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Investigation of adenosinergic pathway in peripheral blood of glioblastoma patients

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“We are all agreed that your theory is crazy. The question which divides us is whether it is crazy enough to have a chance of being correct.”

NIELS BOHR

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“What am I now?
What if I'm someone I don't want around?
I'm falling again”
-Harry Styles (Falling)

To all those who believe in me when I don't believe in myself: thank you so much!

Para todos aqueles que acreditam em mim quando eu mesma não acredito: muito obrigada!

Summary

1. List of abbreviations, symbols, and units

ADO	Adenosine
ADP	Adenosine diphosphate
ADPR	ADP ribose
AMP	Adenosine Monophosphate
ATP	Adenosine Triphosphate
BBB	Blood Brain Barrier
CAR-T	Chimeric antigen receptor T-cell
CD39	NTPDase 1
CD73	Ecto-5'-nucleotidase
CNS	Central Nervous System
CSF-1	Macrophage Colony-Stimulating Factor-
CTLA-4	Cytotoxic T-lymphocyte-Associated Protein 4
DAMP	Damage Associated Molecular Pattern
DC	Dendritic Cell
EANO	European Association of Neuro-Oncology
ECM	Extracellular Matrix
EGFR	Epidermal Growth Factor Receptor
ERK	Extracellular Signal-Regulated Kinase
FDA	Food and Drug Administration
GB	Glioblastoma
GFAP	Glial Fibrillary Acidic Protein
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HGF/SF	Hepatocyte Growth Factor and Scatter Factor (HGF/SF)
IDH	Isocitrate Dehydrogenase
IFN-ɣ	Interferon gama
IL	Interleukin
INCA	Instituto Nacional do Câncer José de Alencar
KPS	Karnofsky Performance Status Scale
MCP-1	Monocyte Chemoattractant Protein-1
MCP-3	Monocyte Chemoattractant Protein-3
MDSC	Myeloid-derived Suppressor Cell
NPP-1	Nucleotide Pyrophosphatase/Phosphodiesterase 1

PD-1	Programmed cell death protein 1
PIK3R1	Phosphoinositide-3-kinase Regulatory subunit 1
pmol	Picomol
PTEN	Phosphatase and Tensin Homolog
TGF-β	Transforming Growth Factor Beta
TME	Tumor Microenvironment
TNF-α	Tumor Necrosis Factor Alfa
µM	Micromolar
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

2. List of tables and figures

3. Abstract

Glioblastoma is a fatal tumor with a median survival of 15 months. Its features challenge current therapies that include surgery, chemotherapy, radiotherapy and, in some cases, immunotherapy. This is partially due to the (1) local and (2) systemic immunosuppression presented by these patients. In the local of tumor, glioblastoma cells together with immune cells, cytokines and other factors modulate the microenvironment for tumor growth and immune escape. Within this context, adenosine is a molecule that stands out as a modulator of this system, inducing a pro-tumor phenotype in the tumor microenvironment. Adenosine is mainly generated through (1) extracellular ATP through the action of NTPDases and ectonucleotidases, CD39 and CD73, respectively, or (2) through the action of CD38 from NAD^+. The convergent point between these pathways is CD73 that converts AMP is adenosine. However, in relation to systemic immunosuppression, there is a lack of evidence in the literature. This study aims to investigate the role of the adenosinergic pathway in the peripheral blood of patients with glioblastoma, due to the importance of this pathway in local immunosuppression. Considering that CD73 is a key enzyme of the adenosinergic pathway, a literature review was carried out pointing out the main relationships of CD73 in glioblastoma, as well as gaps to be elucidated. In patients, analyzes of the levels of nucleotides/nucleosides and enzymatic activity were performed in blood serum and the levels of expression of ectoenzymes and receptors associated with the adenosinergic pathway in PBMCs were evaluated. Relative to healthy controls, patients with glioblastoma do not show differences in serum levels of nucleotides and nucleosides as well as in enzyme activity. Regarding gene expression, PBMCs from patients with glioblastoma have decreased levels of NT5E, the gene that encodes CD73. Then, the effect of the treatment was evaluated, which showed no differences in the patient profile. To the best of our knowledge, this was the first study characterizing the adenosinergic profile in the serum and in PBMCs of patients with glioblastoma.

4. Resumo

O glioblastoma é um tumor fatal com uma sobrevida média de 15 meses. Suas características desafiam as terapias atuais que incluem cirurgia, quimioterapia, radioterapia e, em alguns casos, imunoterapia. Isso se deve, em parte, a imunossupressão local e sistêmica apresentada por esses pacientes. No tumor, células tumorais juntamente com células imunes, citocinas e outros fatores modulam o ambiente para o crescimento tumoral e indução de escape imune. Nesse contexto, a adenosina é uma molécula que se destaca como moduladora desse sistema induzindo um fenótipo pró-tumoral no microambiente tumoral; podendo ser gerada principalmente através de (1) ATP extracelular por meio da ação de NTPDases e ectonucleotidases, CD39 e CD73, respectivamente ou (2) através da ação da CD38 a partir de NAD^+ sendo que o ponto de convergência entre essas vias a CD73 que converte o AMP a adenosina. Todavia, em relação a imunossupressão sistêmica, pouco se sabe. Este estudo buscou investigar o papel da via adenosinérgica no sangue periférico de pacientes com glioblastoma, devido a importância dessa via na imunossupressão local. Considerando-se que a CD73 é uma enzima chave da via adenosinérgica, realizou-se uma revisão de literatura apontando as principais relações da CD73 no glioblastoma, bem como lacunas a serem elucidadas. Em pacientes, realizaram-se análises dos níveis de nucleotídeos/nucleosídeos e atividade enzimática em soro e avaliou-se os níveis de expressão de enzimas e receptores associados a via adenosinérgica em PBMCs isolados de pacientes. Em relação a controles saudáveis, pacientes com glioblastoma não apresentam diferenças nos níveis séricos de nucleotídeos e nucleosídeos bem como na atividade enzimática. Em relação a expressão de genes, pacientes com glioblastoma apresentam diminuição dos níveis de *NT5E,* gene que codifica a CD73. Em seguida, avaliou-se o efeito do tratamento que não mostrou diferenças no perfil de pacientes. Até onde sabemos, esse foi o primeiro estudo caracterizando o perfil adenosinérgico no soro e em PBMCs isolados de pacientes com glioblastoma.

5. Introduction

5.1 **Brain tumors and epidemiology**

Central nervous system (CNS) tumors come from a growth of abnormal cells in the brain and spinal cord (primary tumors) and can be either malignant or benign[1]. Metastatic tumors, or secondary tumors are caused by cancer cells that break away from a primary tumor somewhere else in your body and spread to the CNS[2]. In Brazil, Instituto Nacional do Câncer (INCA) estimated, for the 2020-2022 period, 5.870 new cases of brain tumors in men and 5.220 in women[1]. Brain cancers are not the most prevalent in the population. However, due to brain particularities, e.g., the presence of blood brain barrier (BBB) and the lack of conventional lymphatic draining, it is still a challenge to find treatment alternatives in these cases [3].

Gliomas are brain tumors that originate from glial progenitors - a type of cell that can generate astrocytes and oligodendrocytes in normal conditions and gliomas as a result of homeostasis disturbing [4] (Figure 1).

