundation for the construction of a fictive control group of infants for further use. In general, if we compare the GMB cases with a control group of fictive infants we must consider that not more than 1 % of infants can be HCMV positive, even if infants were not investigated again by a study analyzed.

Claims.
Null hypothesis:
A cytomegalovirus infection is not the cause of glioblastoma multiforme. In other words, $k = 0$.

Alternative hypothesis:
A cytomegalovirus infection is the cause of glioblastoma multiforme. In other words, $k \neq 0$. .
The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.

Proof.
The results of the re-analyses of the data reviewed by this article (**Table 2)** which investigated the causal relationship between a cytomegalovirus infection and glioblastoma multiforme are viewed by the table (**Table 9**). Altogether, 9 studies were meta-analyzed while the level of significance was alpha = 0,05. In toto, 9 from 9 studies provide significant evidence of a causal relationship between a cytomegalovirus infection and glioblastoma multiforme. In the same respect, a cytomegalovirus infection is a necessary, a sufficient and a necessary and sufficient condition of glioblastoma multiforme (**Table 6**). Even if the most cases were compared with *a fictive control group of infants*, the conclusion is inescapable. Human cytomegalovirus is the cause of glioblastoma multiforme. **Q. e. d.**

Table 6. The causal relationship between HCVM and GBM

Study Id	Year	Country	N	a_t	b_t	c_t	d_t	k	p val (k)	X^2(Sine)	X^2(IMP)	X^2(IMP^SINE)
Rahbar et al. 2013	2013	SE	160	79	**1**	1	**79**	0,975	6,02518E-35	0,003125	0,003125	0,00625
Rahbar et al. , 2013	2013	SE	150	74	**1**	1	**74**	0,973	9,21633E-33	0,00333333	0,00333333	0,00666667
Cobbs et al. , 2002	2002	USA	45	22	1	0	22	0,957	1,39404E-10	0,01136364	0,01086957	0,0222332
Scheuer et al., 2008	2008	USA	42	21	**1**	0	**20**	0,953	6,44502E-10	0,01190476	0,01136364	0,0232684
Slinger E, et al. 2010	2010	NL	42	20	**1**	1	**20**	0,905	4,53136E-09	0,01190476	0,01190476	0,02380952
Straat K, et al. 2009	2009	USA	20	10	**1**	0	**9**	0,905	5,22787E-05	0,025	0,02272727	0,04772727
Dziurzynski et al., 2011	2017	USA	10	5	**0**	0	**5**	1	0,001565402	0,05	0,05	0,1
Mitchell et al., 2008	2008	USA	90	42	**1**	3	**44**	0,912	5,05566E-18	0,13888889	0,00581395	0,14470284
Holdhoff et al., 2017	2017	USA	30	8	**0**	7	**15**	0,603	0,000956935	2,81666667	0,03125	2,84791667
		Total	**589**	281	**7**	13	**288**			3,072187049	0,150387523	3,222574572

Cases = a_t+c_t. **Controls = b_t+d_t**.The study of Cobbs et al. presented a control group. The cases of other studies are compared with **a fictive control group of infants**.

3.3. Etanercept and glioblastoma multiforme.

Claims.
Null hypothesis:
Coronary heart diseae (CAD) and an etanaercept therapy are excluding each other.

Alternative hypothesis:
Coronary heart diseae (CAD) and an etanaercept therapy are not excluding each other. .
The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.

Proof.
HCMV is the cause of atherosclerosis (Barukčć, 2018d) and thus far of coronary heart disease and at the end of coronary events. An appropriate immunosuppressive therapy should be able to decrease the incidence of CAD events. Tumor necrosis factor (TNF-a) mediates host-resistance against microorganisms, is elevated during acute viral infections (Haerter et al., 2004) and appears to *inhibit virus replication*. A TNF-a blocking agent like etanercept, an immunosuppressive drug, is able to block the pivotal role of TNF-a in the inflammatory response. In this context, Hung et al. (Hung et al., 2017) investigated the relationship between an etanercept therapy and coronary events. The data as obtained by the study of Hung et al. are viewed by the **Table 7**.

