**Name of Journal:** *World Journal of Clinical Oncology*

**Manuscript NO:** 73633

**Manuscript Type:** LETTER TO THE EDITOR

**Commentary: Evaluating potential glioma serum biomarkers, with future applications**

Goutnik M *et al*. Evaluating potential glioma biomarkers

Michael Goutnik, Brandon Lucke-Wold

**Michael Goutnik, Brandon Lucke-Wold,** Department of Neurosurgery, University of Florida, Gainesville, FL 32608, United States

**Author contributions:** Goutnik M wrote the manuscript; Lucke-Wold B contributed to writing, and edited the manuscript.

**Corresponding author: Michael Goutnik, MS,** Department of Neurosurgery, University of Florida, 1505 SW Archer Rd, Gainesville, FL 32608, United States. mgoutnik@ufl.edu

**Received:** November 28, 2021

**Revised:** March 15, 2022

**Accepted: May 14, 2022**

**Published online:**

**Abstract**

Systemic inflammation within malignant glioma is a topic of ongoing significance. In this commentary, we highlight recent findings from Gandhi *et al* and discuss alternative approaches. We present a counter argument with findings that IL-6 markers are controversial. We highlight the potential benefit of looking at microRNAs and other biomarkers. Finally, we present ideas for future application involving differentiation between radiation necrosis and recurrence. The commentary is intended to serve as a catalyst for further scientific discovery.

**Key Words:** Systemic inflammation; Malignant glioma; Neutrophil-lymphocyte ratio; Interleukin-6

Goutnik M, Lucke-Wold B. Commentary: Evaluating potential glioma serum biomarkers, with future applications. *World J Clin Oncol* 2022; In press

**Core Tip:** Systemic inflammation in malignant glioma, along with the potential for blood-based biomarkers, is an exciting field of ongoing research. We have discussed supporting and contrasting evidence for glioma blood-based biomarkers, along with future research proposals.

**TO THE EDITOR**

The paper titled “Novel molecular panel for evaluating systemic inflammation and survival in therapy naïve glioma patients” by Gandhi *et al*[1] highlights the use of a non-invasive panel consisting of four inflammatory markers to distinguish between histological grades of glioma and IDH-mutant/wildtype glioma, as well as predicting overall survival. The premise behind the potential effectiveness of such a panel is the chronic inflammatory state that results from various stimuli like tumor antigens and oncogenes that promote abnormal growth and leakage of markers into the peripheral circulation. The inflammatory environment of gliomas is not a new finding, as Morimura *et al*[2] previously found. 20%-30% of cells in glioma samples were recognizable by various macrophage/microglia markers and that tumor proliferation correlates with macrophage infiltration[2]. Parney *et al*[3] similarly demonstrated the infiltration of gliomas by macrophages. However, there is conflicting evidence as to whether these infiltrating macrophages are capable of secreting cytokines and promoting an effective immune response[4,5].

Nonetheless, other studies have found similar results with respect to the markers that Gandhi *et al*[1] focused upon within their paper. For example, Adams *et al*[6] found the kynurenine pathway to be significantly activated in plasma samples from glioblastoma (GBM) patients, an effect that is hypothesized to inhibit anti-tumor immunity by depleting tryptophan from the tumor microenvironment and thus suppressing T-cell proliferation. Du *et al*[7] also demonstrated that the serum Kyn/Trp ratio in patients with high grade gliomas was significantly higher than in those with lower grade gliomas. Similarly, Juhász *et al*[8] used dynamic PET imaging of patients with gliomas to demonstrate shunting of tryptophan (Trp) toward kynurenine (Kyn) metabolism. Mitsuka *et al*[9] evaluated the expression of indoleaine 2,3-dioxygenase (IDO), an important enzyme in tryptophan metabolism that yields catabolites including kynurenine, in 75 surgical specimens including diffuse astrocytomas, anaplastic astrocytomas, and GBMs. The authors found IDO expression correlated with glioma grade, expression increased in secondary glioblastoma relative to the initial lower-grade glioma, and stronger expression was associated with worse survival in GBM patients[9]. Zhai *et al*[10] also found GBM patients with high kynurenine/tryptophan ratios to have worse survival compared to those with lower values. However, no other studies were found that replicated Gandhi *et al*[1]’s findings of tryptophan metabolites distinguishing between IDH-wildtype and mutant gliomas.