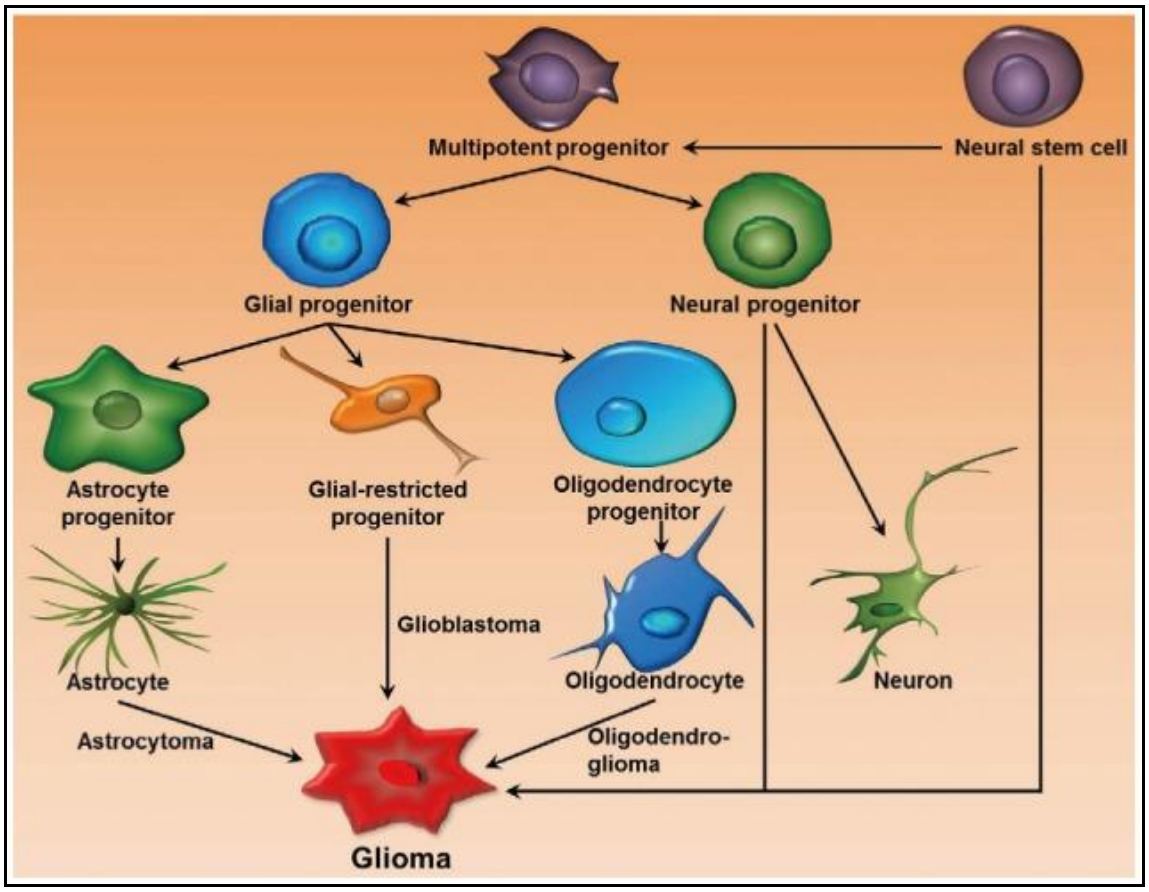

Figure 1. Glioma origins (Sutendra, 2013).

Among gliomas, glioblastoma (GB) is the most common and aggressive primary brain tumor due to its high invasiveness, the propensity to disperse throughout the brain parenchyma, and the elevated vascularity that makes these tumors extremely recidivist[5,6]. It affects around 180,000 people every year in the United States (US) and the survival rate is estimated in 15 months, while just 5% of patients survive up to 5 years after diagnosis[7]. In Brazil, glioblastoma accompted between 2.000 to 3.000 people in 2016[1]. GB are mostly IDH-wildtype tumors and occur mainly in adults after 40 years, mostly between 65 and 75 years. Its preponderance is slightly male, with a 3:2 male: female ratio[8]. Regarding ethnicities, whites are more affected than other ones[9].

5.2 Gliomas' classification

Gliomas are classified by the World Health Organization (WHO) based classically in histology[10]. The last update was in 2021 and divided diffuse gliomas into 4 types: adult-type diffuse gliomas, pediatric-type diffuse glioma low grade or high grade and circumscribed astrocytic gliomas. This

classification considers histologic features and genetic alterations, such as IDH status and 1p/19q deletion[11].

Inside adult type diffuse gliomas are included: (1) astrocytoma, IDH-mutant, (2) oligodendroglioma, IDH-mutant, and 1p/19q-codeleted and (3) glioblastoma, IDH-wild type[11]. Astrocytoma are IDH mutant and do not present 1p19q co-deletion, can be grade 2, 3 or 4 based on characteristics such as microinvasion, mitotic activity and necrosis. In opposite, oligodendrogliomas present a 1p19q co-deletion and, as astrocytoma are IDH mutant. GB, in 2016 WHO consensus could be wild type of mutant for IDH[10]. Now, with the updates only wild type are considered GB, tumors grade 4 mutant IDH enters into astrocytoma classification[11]. A summary of the classifications of adult-type diffuse gliomas are described in Table 1.

Adult type diffuse gliomas

	Astrocytoma	**Oligodendroglioma**	**Glioblastoma**
IDH	mutant	mutant	wild type
1p19q co-deletion	absent	present	—-
Grade	grade 2, 3 or 4	Grade 2 or 3	Grade 4

Table 1: Summary of adult type diffuse gliomas. (The author, 2022).

5.3 GB treatments

GB treatment options can vary depending on patient's performance (KPS score) and age[12,13]. There are some guidelines such as European Association of Neuro-Oncology (EANO) that base the clinical options (Figure 2). Basically, the available options are: (1) surgery at diagnosis, (2) chemotherapy with alkylating agent Temozolomide and (3) radiotherapy or directly palliative care if there are very unfavourable prognostic factors[13–15]. When there is a GB recurrence, the options include palliative care, reoperation, reirradiation, systemic or combined therapies[13,16]. The last approved drug by FDA was Bevacizumab, an anti-VEGF agent that acts in angiogenesis. The treatment did not result in a significant advantage to the overall survival of patients, and a decline in quality of life and neurocognitive function was observed [7,17,18]. Even with maximal efforts in safe

surgical resection and combined radio/chemotherapy, GB patients have a poor prognostic value[16,19].