Table 7. The study of Hung et al. 2017

		Coronary heart disease <B>		
		Yes	No	Total
Etanercept <A>	Yes	**2**	54	56
	No	1251	4953	6204
	Total	1253	5007	6260

k = -0,03904721
p value (k) = **0,00200547**

<A> EXCLUDES <B> and vice versa
p(EXCL)= 0,999680511
X^2(EXCL)= **0,04197426**

According to the data of the study of Hung et al. (Hung et al. 2017) with a sample size of N = 6260, we accept the Null-hypothesis: coronary heart diseae (CAD) and an etanaercept therapy are excluding each other (X^2(Excl) = 0.04, k= -0.03, p value(k) = 0.002) with the consequence that etanercept is a highly effective antidot against CAD. **Q.e.d.**

Based on the data of Hung et al. (Hung et al. 2017), etanercept is highly effective against CAD. CAD itself is caused by HCVM (Barukčć, 2018d). *Conclusio*. Etanercept is highly effective against HCMV. Glioblastoma multiforme is caused by HCVM. Therefore, it is more than justified to considered etanercept for the therapy of glioblastoma multiforme.
Anti-tumor necrosis factor alpha (anti-TNF- alpha) antibodies are widely used to treat several inflammatory diseases and the treatment with a TNFalpha antagonist seems to be associated with various adverse (Bongartz et. al., 2006) events. Petersen at al. (Petersen et al., 2008) reported the history of a 37-year-old male who developed a primary HCMV infection following a month of therapy with etanercept 50mg twice weekly. After discontinuation of etanercept, the patient recovered. Six months later, the same patient restarted on etanercept without HCMV reactivation. This increasingly highlights the importance to stress out *the nature of coincidence of events*. The coincidence of an etanercept therapy and a new HCVM infection does not proof a causal relationship between both. Justification: After discontinuation of the therapy with etanercept, the same patient restarted on etanercept *without* (Petersen et al., 2008) reactivating a HCMV infection. Still, due to Petersen's case (Petersen et al., 2008) the question is justified, whether etanercept's property to control a HCMV infection is dose dependent.

3.4. Leflunomide and glioblastoma multiforme

Leflunomide (N-(4'-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide) introduced for the treatment of rheumatoid arthritis in 1998 is an inhibitor of protein kinase activity and pyrimidine synthesis. Leflunomide with its antiviral properties (Teschner et al., 2010) appears not to inhibit viral DNA synthesis but rather seems to interfere with *virion assembly* (Sudarsanam et al., 2006). Leflunomide as an inhibitor of protein kinase activity and pyrimidine synthesis is an immunosuppressive agent which is effective against CMV (Waldman et al., 1999; John et al., 2004; Sudarsanam et al., 2006; Verkaik et al., 2013; Lu et al., 2015). Cytomegalovirus (CMV) itself is a major cause of mortality especially among pharmacologically immunosuppressed transplant recipients. Furthermore, HCMV is the cause of CAD (Barukčć, 2018d). An anti-CMV drug like leflunomide should be able to decrease coronary artery disease events like acute myocardial infarction.

Claims.
Null hypothesis:
Leflunomide and acute myocardial infarction are excluding each other.

Alternative hypothesis:
Leflunomide and acute myocardial infarction are not excluding each other. .
The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.

Proof.
Suissa et al. (Suissa et al., 2006) investigated whether the risk of acute myocardial infarction (AMI) is associated with several disease-modifying antirheumatic drugs (DMARDs) commonly used in rheumatoid arthritis (RA) therapy including leflunomide. The data as obtained by Suissa et al. are viewed by the **Table 8**.