The neutrophil-lymphocyte ratio was another significant marker in Gandhi *et al*[1]’s study, which has been shown to be effective in distinguishing between different grades of glioma and predicting overall survival and progression-free survival in a variety of gliomas[11-19]. Concurrent with Gandhi *et al*[1]’s results, NLR has also been shown to distinguish between IDH-mutant and wildtype gliomas, with mutant IDH1 gliomas featuring lower levels of NLR[17]. Furthermore, telomerase activity has also been associated with glioma grade and overall survival, which Gandhi *et al*[22] also demonstrated[20-22]. However, IDH mutant cell lines appear to indirectly reactivate hTERT, which contrasts with Gandhi *et al*[22]’s finding of higher hTERT in IDH-wildtype tumors[23].

Gandhi *et al*[1] highlighted positive correlations between median marker values and tumor grade, as well as significantly higher molecular marker values for IDH-wildtype compared to IDH-mutant gliomas. Furthermore, they found that IL-6 had a strong correlation with tumor grade, which has been replicated by immunohistochemistry, gene expression studies and CSF and serum analysis[24,25]. Some of these findings have been challenged in the literature, however. Cytokines interact with receptors, antibodies, binding proteins, and also often have short half-lives, so total concentrations may not reflect production and/or secretion levels[26]. Samaras *et al*[26] thus used the ELISPOT method (a cell-based cytokine measuring system) to demonstrate greater IL-6 secretion from peripheral monocytes and greater IL-10 secretion from peripheral mononuclear and tumor cells in glioma patients compared to controls. However, there was only a marginal increase in significance in median IL-6 secretion between glioma grades, but this may be due to small sample size[26]. Holst *et al*[27] studied 158 patients and found no difference in serum IL-6 between GBM and lower grade gliomas once age was accounted for, and that IL-6 was significant for worse survival only in univariate analysis. However, Holst *et al*[27] and Jiang *et al*[28] did find *IL6* RNA expression to differ between IDH-mutant and wild type gliomas, which parallels the finding of Gandhi *et al*[1]. Other studies have not found a relationship between IL-6 Levels and survival in GBM[29,30]. In one study involving 38 glioma patients, serum IL-6 decreased in glioma patients and inversely correlated with grade, while serum IL-17A was specific to gliomas (compared to meningiomas and schwannomas) and positively correlated with grade[31]. However, serum IL-6 has been associated with a negative prognosis in other cancers[32].

Divergent results regarding IL-6 may reflect confounding bias and/or differential treatment, as corticosteroid treatment may decrease plasma IL-6[27,33]. Similarly, brain surgery may increase serum inflammatory markers, suggesting that these proteins reflect brain injury and disruption of the blood-brain barrier rather than tumor burden[34]. There may also be false positives in patients with other inflammatory or malignant processes[12]. Furthermore, there are a variety of other circulating biomarkers that may influence survival, such as circulating tumor cells and microRNAs[35,36]. In addition, other non-serum based noninvasive biomarkers like urinary 2-hydroxyglutarate (2-HG), a product of mutant IDH acting on α-ketoglutarate, may distinguish between IDH-mutant and IDH-wild type glioma[37,38]. This metabolite may also be detected by magnetic resonance spectroscopy, and correlates with IDH mutation status[39]. Nonetheless, Gandhi *et al*[1]’s panel is promising with a 94.4% sensitivity and 96.7% specificity, suggesting potential therapeutic targets. More prospective work with larger cohorts is needed to evaluate the efficacy of Gandhi *et al*[1]’s proposed immune marker panel in predicting tumor grade and survival, and whether adding, removing, and/or combining other circulating and non-circulating biomarkers may be more effective in terms of accuracy and cost.

An interesting application of Gandhi *et al*[1]’s work would involve testing the ability of their panel to differentiate tumor progression from radiation necrosis[40]. Inflammation, including the pro-inflammatory IL-6 cytokine, likely contributes to the pathophysiology of radiation necrosis[41,42]. It is feasible that a different set of thresholds for the four molecular markers, or the inclusion of other markers like miR-21[43], predicts radiation necrosis compared to tumor progression. Furthermore, a different choice of patient controls could be useful in further evaluating the panel’s specificity. Instead of forty-five healthy controls without a history of inflammation or autoimmune disease, patients with non-glial brain tumors and/or other inflammatory conditions may serve as controls.