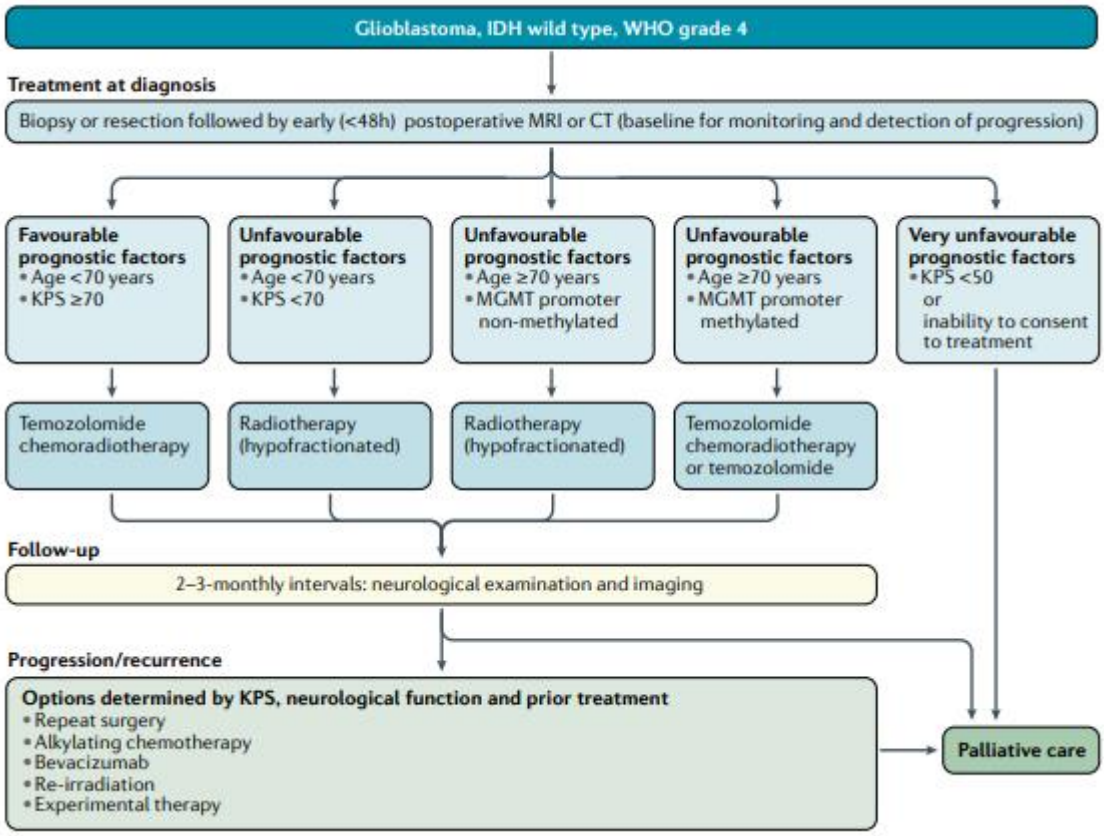

Figure 2. EANO treatment guidelines for GB (Weller *et al, 2021)*

Regarding new strategies, many therapies have been proposed, including immune checkpoint inhibitors, CAR-T cells, tumor vaccines, dendritic cells (DC) vaccines and viral gene therapy[20–23]. Despite the advances, GB keeps itself refractory to new therapies and even to immunotherapies that succeed to other types of tumor, e.g. anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab)[24].

5.4 Brain microenvironment: The physiology and alterations in GB

Brain microenvironment, physiologically, is formed mainly by BBB, neurons, glial cells, and immune cells (Figure 3)[25,26]. The BBB contributes to keeping a stable environment by regulating the transport of molecules, including oxygen, small lipophilic molecules, and glucose[27]. The microglia influence neural progenitor fate decisions, astrocyte activation, neuronal homeostasis, and synaptogenesis[28]. The astrocytes are involved with long-distance communication, information integration and metabolic support[29,30]. The immune cells in the brain are most represented by lymphocytes, regulatory T cells, and a

small percentage of infiltrating monocytes/macrophages, B cells and others, which are mainly located at meninges and choroid plexus[31].

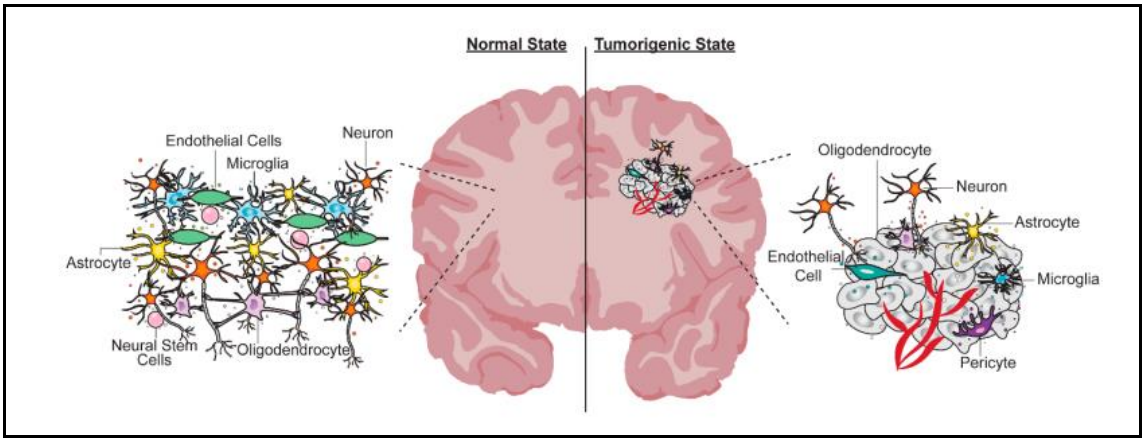

Figure 3. Normal and tumorigenic state of brain (Balakrishnan, 2020)

GB shares characteristics of glial cells, such as GFAP and vimentin expression[32,33]. As other cancers, the process of tumor development involves genetic alterations such as alterations in the tumor protein p53 (TP53) - a cell cycle checkpoint, phosphatase and tensin homolog (PTEN) - a tumor suppressor gene, epidermal growth factor receptor (EGFR) that induces proliferation and angiogenesis, and phosphoinositide- 3-kinase regulatory subunit 1 (PIK3R1); these genes acts in tumor suppressing functions [33,34]. In addition, the brain microenvironment suffers substantial changes, supporting cancer growth, promoting escape of immune surveillance, and resistance to the treatment [6,27].

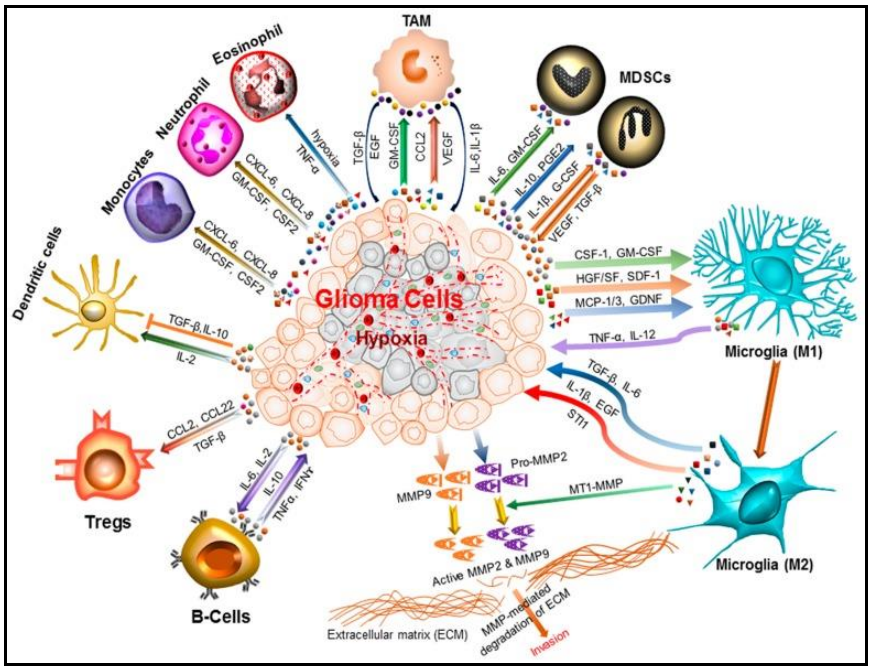

Figure 4. GB microenvironment (Mostofa, *et al*; 2017)

The BBB is altered in a way to impair the drug delivery to the tumor cells and allows changes in the microenvironment[35,36]. Indeed, the cells in tumor microenvironment (TME) assumes different roles: Resident cells, such as microglia and myeloid-derived suppressor cells (MDSCs) and peripheral cells, such as monocytes/macrophages and neutrophils, are recruited to the tumor area and a modulation happens to evade the immune system[37–41].