Table 8. The study of Suissa et al., 2006

		Acute myocardial infarction <B>		
		Yes	No	Total
Leflunomide <A>	Yes	**6**	194	200
	No	552	5386	5938
	Total	558	5580	6138

k = -0,03888389
p value (k) = **0,0023162**

<A> EXCLUDES <B> and vice versa
p(EXCL)= 0,999022483
X^2(EXCL)= **0,20546147**

According to the study of Suissa et al. (Suissa et al., 2006) with a sample size of N = 6138, we accept the Null-hypothesis. Leflunomide and acute myocardial infarction (AMI) are excluding each other (X^2(Excl) = 0.2, k=-0.03, p value(k) = 0.002). **Q. e. d.**

Suissa et al. (Suissa et al., 2006) were able to provide evidence that the use of leflunomide is associated with a reduction in AMI in patients with RA while AMI (i. e. CAD) itself is caused by HCVM (Barukčć, 2018d). *Conclusio*. Leflunomide is highly effective against HCMV (Waldman et al., 1999; Sudarsanam et al., 2006; Verkaik et al., 2013; Lu et al., 2015). Glioblastoma multiforme is caused by HCVM. Therefore, to date it is more than necessary that leflunomide becomes part of a therapy against glioblastoma multiforme.

3.4. Etoricoxib and glioblastoma multiforme.

Etoricoxib is an anti-rheumatic drug used to help to control the inflammatory process in rheumatoid arthritis. Etoricoxib can be associated with an increased or decreased risk of coronary artery disease (CAD) in rheumatoid arthritis (RA) patients.

Claims.

Null hypothesis:

Etoricoxib and coronary artery disease (CAD) are excluding each other.

Alternative hypothesis:

Etoricoxib and coronary artery disease (CAD) are not excluding each other.

The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.

Proof.

Hung et al. (Hung et al., 2017) investigated whether an anti-rheumatic drug like etoricoxib is associated with an increased risk of coronary artery disease (CAD) in rheumatoid arthritis (RA) patients. The data of the study of Hung et al. are viewed by the **Table 9**.

Table 9. The study of Hung et al. 2017

		CAD <B>		
		Yes	No	Total
Etoricoxib <A>	Yes	**12**	144	156
	No	1241	4863	6104
	Total	1253	5007	6260

k = -0,04923852

p value (k) = **9,7891E-05**

<A> EXCLUDES <B> and vice versa

p(EXCL)= 0,998083067

X^2(EXCL)= **0,9533031**

The use of etoricoxib and CAD are excluding each other. The study of Hung et al. (Hung et al., 2017) with a sample size of N = 6260 provided significant evidence that etoricoxib is effective against CAD. We accept the Null-hypothesis: Etoricoxib and coronary artery disease (CAD) are excluding each other (X^2(Excl) = 0,9533031, k = -0.04, p value = 9,7891E-05). **Q.e.d.**

Based on the data of Hung et al. (Hung et al. 2017), etoricoxib is an anti-dot and effective against CAD. CAD itself is caused by HCVM (Barukčć, 2018d). *Conclusio*. Etoricoxib is effective against HCMV. Glioblastoma multiforme is caused by HCVM. Therefore, etoricoxib is of use for the therapy of glioblastoma multiforme.

4. Discussion

Due to the conflicting reports concerning the presence of the human cytomegalovirus in glioma tissue the association between human cytomegalovirus (HCMV) infection and glioblastoma is still a source of debate. While some studies detected HCMV DNA, RNA, and proteins et cetera in GBM tissues others studies (Taha et al., 2016) have not. In most of the previous studies, only a very restricted number of HCMV viral targets with different sensitive techniques (Immunoglobulin G antibodies, immunohistochemical analysis, PCR, in situ hybridization, immunohistochemistry, real-time PCR et cetera) accompanied by a very different personal skill were analysed. Thus, the question is justified to which extent was the entire viral genome present when detected.

Furthermore, complicating issues are creating uncertainty about the results of the studies above which detected a strong association of HCMV with GBM tumours due to the relatively limited study population and non-randomization. In particular, sample quality (age or method of preservation) and primer selection has substantial effects on the outcome of a study. All these factors may have contributed to the few studies which were not able (Taha et al., 2016) to detect HCMV in GBMs tissues. In contrast to results like these, the question is justified how the studies presented could provide such an impressive evidence of a cause effect relationship between HCMV and GBM. Therefore, any purported association of HCMV with GBM may remain controversial. Until we have a better explanation, it is justified to assume in agreement with the majority of studies presented that human cytomegalovirus is the cause of glioblastoma multiforme.