Further testing of the panel may include other potentially important molecules like IL-33. IL-33 has been shown to induce a pro-inflammatory environment within gliomas and inversely correlates with survival[44-46]. De Boeck *et al*[44] also demonstrated IL-33 induced upregulation of inflammatory gene expression, including IL-6, and proposed that IL-33 secretion from glioma cells recruits monocytic cells from the circulation. Thus, IL-33 may be more specific to glioma than Gandhi *et al*[1]’s markers, and may also be sufficient alone as a marker. Differentiating the markers that distinguish high grade verse low grade gliomas early will be valuable and can be validated in preclinical studies.

**REFERENCES**

1 **Gandhi P**, Shrivastava R, Garg N, Sorte SK. Novel molecular panel for evaluating systemic inflammation and survival in therapy naïve glioma patients. *World J Clin Oncol* 2021; **12**: 947-959 [PMID: 34733616 DOI: 10.5306/wjco.v12.i10.947]

2 **Morimura T**, Neuchrist C, Kitz K, Budka H, Scheiner O, Kraft D, Lassmann H. Monocyte subpopulations in human gliomas: expression of Fc and complement receptors and correlation with tumor proliferation. *Acta Neuropathol* 1990; **80**: 287-294 [PMID: 2399810 DOI: 10.1007/BF00294647]

3 **Parney IF**, Waldron JS, Parsa AT. Flow cytometry and in vitro analysis of human glioma-associated macrophages. Laboratory investigation. *J Neurosurg* 2009; **110**: 572-582 [PMID: 19199469 DOI: 10.3171/2008.7.JNS08475]

4 **Hussain SF**, Yang D, Suki D, Aldape K, Grimm E, Heimberger AB. The role of human glioma-infiltrating microglia/macrophages in mediating antitumor immune responses. *Neuro Oncol* 2006; **8**: 261-279 [PMID: 16775224 DOI: 10.1215/15228517-2006-008]

5 **Charles NA**, Holland EC, Gilbertson R, Glass R, Kettenmann H. The brain tumor microenvironment. *Glia* 2011; **59:** 1169-1180 [PMID: 21446047 DOI: 10.1002/glia.21136]

6 **Adams S**, Teo C, McDonald KL, Zinger A, Bustamante S, Lim CK, Sundaram G, Braidy N, Brew BJ, Guillemin GJ. Involvement of the kynurenine pathway in human glioma pathophysiology. *PLoS One* 2014; **9**: e112945 [PMID: 25415278 DOI: 10.1371/journal.pone.0112945]

7 **Du L**, Xing Z, Tao B, Li T, Yang D, Li W, Zheng Y, Kuang C, Yang Q. Both IDO1 and TDO contribute to the malignancy of gliomas via the Kyn-AhR-AQP4 signaling pathway. *Signal Transduct Target Ther* 2020; **5**: 10 [PMID: 32296044 DOI: 10.1038/s41392-019-0103-4]

8 **Juhász C**, Chugani DC, Barger GR, Kupsky WJ, Chakraborty PK, Muzik O, Mittal S. Quantitative PET imaging of tryptophan accumulation in gliomas and remote cortex: correlation with tumor proliferative activity. *Clin Nucl Med* 2012; **37**: 838-842 [PMID: 22889771 DOI: 10.1097/RLU.0b013e318251e458]

9 **Mitsuka K**, Kawataki T, Satoh E, Asahara T, Horikoshi T, Kinouchi H. Expression of indoleamine 2,3-dioxygenase and correlation with pathological malignancy in gliomas. *Neurosurgery* 2013; **72**: 1031-8; discussion 1038-9 [PMID: 23426156 DOI: 10.1227/NEU.0b013e31828cf945]

10 **Zhai L**, Dey M, Lauing KL, Gritsina G, Kaur R, Lukas RV, Nicholas MK, Rademaker AW, Dostal CR, McCusker RH, Raizer JJ, Parsa AT, Bloch O, Wainwright DA. The kynurenine to tryptophan ratio as a prognostic tool for glioblastoma patients enrolling in immunotherapy. *J Clin Neurosci* 2015; **22**: 1964-1968 [PMID: 26279502 DOI: 10.1016/j.jocn.2015.06.018]

11 **Wang PF**, Meng Z, Song HW, Yao K, Duan ZJ, Yu CJ, Li SW, Yan CX. Preoperative Changes in Hematological Markers and Predictors of Glioma Grade and Survival. *Front Pharmacol* 2018; **9**: 886 [PMID: 30154718 DOI: 10.3389/fphar.2018.00886]