The microglia and TAMs are recruited by factors, e.g. monocyte chemoattractant protein-1 and 3 (MCP- 1, MCP-3), hepatocyte growth factor and scatter factor (HGF/SF), granulocyte macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor-1 (CSF-1) while secreting IL-6, IL-1β, TGF-β and others[33,42]. IL-6 promotes migration and reduces apoptosis, IL-1β is involved in proliferation, increase of ERK activity, invasiveness, and drug resistance. TNF-α, by the way, enhances invasion and its stimulation also upregulates the protein expression of ERK [43]. TGF-β and IL-8 play a role in tumor growth and angiogenesis[44,45]. IL-10 is involved in cell growth and proliferation and downregulates antigen presentation[27]. The crosstalk between tumor and immune cells, in combination with cytokines, extracellular matrix (ECM), growth factors and conditions such as hypoxia and acidosis, results in immunosuppression[27,46] (Figure 4).

5.5 Purinergic signaling and adenosinergic pathway

Purinergic signaling has emerged in the past years as an important key point to the immune evasion in GBs and other tumors[47–51]. When ATP is released in the extracellular medium, by changes in osmotic pressure, cell stress by shear or apoptosis - through cell-surface membrane channels (e.g., pannexin 1), it acts as a damage associated molecular pattern (DAMP) stimulating P2 purinergic receptors which are located on cell membrane of tumor and immune cells as well[52–54]. The P2 receptors are further classified in 2 classes: P2X (1-7) - inotropic channels, and $P2Y_{1,2,4,6,11,12,13,14}$ - G protein-coupled receptors[54,55]. P2X receptors are exclusively sensitized by ATP, while P2Y are stimulated by nucleotides of purine and pyrimidine, including ATP, ADP, UTP, and UDP[54]. When purinergic receptors are sensitized, the generated signals induce neutrophil chemotaxis, platelet aggregation, chemotaxis and activation of granulocytes, macrophages, and monocytes[56,57]. Otherwise, ATP can be converted by ectonucleotidases family: NTPDases (ecto-nucleoside triphosphate diphosphate-hydrolase) such as CD39, which hydrolyzes extracellular ATP to ADP and further to AMP, which is subsequently converted to adenosine (ADO) by ecto-5'-nucleotidase/CD73[49,58].

ADO interacts with P1 receptors, which are subdivided in four classes: A1, A2A, A2B and A3[59]. A1 receptors are expressed in neutrophils and immature DCs and are involved with neutrophil chemotaxis[30,56]. A2A is expressed in most immune cells and platelets promoting immunosuppressive/immunomodulatory responses in immune cells and preventing platelet aggregation[47,60]. A2B is expressed in macrophages, DCs and mast cells promoting IL-6 and VEGF release by macrophages and DCs and drives mast cell degranulation[15,61,62]. Finally, A3 is also expressed in neutrophils and mast cells reducing the neutrophil chemotaxis and stimulating mast cells degranulation[56,61,63,64].

The purinergic signaling corresponds to canonical pathway of ADO production[65]. Non canonical pathway comes from NAD^+ and it is converted to ADPR, through the action of CD38 and from AMP by NPP-1CD203a/PC-1[65]. Again, CD73 catalyses the conversion of AMP to ADO connecting both pathways[65,66]. Finally, ADO can be converted to inosine by ADA[59,67,68]. An overview of adenosinergic pathway is showed in Figure 5.

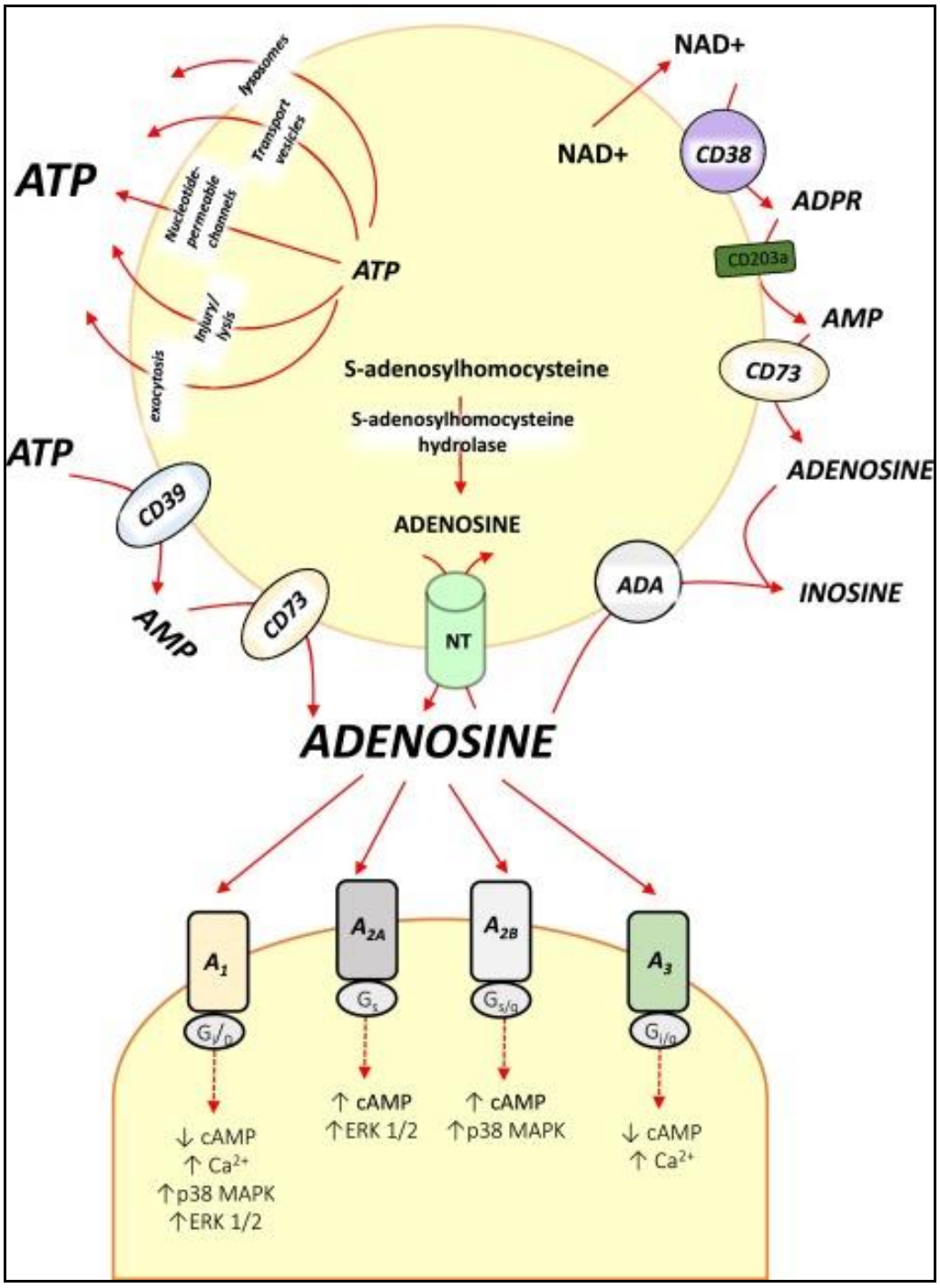

Figure 5. Adenosinergic pathway (Antonioli *et al,* 2018)

5.6 Adenosine modulatory effects in GB

ADO, in general, antagonizes the pro-inflammatory response of ATP[17]. In physiological conditions, ADO reduces tissue injury in cellular stress to keep the tissue homeostasis[47]. However, in TME ADO accumulates causing dysregulation of immune cell subtypes performing an overall immunosuppression (Figure 6)[18].