To date, aggressive treatment of glioblastoma multiforme with surgery, radiation therapy, and chemotherapy provides only limited overall survival benefit. In fact, there is no effective therapy for glioblastoma multiforme while the life of the patients suffering from this disease is extremely (Smoll et al., 2013) endangered. This study was able to provide evidence that etanercept, etoricoxib (Hung et al., 2017) and leflunomide (John et al., 2004; Suissa et al., 2006) are effective against human cytomegalovirus and are of strategic importance for the therapy of glioblastoma multiforme. In this context it is useful to point out that John et al. (John et al., 2004) documented the efficacy of leflunomide in humans with CMV disease who received loading dose of 100 mg of leflunomide once daily on days 1–3 and then 20 mg once daily for three months. To date, etanercept, etoricoxib and leflunomide should become part of an effective intervention against glioblastoma multiforme. The development of a vaccine against a CMV infection and a DNA CMV therapeutic vaccine is a major public health duty.

5. Conclusion

Human cytomegalovirus is the cause of glioblastoma multiforme

6. Acknowledgments

Dedicated to Celina. Celina, may this article be of help for you.

7. References

Barukčić, I. (2016) The Mathematical Formula of the Causal Relationship k. *International Journal of Applied Physics and Mathematics*, **6**, 45–65. https://doi.org/10.17706/ijapm.2016.6.2.45-65

Barukčić, I. (2017) Anti Bohr — Quantum Theory and Causality. *International Journal of Applied Physics and Mathematics*, **7**, 93–111. https://doi.org/10.17706/ijapm.2017.7.2.93-111

Barukčić, I. (2017). *Die Kausalität*. Norderstedt: Books on Demand.

Barukčić, I. (2017). *Theoriae causalitatis principia mathematica*. Norderstedt: Books on Demand.

Barukčić, I. (2018) Epstein Bar Virus—The Cause of Hodgkin's Lymphoma. *Journal of Biosciences and Medicines*, **06**, 75–100. https://doi.org/10.4236/jbm.2018.61008

Barukčić, I. (2018) Fusobacterium nucleatum—The Cause of Human Colorectal Cancer. *Journal of Biosciences and Medicines*, **06**, 31–69. https://doi.org/10.4236/jbm.2018.63004

Barukčić, I. (2018) Human Papillomavirus—The Cause of Human Cervical Cancer. *Journal of Biosciences and Medicines*, **06**, 106–125. https://doi.org/10.4236/jbm.2018.64009

Boeckh, M., Murphy, W. J., & Peggs, K. S. (2015) Recent advances in cytomegalovirus: an update on pharmacologic and cellular therapies. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*, **21**, 24–29. https://doi.org/10.1016/j.bbmt.2014.11.002

Bongartz, T., Sutton, A. J., Sweeting, M. J., Buchan, I., Matteson, E. L., & Montori, V. (2006) Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*, **295**, 2275–2285. https://doi.org/10.1001/jama.295.19.2275

Cobbs, C. S., Harkins, L., Samanta, M., Gillespie, G. Y., Bharara, S., King, P. H.,. . . Britt, W. J. (2002) Human cytomegalovirus infection and expression in human malignant glioma. *Cancer Research*, **62**(12), 3347–3350.