12 **Zheng SH**, Huang JL, Chen M, Wang BL, Ou QS, Huang SY. Diagnostic value of preoperative inflammatory markers in patients with glioma: a multicenter cohort study. *J Neurosurg* 2018; **129**: 583-592 [PMID: 29099300 DOI: 10.3171/2017.3.JNS161648]

13 **Lei YY**, Li YT, Hu QL, Wang J, Sui AX. Prognostic impact of neutrophil-to-lymphocyte ratio in gliomas: a systematic review and meta-analysis. *World J Surg Oncol* 2019; **17**: 152 [PMID: 31472673 DOI: 10.1186/s12957-019-1686-5]

14 **Weng W**, Chen X, Gong S, Guo L, Zhang X. Preoperative neutrophil-lymphocyte ratio correlated with glioma grading and glioblastoma survival. *Neurol Res* 2018; **40**: 917-922 [PMID: 30074469 DOI: 10.1080/01616412.2018.1497271]

15 **Gomes Dos Santos A**, de Carvalho RF, de Morais ANLR, Silva TM, Baylão VMR, Azevedo M, de Oliveira AJM. Role of neutrophil-lymphocyte ratio as a predictive factor of glioma tumor grade: A systematic review. *Crit Rev Oncol Hematol* 2021; **163**: 103372 [PMID: 34062242 DOI: 10.1016/j.critrevonc.2021.103372]

16 **Clavreul A**, Lemée JM, Soulard G, Rousseau A, Menei P. A Simple Preoperative Blood Count to Stratify Prognosis in Isocitrate Dehydrogenase-Wildtype Glioblastoma Patients Treated with Radiotherapy plus Concomitant and Adjuvant Temozolomide. *Cancers (Basel)* 2021; **13** [PMID: 34830935 DOI: 10.3390/cancers13225778]

17 **Auezova R**, Ivanova N, Akshulakov S, Zhetpisbaev B, Kozhakhmetova A, Ryskeldiyev N, Mustafin K, Teltayev D, Auezova L. Isocitrate dehydrogenase 1 mutation is associated with reduced levels of inflammation in glioma patients. *Cancer Manag Res* 2019; **11**: 3227-3236 [PMID: 31114362 DOI: 10.2147/CMAR.S195754]

18 **Gan Y**, Zhou X, Niu X, Li J, Wang T, Zhang H, Yang Y, Liu Y, Mao Q. Neutrophil/Lymphocyte Ratio Is an Independent Prognostic Factor in Elderly Patients with High-Grade Gliomas. *World Neurosurg* 2019; **127**: e261-e267 [PMID: 30898756 DOI: 10.1016/j.wneu.2019.03.085]

19 **Tan Z**, Shen L, Wu H, Deng L, Li Z, Huang X. Preoperative Neutrophil/Lymphocyte Ratio Is an Independent Prognostic Biomarker in Patients with Low-Grade Gliomas. *World Neurosurg* 2019; **132**: e585-e590 [PMID: 31442642 DOI: 10.1016/j.wneu.2019.08.068]

20 **Huang F**, Kanno H, Yamamoto I, Lin Y, Kubota Y. Correlation of clinical features and telomerase activity in human gliomas. *J Neurooncol* 1999; **43:** 137-142 [PMID: 10533725 DOI: 10.1023/a:1006258817785]

21 **Dorris K**, Sobo M, Onar-Thomas A, Panditharatna E, Stevenson CB, Gardner SL, Dewire MD, Pierson CR, Olshefski R, Rempel SA, Goldman S, Miles L, Fouladi M, Drissi R. Prognostic significance of telomere maintenance mechanisms in pediatric high-grade gliomas. *J Neurooncol* 2014; **117**: 67-76 [PMID: 24477622 DOI: 10.1007/s11060-014-1374-9]

22 **Gandhi P**, Khare R, Garg N. Evaluating the potential of circulating hTERT levels in glioma: can plasma levels serve as an independent prognostic marker? *J Neurooncol* 2017; **135**: 255-261 [PMID: 28756592 DOI: 10.1007/s11060-017-2578-6]

23 **Ohba S**, Mukherjee J, Johannessen TC, Mancini A, Chow TT, Wood M, Jones L, Mazor T, Marshall RE, Viswanath P, Walsh KM, Perry A, Bell RJ, Phillips JJ, Costello JF, Ronen SM, Pieper RO. Mutant IDH1 Expression Drives TERT Promoter Reactivation as Part of the Cellular Transformation Process. *Cancer Res* 2016; **76**: 6680-6689 [PMID: 27758882 DOI: 10.1158/0008-5472.CAN-16-0696]