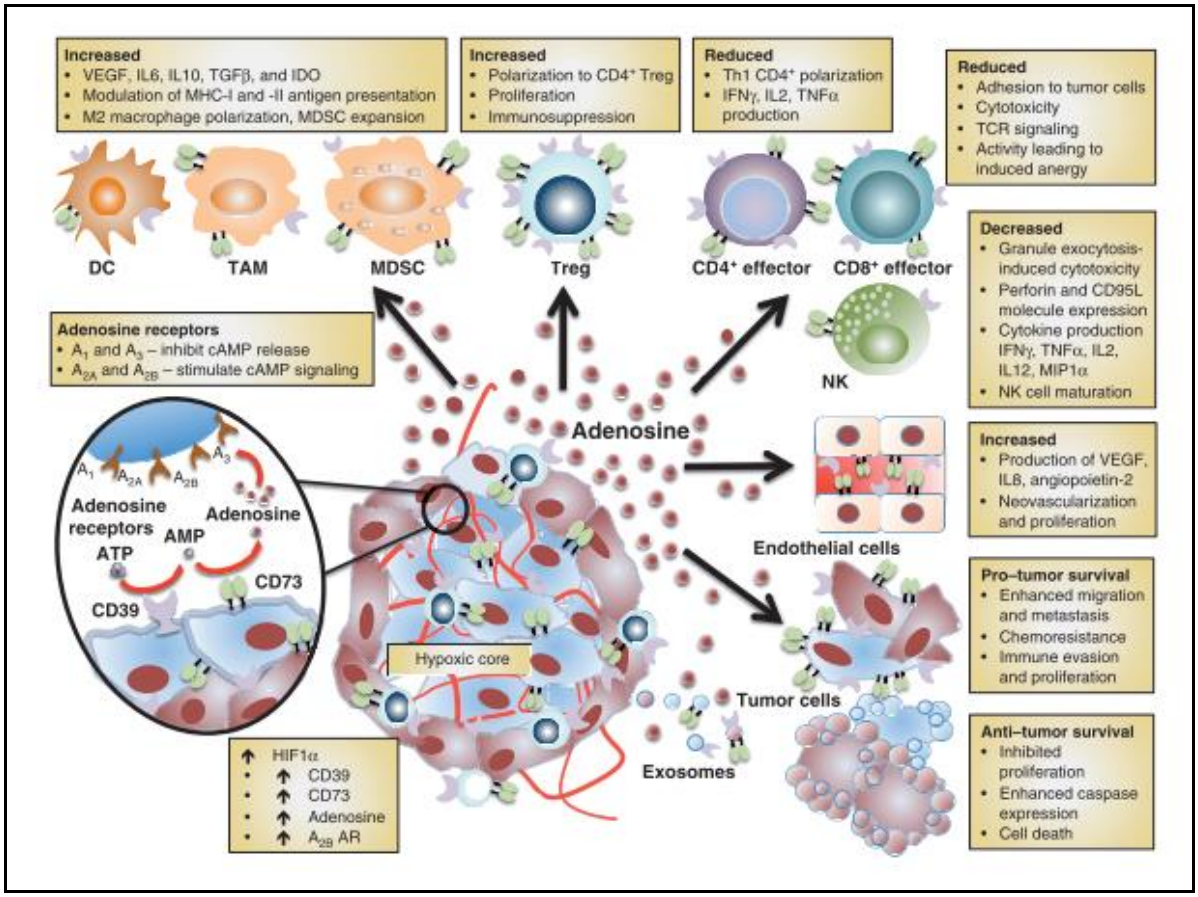

Figure 6. Adenosine mediated pro-tumor effects (Young *et al*, 2014)

Myeloid cells are polarized by ADO and develop a protumoral phenotype: macrophages assume a M2 phenotype, dendritic cells modify the antigen presentation and MDSC cell population is expanded [41,69–72].

In lymphoid population, lymphocytes are polarized to Treg, there is a reduction in T helper and T cytotoxic population and there are changes in cytokine environment: decrease of inflammatory cytokines, e.g., IFN-ɣ, IL-2 and TNF-α and increased production of VEGF and IL-8 contributing to a impairment in antitumor response and tumor growth [30,37,47,48,69,73].

In addiction, GB produces exosomes containing ADO and CD73 that could regulate distant sites that not comprises the TME[69].

5.7 Systemic immunosuppression in GB

Despite the advances in understanding the local immunosuppression in GB, these patients also present a profound systemic immunosuppression that is not well understood[74,75].

GB patients present reduced T cell counts and functionality[76]. In addition, they have small spleens compared to healthy volunteers and their blood-derived monocytes have lower class II MHC expression levels[37,77].

Preclinical GBM models also found reduced CD4 T cell counts in mice[78,79]. Ayasoufi *et al* (2020) extensively studied immune organs and found different facets of immunosuppression in GB including thymic and spleen involution, lost of CD4 and CD8 T cells from circulation, downregulation of MHCII on hematopoietic cells, release of non-steroid immunosuppressive factors with large molecular weight in serum that block proliferation of cells, and phenotypic changes in resident T cells in bone marrow [79].

In patients, Zisaski and colleagues (2007) have demonstrated a Th2 profile in lymphocytes from GB patients [80]. Vasco and colleagues (2013) showed that supernatants collected from GB cell lines were more attractant to T regulatory lymphocytes (Treg) when compared to complete standard medium in a MCP-1 (CCL-2) dependent way [73]. Recent studies found that patients with GB have MDSCs increased in peripheral blood, CD73 high $CD4^+$ T cells, presents the soluble form of CD73 and showed increased A2A receptors [72,81].

5.8 Hypothesis and objective

Our group is interested in the immune microenvironment and purinergic signaling in immunosuppressive GB periphery. Preliminary data showed that in the patients the immunosuppressive status in the peripheral blood with elevated levels of IL-10 and MCP-1 persists after removal of tumor by surgery and treatment (unpublished data). These data combined with previous literature presented above indicate that the periphery contributes to poor patients' prognosis. New checkpoints are emerging, especially the "CD39-CD73-ADO-P1 Receptors" axis in GB, demonstrated by our group and others [59,63,82,83].

Based on the TME, that shows high levels of ADO combined with the data that GB patients presents exosomes containing ADO, CD39 and CD73, we hypothesize that this axis can be altered not just in the local TME but in the peripheral system. This work objective is to explore what is the role of the adenosinergic signaling pathway for the establishment and maintenance of the peripheral immunosuppression associated with GB: to this we aim to characterize the adenosinergic pathway in peripheral blood of GB patients.