Dziurzynski, K., Wei, J., Qiao, W., Hatiboglu, M. A., Kong, L.-Y., Wu, A.,. . . Heimberger, A. B. (2011) Glioma-associated cytomegalovirus mediates subversion of the monocyte lineage to a tumor propagating phenotype. *Clinical Cancer Research : an Official Journal of the American Association for Cancer Research*, **17**, 4642–4649. https://doi.org/10.1158/1078-0432.CCR-11-0414

Fowler, K. B., Ross, S. A., Shimamura, M., Ahmed, A., Palmer, A. L., Michaels, M. G.,. . . Boppana, S. (2018) Racial and Ethnic Differences in the Prevalence of Congenital Cytomegalovirus Infection. *The Journal of Pediatrics.* Advance online publication. https://doi.org/10.1016/j.jpeds.2018.04.043

Haerter, G., Manfras, B. J., Jong-Hesse, Y. de, Wilts, H., Mertens, T., Kern, P., & Schmitt, M. (2004) Cytomegalovirus retinitis in a patient treated with anti-tumor necrosis factor alpha antibody therapy for rheumatoid arthritis. *Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America*, **39**, e88-94. https://doi.org/10.1086/425123

Hanley, J. A. (1983) If Nothing Goes Wrong, Is Everything All Right? *JAMA*, **249**, 1743. https://doi.org/10.1001/jama.1983.03330370053031

Holdhoff, M., Guner, G., Rodriguez, F. J., Hicks, J. L., Zheng, Q., Forman, M. S.,. . . Arav-Boger, R. (2017) Absence of Cytomegalovirus in Glioblastoma and Other High-grade Gliomas by Real-time PCR, Immunohistochemistry, and In Situ Hybridization. *Clinical Cancer Research : an Official Journal of the American Association for Cancer Research*, **23**, 3150–3157. https://doi.org/10.1158/1078-0432.CCR-16-1490

Holdhoff, M., Rothenberger, R., & Browner, I. E. (2018) Glioblastoma in older adults. *Aging*, **10**, 154–155. https://doi.org/10.18632/aging.101377

Hung, Y.-M., Lin, L., Chen, C.-M., Chiou, J.-Y., Wang, Y.-H., Wang, P. Y.-P., & Wei, J. C.-C. (2017) The effect of anti-rheumatic medications for coronary artery diseases risk in patients with rheumatoid arthritis might be changed over time: A nationwide population-based cohort study. *PloS One*, **12**, e0179081. https://doi.org/10.1371/journal.pone.0179081

JOHN, G. T., MANIVANNAN, J., CHANDY, S., PETER, S., & JACOB, C. K. (2004) Leflunomide therapy for cytomegalovirus disease in renal allograft recepients. *Transplantation*, **77**, 1460–1461. https://doi.org/10.1097/01.TP.0000122185.64004.89

Jovanovic, B. D., & Levy, P. S. (1997) A Look at the Rule of Three. *The American Statistician*, **51**, 137. https://doi.org/10.2307/2685405

Kenneson, A., & Cannon, M. J. (2007) Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Reviews in Medical Virology*, **17**, 253–276. https://doi.org/10.1002/rmv.535

Louis, T. A. (1981) Confidence Intervals for a Binomial Parameter after Observing No Successes. *The American Statistician*, **35**, 154. https://doi.org/10.1080/00031305.1981.10479337

Lu, C.-H., Tsai, J.-H., Wu, M.-Z., Yu, C.-L., & Hsieh, S.-C. (2015) Can leflunomide play a role in cytomegalovirus disease prophylaxis besides its antirheumatic effects? *Antiviral Therapy*, **20**, 93–96. https://doi.org/10.3851/IMP2796

Lucas, K. G., Bao, L., Bruggeman, R., Dunham, K., & Specht, C. (2011) The detection of CMV pp65 and IE1 in glioblastoma multiforme. *Journal of Neuro-Oncology*, **103**, 231–238. https://doi.org/10.1007/s11060-010-0383-6

Mitchell, D. A., Xie, W., Schmittling, R., Learn, C., Friedman, A., McLendon, R. E., & Sampson, J. H. (2008) Sensitive detection of human cytomegalovirus in tumors and peripheral blood of patients diagnosed with glioblastoma. *Neuro-Oncology*, **10**, 10–18. https://doi.org/10.1215/15228517-2007-035