24 **Rolhion C**, Penault-Llorca F, Kémény JL, Lemaire JJ, Jullien C, Labit-Bouvier C, Finat-Duclos F, Verrelle P. Interleukin-6 overexpression as a marker of malignancy in human gliomas. *J Neurosurg* 2001; **94**: 97-101 [PMID: 11147905 DOI: 10.3171/jns.2001.94.1.0097]

25 **Shan Y**, He X, Song W, Han D, Niu J, Wang J. Role of IL-6 in the invasiveness and prognosis of glioma. *Int J Clin Exp Med* 2015; **8**: 9114-9120 [PMID: 26309566]

26 **Samaras V**, Piperi C, Korkolopoulou P, Zisakis A, Levidou G, Themistocleous MS, Boviatsis EI, Sakas DE, Lea RW, Kalofoutis A, Patsouris E. Application of the ELISPOT method for comparative analysis of interleukin (IL)-6 and IL-10 secretion in peripheral blood of patients with astroglial tumors. *Mol Cell Biochem* 2007; **304**: 343-351 [PMID: 17551671 DOI: 10.1007/s11010-007-9517-3]

27 **Holst CB**, Christensen IJ, Skjøth-Rasmussen J, Hamerlik P, Poulsen HS, Johansen JS. Systemic Immune Modulation in Gliomas: Prognostic Value of Plasma IL-6, YKL-40, and Genetic Variation in YKL-40. *Front Oncol* 2020; **10**: 478 [PMID: 32363159 DOI: 10.3389/fonc.2020.00478]

28 **Jiang Y**, Han S, Cheng W, Wang Z, Wu A. NFAT1-regulated IL6 signalling contributes to aggressive phenotypes of glioma. *Cell Commun Signal* 2017; **15**: 54 [PMID: 29258522 DOI: 10.1186/s12964-017-0210-1]

29 **Chiorean R**, Berindan-Neagoe I, Braicu C, Florian IS, Leucuta D, Crisan D, Cernea V. Quantitative expression of serum biomarkers involved in angiogenesis and inflammation, in patients with glioblastoma multiforme: correlations with clinical data. *Cancer Biomark* 2014; **14**: 185-194 [PMID: 24878820 DOI: 10.3233/CBM-130310]

30 **Reynés G**, Vila V, Martín M, Parada A, Fleitas T, Reganon E, Martínez-Sales V. Circulating markers of angiogenesis, inflammation, and coagulation in patients with glioblastoma. *J Neurooncol* 2011; **102**: 35-41 [PMID: 20607353 DOI: 10.1007/s11060-010-0290-x]

31 **Doroudchi M**, Pishe ZG, Malekzadeh M, Golmoghaddam H, Taghipour M, Ghaderi A. Elevated serum IL-17A but not IL-6 in glioma versus meningioma and schwannoma. *Asian Pac J Cancer Prev* 2013; **14**: 5225-5230 [PMID: 24175805 DOI: 10.7314/apjcp.2013.14.9.5225]

32 **Lippitz BE.** Cytokine patterns in patients with cancer: a systematic review. *Lancet Oncol* 2013; **14:** e218-e228 [PMID: 23639322 DOI: 10.1016/S1470-2045(12)70582-X]

33 **Fujio N**, Masuoka S, Shikano K, Kusunoki N, Nanki T, Kawai S. Apparent Hypothalamic-Pituitary-Adrenal Axis Suppression via Reduction of Interleukin-6 by Glucocorticoid Therapy in Systemic Autoimmune Diseases. *PLoS One* 2016; **11**: e0167854 [PMID: 27930715 DOI: 10.1371/journal.pone.0167854]

34 **Holdhoff M**, Yovino SG, Boadu O, Grossman SA. Blood-based biomarkers for malignant gliomas. *J Neurooncol* 2013; **113**: 345-352 [PMID: 23670054 DOI: 10.1007/s11060-013-1144-0]

35 **He J**, Jiang Y, Liu L, Zuo Z, Zeng C. Circulating MicroRNAs as Promising Diagnostic Biomarkers for Patients With Glioma: A Meta-Analysis. *Front Neurol* 2020; **11**: 610163 [PMID: 33597912 DOI: 10.3389/fneur.2020.610163]