6. Conclusion

At the end of this study, we have reviewed CD73 roles and explored new insights about immunosuppression axis in GB by a literature review. CD73 presents multiple roles in GB, especially through adenosine production and its

interaction with P1 receptors including migration, cell growth, EMT, immune escape, modulation of immune cells, etc. Due to this, research modulating the axis “CD39-CD73-P1 receptors” emerged in literature. Some of them, such as NE-siRNA-CD73 have been deeply investigated and are closer to clinical trials, while the majority have been tested only in *in vitro* assays [82-83]. In addiction, the recent discovery of TEVs open new possibilities to modulate this axis [69]. This review can be used by us and others to define future research in this field, focusing on the points that need further investigation, optimizing time and financial resources.

While most studies focus on ADO modulation in TME, few is known about this pathway systemically in GB context. We characterized the adenosinergic signaling in peripheral blood of GB patients and not found enormous differences between GB patients and healthy people. In addiction, the surgery and RT did not produce significant changes on this pathway. To the best of our knowledge, this study was a pioneer and established a baseline of this patients to serve as a basis of comparison.

In this study we found some divergences with other that have seen differences in peripheral blood cells, especially T cells [43]. This divergence because we used serum samples that could not detect effects of lower magnitude.

Other interesting finding is the huge variability between different individuals. Explore the role of individual cells in this pathway could help to explain the changes observed here.

Finally, more research would be useful specially to test in a protein level the findings into molecular biology field and to confirm if ADO production could be used as a predictor of survival.

7. Perspectives

Perspectives of this work include:

1) Evaluate the molecular biology findings by other techniques to confirm the protein expression (Flow cytometry)

2) Compare the findings with available databanks of patients
3) Study the specific blood cells status of adenosinergic pathway using *in vitro* models and/or primary cultures

8. References

1. Instituto Nacional de Câncer José Alencar Gomes da Silva/ Ministério da Saúde. *Estimativa 2020 Incidência de Câncer no Brasil*. *News.Ge* (2019).
2. Tumors, S. C., Therapy, R., Therapy, T., Therapy, C. & Conditions, T.

Brain and Spinal Cord Tumors : Hope Through Research What are Brain and Spinal Cord. 1–13 (2022).

3. Dutoit, V., Migliorini, D., Dietrich, P. Y. & Walker, P. R. Immunotherapy of malignant tumors in the brain: How Different from other sites? *Frontiers in Oncology* vol. 6 (2016).
4. Sutendra, G. & Michelakis, E. D. Pyruvate dehydrogenase kinase as a novel therapeutic target in oncology. *Front. Oncol.* **3 MAR**, 57–63 (2013).
5. Schwartzbaum, J. *et al.* Article in Nature Clinical Practice Neurology. (2006) doi:10.1038/ncpneuro0289.
6. D'Alessio, A., Proietti, G., Sica, G. & Scicchitano, B. M. Pathological and molecular features of glioblastoma and its peritumoral tissue. *Cancers* vol. 11 469 (2019).
7. Tan, A. C. *et al.* Management of glioblastoma: State of the art and future directions. *CA. Cancer J. Clin.* **70**, 299–312 (2020).
8. Wolfgang Dähnert. *Radiology Review Manual*. (2003).
9. Louis, D. N. *et al.* The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol.* **114**, 97–109 (2007).
10. Louis, D. N. *et al.* The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* **131**, 803–820 (2016).
11. Whitfield, B. T. & Huse, J. T. Classification of adult-type diffuse gliomas: Impact of the World Health Organization 2021 update. *Brain Pathol.* **32**, 1–12 (2022).
12. Mrugala, M. M. Advances and challenges in the treatment of glioblastoma: a clinician's perspective. *Discovery medicine* (2013).
13. Weller, M. *et al.* EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat. Rev. Clin. Oncol.* **18**, 170–186 (2021).
14. Stupp, R. *et al.* Radiotherapy plus Concomitant\nand Adjuvant Temozolomide for Glioblastoma. *N. Engl. J. Med.* (2005) doi:10.1056/NEJMoa043330.
15. Arab, S. & Hasannejad, F. An overview of current therapeutic strategies for glioblastoma and the role of CD73 as an alternative curative approach. *Clin. Transl. Oncol.* **24**, 742–756 (2022).
16. Fernandes C, Costa A, Osório L, et al. Current Standards of Care in

Glioblastoma Therapy. *Codon Publ.* (2017).

17. Jin, K. *et al.* Review adenosinergic pathway: A hope in the immunotherapy of glioblastoma. *Cancers* vol. 13 1–21 (2021).
18. Ott, M. *et al.* Profiling of patients with glioma reveals the dominant immunosuppressive axis is refractory to immune function restoration. *JCI Insight* **5**, 1–17 (2020).
19. Andreucci, E. *et al.* The acidic tumor microenvironment drives a stem-like phenotype in melanoma cells. *J. Mol. Med.* (2020) doi:10.1007/s00109-020-01959-y.
20. Dutoit, V., Migliorini, D., Dietrich, P. Y. & Walker, P. R. Immunotherapy of malignant tumors in the brain: How Different from other sites? *Front. Oncol.* **6**, (2016).
21. Bushey, R. T. *et al.* A Therapeutic Antibody for Cancer, Derived from Single Human B Cells. *Cell Rep.* **15**, 1505–1513 (2016).
22. Augustin, R. C. *et al.* Next steps for clinical translation of adenosine pathway inhibition in cancer immunotherapy. *J. Immunother. Cancer* **10**, 1–13 (2022).
23. Li, R.-H. *et al.* Temozolomide for Treating Malignant Melanoma. *J. Coll. Physicians Surg. Pak.* **25**, 680–8 (2015).
24. Kamath, S. D. & Kumthekar, P. U. Immune Checkpoint Inhibitors for the Treatment of Central Nervous System (CNS) Metastatic Disease. *Front. Oncol.* (2018) doi:10.3389/fonc.2018.00414.
25. Vasile, F., Dossi, E. & Rouach, N. Human astrocytes: structure and functions in the healthy brain. *Brain Structure and Function* vol. 222 2017–2029 (2017).
26. Schuurmans, C., Balakrishnan, A., Roy, S., Fleming, T. & Leong, H. S. The emerging role of extracellular vesicles in the glioma microenvironment: Biogenesis and clinical relevance. *Cancers (Basel).* **12**, 1–25 (2020).
27. Da Ros, M. *et al.* Glioblastoma chemoresistance: the double play by microenvironment and blood-brain barrier. *International Journal of Molecular Sciences* vol. 19 (2018).
28. Wright-Jin, E. C. & Gutmann, D. H. Microglia as Dynamic Cellular Mediators of Brain Function. *Trends in Molecular Medicine* vol. 25 967–

979 (2019).