Najafi, S., Ghane, M., Poortahmasebi, V., Jazayeri, S. M., & Yousefzadeh-Chabok, S. (2016) Prevalence of Cytomegalovirus in Patients With Multiple Sclerosis: A Case-Control Study in Northern Iran. *Jundishapur Journal of Microbiology*, **9**, e36582. https://doi.org/10.5812/jjm.36582

Ohgaki, H. (2009) Epidemiology of brain tumors. *Methods in Molecular Biology (Clifton, N.J.)*, **472**, 323–342. https://doi.org/10.1007/978-1-60327-492-0_14

Pearson, K. (1896) Mathematical Contributions to the Theory of Evolution. III. Regression, Heredity, and Panmixia. *Philosophical Transactions of the Royal Society a: Mathematical, Physical and Engineering Sciences*, **187**, 253–318. https://doi.org/10.1098/rsta.1896.0007

Pearson, K. (1900) X. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science*, **50**, 157–175. https://doi.org/10.1080/14786440009463897

Petersen, B., & Lorentzen, H. (2008) Cytomegalovirus complicating biological immunosuppressive therapy in two patients with psoriasis receiving treatment with etanercept or efalizumab. *Acta Dermato-Venereologica*, **88**, 523–524. https://doi.org/10.2340/00015555-0491

Priel, E., Wohl, A., Teperberg, M., Nass, D., & Cohen, Z. R. (2015) Human cytomegalovirus viral load in tumor and peripheral blood samples of patients with malignant gliomas. *Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia*, **22**, 326–330. https://doi.org/10.1016/j.jocn.2014.06.099

Rahbar, A., Orrego, A., Peredo, I., Dzabic, M., Wolmer-Solberg, N., Stråât, K.,. . . Söderberg-Nauclér, C. (2013) Human cytomegalovirus infection levels in glioblastoma multiforme are of prognostic value for survival. *Journal of Clinical Virology : the Official Publication of the Pan American Society for Clinical Virology*, **57**, 36–42. https://doi.org/10.1016/j.jcv.2012.12.018

Rahbar, A., Stragliotto, G., Orrego, A., Peredo, I., Taher, C., Willems, J., & Söderberg-Naucler, C. (2012) Low levels of Human Cytomegalovirus Infection in Glioblastoma multiforme associates with patient survival; -a case-control study. *Herpesviridae*, **3**, 3. https://doi.org/10.1186/2042-4280-3-3

Ranganathan, P., Clark, P. A., Kuo, J. S., Salamat, M. S., & Kalejta, R. F. (2012) Significant association of multiple human cytomegalovirus genomic Loci with glioblastoma multiforme samples. *Journal of Virology*, **86**, 854–864. https://doi.org/10.1128/JVI.06097-11

Rumke, C. L. (1975) Implications of the Statement: No Side Effects Were Observed. *New England Journal of Medicine*, **292**, 372–373. https://doi.org/10.1056/NEJM197502132920723

Scheurer, M. E., Bondy, M. L., Aldape, K. D., Albrecht, T., & El-Zein, R. (2008) Detection of human cytomegalovirus in different histological types of gliomas. *Acta Neuropathologica*, **116**, 79–86. https://doi.org/10.1007/s00401-008-0359-1

Schleiss, M. R. (2013) Cytomegalovirus in the neonate: immune correlates of infection and protection. *Clinical & Developmental Immunology*, **2013**, 501801. https://doi.org/10.1155/2013/501801

Slinger, E., Maussang, D., Schreiber, A., Siderius, M., Rahbar, A., Fraile-Ramos, A.,. . . Smit, M. J. (2010) HCMV-encoded chemokine receptor US28 mediates proliferative signaling through the IL-6-STAT3 axis. *Science Signaling*, **3**, ra58. https://doi.org/10.1126/scisignal.2001180

Smoll, N. R., Schaller, K., & Gautschi, O. P. (2013) Long-term survival of patients with glioblastoma multiforme (GBM). *Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia*, **20**, 670–675. https://doi.org/10.1016/j.jocn.2012.05.040