36 **Müller Bark J**, Kulasinghe A, Chua B, Day BW, Punyadeera C. Circulating biomarkers in patients with glioblastoma. *Br J Cancer* 2020; **122**: 295-305 [PMID: 31666668 DOI: 10.1038/s41416-019-0603-6]

37 **Fathi AT**, Nahed BV, Wander SA, Iafrate AJ, Borger DR, Hu R, Thabet A, Cahill DP, Perry AM, Joseph CP, Muzikansky A, Chi AS. Elevation of Urinary 2-Hydroxyglutarate in IDH-Mutant Glioma. *Oncologist* 2016; **21**: 214-219 [PMID: 26834160 DOI: 10.1634/theoncologist.2015-0342]

38 **Lombardi G**, Corona G, Bellu L, Della Puppa A, Pambuku A, Fiduccia P, Bertorelle R, Gardiman MP, D'Avella D, Toffoli G, Zagonel V. Diagnostic value of plasma and urinary 2-hydroxyglutarate to identify patients with isocitrate dehydrogenase-mutated glioma. *Oncologist* 2015; **20**: 562-567 [PMID: 25862748 DOI: 10.1634/theoncologist.2014-0266]

39 **Choi C**, Ganji SK, DeBerardinis RJ, Hatanpaa KJ, Rakheja D, Kovacs Z, Yang XL, Mashimo T, Raisanen JM, Marin-Valencia I, Pascual JM, Madden CJ, Mickey BE, Malloy CR, Bachoo RM, Maher EA. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. *Nat Med* 2012; **18**: 624-629 [PMID: 22281806 DOI: 10.1038/nm.2682]

40 **Zachariah MA**, Oliveira-Costa JP, Carter BS, Stott SL, Nahed BV. Blood-based biomarkers for the diagnosis and monitoring of gliomas. *Neuro Oncol* 2018; **20**: 1155-1161 [PMID: 29746665 DOI: 10.1093/neuonc/noy074]

41 **Yoritsune E**, Furuse M, Kuwabara H, Miyata T, Nonoguchi N, Kawabata S, Hayasaki H, Kuroiwa T, Ono K, Shibayama Y, Miyatake S. Inflammation as well as angiogenesis may participate in the pathophysiology of brain radiation necrosis. *J Radiat Res* 2014; **55**: 803-811 [PMID: 24676944 DOI: 10.1093/jrr/rru017]

42 **Sultana N**, Sun C, Katsube T, Wang B. Biomarkers of Brain Damage Induced by Radiotherapy. *Dose Response* 2020; **18**: 1559325820938279 [PMID: 32694960 DOI: 10.1177/1559325820938279]

43 **Westphal M**, Lamszus K. Circulating biomarkers for gliomas. *Nat Rev Neurol* 2015; **11**: 556-566 [PMID: 26369507 DOI: 10.1038/nrneurol.2015.171]

44 **De Boeck A**, Ahn BY, D'Mello C, Lun X, Menon SV, Alshehri MM, Szulzewsky F, Shen Y, Khan L, Dang NH, Reichardt E, Goring KA, King J, Grisdale CJ, Grinshtein N, Hambardzumyan D, Reilly KM, Blough MD, Cairncross JG, Yong VW, Marra MA, Jones SJM, Kaplan DR, McCoy KD, Holland EC, Bose P, Chan JA, Robbins SM, Senger DL. Glioma-derived IL-33 orchestrates an inflammatory brain tumor microenvironment that accelerates glioma progression. *Nat Commun* 2020; **11**: 4997 [PMID: 33020472 DOI: 10.1038/s41467-020-18569-4]

45 **Zhang J**, Wang P, Ji W, Ding Y, Lu X. Overexpression of interleukin-33 is associated with poor prognosis of patients with glioma. *Int J Neurosci* 2017; **127**: 210-217 [PMID: 27050560 DOI: 10.1080/00207454.2016.1175441]

46 **Gramatzki D**, Frei K, Cathomas G, Moch H, Weller M, Mertz KD. Interleukin-33 in human gliomas: Expression and prognostic significance. *Oncol Lett* 2016; **12**: 445-452 [PMID: 27347163 DOI: 10.3892/ol.2016.4626]

**Footnotes**

**Conflict-of-interest statement:** The authors deny any conflicts of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** November 28, 2021

**First decision:** February 15, 2022

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Yu HC, China; Lei T, China **S-Editor:** Liu JH **L-Editor:** A **P-Editor:** Liu JH