29. Holland, E. C. Progenitor cells and glioma formation. *Current Opinion in Neurology* (2001) doi:10.1097/00019052-200112000-00002.
30. Debom, G. N., Rubenich, D. S. & Braganhol, E. Adenosinergic Signaling as a Key Modulator of the Glioma Microenvironment and Reactive Astrocytes. *Front. Neurosci.* **15**, 1–14 (2022).
31. Korin et al, 2017 _ infiltrado imune naive brain.pdf.
32. Madhunapantula, S. R. V., Mosca, P. J. & Robertson, G. P. The Akt signaling pathway: An emerging therapeutic target in malignant melanoma. *Cancer Biology and Therapy* (2011) doi:10.4161/cbt.12.12.18442.
33. Mostofa, A. G. M., Punganuru, S. R., Madala, H. R., Al-Obaide, M. & Srivenugopal, K. S. The process and regulatory components of inflammation in brain oncogenesis. *Biomolecules* **7**, 1–33 (2017).
34. Huse, J. T. & Holland, E. C. Targeting brain cancer: Advances in the molecular pathology of malignant glioma and medulloblastoma. *Nature Reviews Cancer* vol. 10 319–331 (2010).
35. Pardridge, W. M. Blood-brain barrier delivery. *Drug Discovery Today* vol. 12 54–61 (2007).
36. Hitchcock, S. A. Blood-brain barrier permeability considerations for CNS-targeted compound library design. *Current Opinion in Chemical Biology* vol. 12 318–323 (2008).
37. Grabowski, M. M. *et al.* Immune suppression in gliomas. *J. Neurooncol.* **151**, 3–12 (2021).
38. Dapash, M., Hou, D., Castro, B., Lee-Chang, C. & Lesniak, M. S. The interplay between glioblastoma and its microenvironment. *Cells* **10**, 1–14 (2021).
39. Ali, S. *et al.* Changes in the tumor microenvironment and outcome for TME-targeting therapy in glioblastoma: A pilot study. *PLoS One* **16**, 1–23 (2021).
40. Holl, E. K. *et al.* Examining Peripheral and Tumor Cellular Immunome in Patients With Cancer. *Front. Immunol.* **10**, 1767 (2019).
41. Rodrigues, J. C. *et al.* Normal human monocytes exposed to glioma cells acquire myeloid-derived suppressor cell-like properties. *Neuro. Oncol.* **12**,

351–365 (2010).

42. Vasco, C. *et al.* Circulating T regulatory cells migration and phenotype in glioblastoma patients: An in vitro study. *J. Neurooncol.* **115**, 353–363 (2013).
43. Ramaswamy, P., Goswami, K., Dalavaikodihalli Nanjaiah, N., Srinivas, D. & Prasad, C. TNF-α mediated MEK–ERK signaling in invasion with putative network involving NF-κB and STAT-6: a new perspective in glioma. *Cell Biol. Int.* **43**, 1257–1266 (2019).
44. Seystahl, K. *et al.* Biological role and therapeutic targeting of TGF-b3 in glioblastoma. *Mol. Cancer Ther.* **16**, 1177–1186 (2017).
45. Yeung, Y. T., McDonald, K. L., Grewal, T. & Munoz, L. Interleukins in glioblastoma pathophysiology: Implications for therapy. *British Journal of Pharmacology* vol. 168 591–606 (2013).
46. Seano, G. Targeting the perivascular niche in brain tumors. *Current Opinion in Oncology* vol. 30 54–60 (2018).
47. Young, A., Mittal, D., Stagg, J. & Smyth, M. J. Targeting cancer-derived adenosine: New therapeutic approaches. *Cancer Discovery* vol. 4 879–888 (2014).
48. Yegutkin, G. G. *et al.* Altered purinergic signaling in CD73-deficient mice inhibits tumor progression. *Eur. J. Immunol.* **41**, 1231–1241 (2011).
49. Ceruti, S. & Abbracchio, M. P. Adenosine Signaling in Glioma Cells. *Adv. Exp. Med. Biol.* **1202**, 13–33 (2020).
50. Gao, Z. W., Dong, K. & Zhang, H. Z. The roles of CD73 in cancer. *Biomed Res. Int.* **2014**, (2014).
51. Coy, S. *et al.* Single cell spatial analysis reveals the topology of immunomodulatory purinergic signaling in glioblastoma. *Nat. Commun.* **13**, (2022).
52. Gaudreau, P.-O., Allard, B., Turcotte, M. & Stagg, J. CD73-adenosine reduces immune responses and survival in ovarian cancer patients. *Oncoimmunology* (2016) doi:10.1080/2162402X.2015.1127496.
53. Chekeni, F. B. *et al.* Pannexin 1 channels mediate 'find-me' signal release and membrane permeability during apoptosis. *Nature* **467**, 863–867 (2010).
54. Burnstock, G. Introductory overview of purinergic signalling. *Front. Biosci.*

- *Elit.* **3 E**, 896–900 (2011).

55. Di Virgilio, F., Sarti, A. C., Falzoni, S., De Marchi, E. & Adinolfi, E. Extracellular ATP and P2 purinergic signalling in the tumour microenvironment. *Nature Reviews Cancer* vol. 18 601–618 (2018).
56. Cekic, C. & Linden, J. Purinergic regulation of the immune system. *Nature Reviews Immunology* vol. 16 177–192 (2016).
57. Manica, A. *et al.* High levels of extracellular ATP lead to chronic inflammatory response in melanoma patients. *J. Cell. Biochem.* **119**, 3980–3988 (2018).
58. Stagg, J. *et al.* CD73-Deficient Mice Have Increased Antitumor Immunity and Are Resistant to Experimental Metastasis. *Cancer Res.* **71**, 2892–2900 (2011).
59. Antonioli, L., Yegutkin, G. G., Pacher, P., Blandizzi, C. & Haskó, G. Anti-CD73 in Cancer Immunotherapy: Awakening New Opportunities. *Trends in Cancer* (2016) doi:10.1016/j.trecan.2016.01.003.
60. Ohta, A. A metabolic immune checkpoint: Adenosine in Tumor Microenvironment. *Frontiers in Immunology* (2016) doi:10.3389/fimmu.2016.00109.
61. Borea, P. A., Gessi, S., Merighi, S. & Varani, K. Adenosine as a Multi-Signalling Guardian Angel in Human Diseases: When, Where and How Does it Exert its Protective Effects? *Trends Pharmacol. Sci.* **37**, 419–434 (2016).
62. Chen, S. *et al.* The expression of adenosine A2B receptor on antigen-presenting cells suppresses CD8+T-cell responses and promotes tumor growth. *Cancer Immunol. Res.* **8**, 1064–1074 (2020).
63. Quezada, C. *et al.* 5′-Ectonucleotidase Mediates Multiple-Drug Resistance in Glioblastoma Multiforme Cells. *J. Cell. Physiol.* **228**, 602–608 (2013).
64. Borea, P. A., Gessi, S., Merighi, S., Vincenzi, F. & Varani, K. Pharmacology of adenosine receptors: The state of the art. *Physiol. Rev.* **98**, 1591–1625 (2018).
65. Ferretti, E., Horenstein, A. L., Canzonetta, C., Costa, F. & Morandi, F. Canonical and non-canonical adenosinergic pathways. *Immunology Letters* vol. 205 25–30 (2019).