Sudarsanam, T. D., Sahni, R. D., & John, G. T. (2006) Leflunomide: a possible alternative for gangciclovir sensitive and resistant cytomegalovirus infections. *Postgraduate Medical Journal*, **82**, 313–314. https://doi.org/10.1136/pgmj.2005.038521

Suissa, S., Bernatsky, S., & Hudson, M. (2006) Antirheumatic drug use and the risk of acute myocardial infarction. *Arthritis and Rheumatism*, **55**, 531–536. https://doi.org/10.1002/art.22094

Taha, M. S., Abdalhamid, B. A., El-Badawy, S. A., Sorour, Y. M., Almsned, F. M., & Al-Abbadi, M. A. (2016) Expression of cytomegalovirus in glioblastoma multiforme: Myth or reality? *British Journal of Neurosurgery*, **30**, 307–312. https://doi.org/10.3109/02688697.2015.1119241

Verkaik, N. J., Hoek, R. A. S., van Bergeijk, H., van Hal, P. T. W., Schipper, M. E. I., Pas, S. D.,. . . Murk, J. L. (2013) Leflunomide as part of the treatment for multidrug-resistant cytomegalovirus disease after lung transplantation: case report and review of the literature. *Transplant Infectious Disease : an Official Journal of the Transplantation Society*, **15**, E243-9. https://doi.org/10.1111/tid.12156

Waldman, W. J., Knight, D. A., Blinder, L., Shen, J., Lurain, N. S., Miller, D. M.,. . . Chong, A. S. (1999) Inhibition of cytomegalovirus in vitro and in vivo by the experimental immunosuppressive agent leflunomide. *Intervirology*, **42**, 412–418. https://doi.org/10.1159/000053979

Wang, C., Zhang, X., Bialek, S., & Cannon, M. J. (2011) Attribution of congenital cytomegalovirus infection to primary versus non-primary maternal infection. *Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America*, **52**, e11-3. https://doi.org/10.1093/cid/ciq085

Wrensch, M., Weinberg, A., Wiencke, J., Miike, R., Sison, J., Wiemels, J.,. . . Kelsey, K. (2005) History of chickenpox and shingles and prevalence of antibodies to varicella-zoster virus and three other herpesviruses among adults with glioma and controls. *American Journal of Epidemiology*, **161**, 929–938. https://doi.org/10.1093/aje/kwi119

Xing, Y., Wang, Y., Wang, S., Wang, X., Fan, D., Zhou, D., & An, J. (2016) Human cytomegalovirus infection contributes to glioma disease progression via upregulating endocan expression. *Translational Research : the Journal of Laboratory and Clinical Medicine*, **177**, 113–126. https://doi.org/10.1016/j.trsl.2016.06.008

Yi, F., Zhao, J., Luckheeram, R. V., Lei, Y., Wang, C., Huang, S.,. . . Xia, B. (2013) The prevalence and risk factors of cytomegalovirus infection in inflammatory bowel disease in Wuhan, Central China. *Virology Journal*, **10**, 43. https://doi.org/10.1186/1743-422X-10-43

Yuan, X., Curtin, J., Xiong, Y., Liu, G., Waschsmann-Hogiu, S., Farkas, D. L.,. . . Yu, J. S. (2004) Isolation of cancer stem cells from adult glioblastoma multiforme. *Oncogene*, **23**, 9392–9400. https://doi.org/10.1038/sj.onc.1208311

Zavala-Vega, S., Castro-Escarpulli, G., Hernández-Santos, H., Salinas-Lara, C., Palma, I., Mejía-Aranguré, J. M.,. . . Arellano-Galindo, J. (2017) An overview of the infection of CMV, HSV 1/2 and EBV in Mexican

patients with glioblastoma multiforme. *Pathology, Research and Practice*, **213**, 271–276. https://doi.org/10.1016/j.prp.2016.12.006

Zhu, Y., & Parada, L. F. (2002) The molecular and genetic basis of neurological tumours. *Nature Reviews. Cancer*, **2**, 616–626. https://doi.org/10.1038/nrc866