66. Wang, B. *et al.* The role of extracellular-5′-nucleotidase/CD73 in glioma peritumoural brain edema. *Neurol. Sci.* **37**, 603–611 (2016).
67. Giusti, G. & Gakis, C. Temperature conversion factors, activation energy, relative substrate specificity and optimum pH of adenosine deaminase from human serum and tissues. *Enzyme* **12**, 417–425 (1971).
68. Zhulai, G., Oleinik, E., Shibaev, M. & Ignatev, K. Adenosine-Metabolizing Enzymes, Adenosine Kinase and Adenosine Deaminase, in Cancer. *Biomolecules* **12**, 1–18 (2022).
69. Azambuja, J. H. *et al.* Molecular profiles and immunomodulatory activities of glioblastoma-derived exosomes. *Neuro-Oncology Adv.* **2**, 1–11 (2020).
70. Novitskiy, S. V. *et al.* Adenosine receptors in regulation of dendritic cell differentiation and function. *Blood* **112**, 1822–1831 (2008).
71. Kohanbash, G. & Okada, H. Myeloid-derived Suppressor Cells (MDSCs) in gliomas and glioma-development. *Immunol. Invest.* **41**, 658–679 (2012).
72. Alban, T. J. *et al.* Global immune fingerprinting in glioblastoma patient peripheral blood reveals immune-suppression signatures associated with prognosis. *JCI insight* **3**, (2018).
73. Vasco, C. *et al.* Circulating T regulatory cells migration and phenotype in glioblastoma patients: An in vitro study. *J. Neurooncol.* **115**, 353–363 (2013).
74. Himes, B. T. *et al.* Immunosuppression in Glioblastoma: Current Understanding and Therapeutic Implications. *Front. Oncol.* **11**, 1–11 (2021).
75. Parney, I. F. Chapter 4 Basic Concepts. 97–112 (2012).
76. Waziri, A. Glioblastoma-Derived Mechanisms of Systemic Immunosuppression. *Neurosurg. Clin. N. Am.* **21**, 31–42 (2010).
77. Gustafson, M. P. *et al.* Systemic immune suppression in glioblastoma: The interplay between CD14 +HLA-DR lo/neg monocytes, tumor factors, and dexamethasone. *Neuro. Oncol.* **12**, 631–644 (2010).
78. Chongsathidkiet, P. *et al.* HHS Public Access. **24**, 1459–1468 (2019).
79. Ayasoufi, K. *et al.* Brain cancer induces systemic immunosuppression through release of non-steroid soluble mediators. *Brain* **143**, 3629–3652 (2020).

80. Zisakis, A. *et al.* Comparative analysis of peripheral and localised cytokine secretion in glioblastoma patients. *Cytokine* **39**, 99–105 (2007).
81. Zhang, Z. *et al.* Interleukin 10 promotes growth and invasion of glioma cells by up-regulating KPNA 2 in vitro. *J. Cancer Res. Ther.* **15**, 927–932 (2019).
82. Azambuja, J. H. *et al.* Nasal Administration of Cationic Nanoemulsions as CD73-siRNA Delivery System for Glioblastoma Treatment: a New Therapeutical Approach. *Mol. Neurobiol.* (2019) doi:10.1007/s12035-019-01730-6.
83. Azambuja, J. H. *et al.* CD73 Downregulation Decreases In Vitro and In Vivo Glioblastoma Growth. (2018).

9. Appendix

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Determinação de uma assinatura imune em glioblastoma
Pesquisador: Elizandra Braganhol
Área Temática:
Versão: 4
CAAE: 78664117.0.0000.5345
Instituição Proponente: Universidade Federal de Ciências da Saúde de Porto Alegre
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.204.937

Apresentação do Projeto:
Trata-se de emenda com a finalidade de incluir pacientes do hospital São José e do hospital Santa Rita da ISCMPA.

Objetivo da Pesquisa:
Inclusão de pacientes dos hospitais São José e Santa Rita

Avaliação dos Riscos e Benefícios:
Não há

Comentários e Considerações sobre a Pesquisa:
Não há

Considerações sobre os Termos de apresentação obrigatória:
Apresentados adequadamente

Conclusões ou Pendências e Lista de Inadequações:
Aprovado

Considerações Finais a critério do CEP:
De acordo com o parecer do Relator.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1274581_E1.pdf	18/01/2019 21:16:11		Aceito
Outros	FORMULARIODEPROJETOSDEPESQUISA.pdf	18/01/2019 20:54:48	ALINE MORAES DE ABREU	Aceito
Outros	FORMULARIODECADASTRODEPROJETOSNAUNIDADEDEPESQUISA.pdf	18/01/2019 20:54:15	ALINE MORAES DE ABREU	Aceito
Outros	DECLARACAODEUTILIZACAODEDADOSDEPRONTUARIOEUSODEPUBLICACAO.pdf	18/01/2019 20:52:47	ALINE MORAES DE ABREU	Aceito
Outros	DECLARACAODEISENCAODEONUSAINSTITUICAO.pdf	18/01/2019 20:51:21	ALINE MORAES DE ABREU	Aceito
Outros	DECLARACAODECONFIDENCIALIDADE.pdf	18/01/2019 20:50:59	ALINE MORAES DE ABREU	Aceito
Outros	DECLARACAODECOMPROMISSOPARAUTILIZACAODEDADOSDEMATERIALBIOLOGICO.pdf	18/01/2019 20:50:08	ALINE MORAES DE ABREU	Aceito
Outros	DECLARACAODACHEFIARESPONSAVEL.pdf	18/01/2019 20:48:13	ALINE MORAES DE ABREU	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_ISCMPA.pdf	11/12/2018 11:46:30	Elizandra Braganhol	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_GBMCEP_ISCM.pdf	11/12/2018 11:46:03	Elizandra Braganhol	Aceito
Outros	anuenciaHDP.pdf	10/03/2018 05:58:46	Elizandra Braganhol	Aceito
Outros	CartaCEPR2.pdf	10/03/2018 05:57:10	Elizandra Braganhol	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEreadequadoR2.pdf	10/03/2018 05:56:35	Elizandra Braganhol	Aceito
Projeto Detalhado / Brochura Investigador	ProjGBMCEPR2.pdf	10/03/2018 05:54:16	Elizandra Braganhol	Aceito
Outros	CartaanuenciaGliomasPF.pdf	02/01/2018 02:26:09	Elizandra Braganhol	Aceito
Outros	Termo_entrega_relatorio.pdf	09/10/2017 17:08:24	Elizandra Braganhol	Aceito
Folha de Rosto	folha_rosto_assinada.pdf	16/06/2017 14:45:59	Elizandra Braganhol	Aceito

Situação do Parecer:

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Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 18 de Março de 2019

Assinado por:
Luciane Dalcanale Moussalle
(Coordenador(a))

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Currículo Lattes

Imprimir currículo

Nicolly Espindola Gelsleichter

Endereço para acessar este CV: **http://lattes.cnpq.br/9491161182519535**

Última atualização do currículo em 29/09/2022

Resumo informado pelo autor

Possui curso Técnico em Química pelo Instituto Federal de Santa Catarina (IFSC) e Bacharelado em Biomedicina pela Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) habilitada nas áres de Patologia Clínica (Análises Clínicas) e Farmacologia. Recebeu os prêmios de Menção Honrosa na Olimpíada Catarinense de Química, Trabalho Destaque no IV Encontro do PPG Biociências e 17º Prêmio Destaque na Iniciação Científica e Tecnológica do CNPq. Possui experiência nas áreas de biologia celular e molecular onde atuou durante a graduação na iniciação científica e em Pesquisa Clínica onde atuou como Coordenadora de Estudos no centro de Pesquisa Clínica Novos Tratamentos em Câncer na Santa Casa de Porto Alegre. Atualmente é aluna de mestrado no PPG-Biociências da UFCSPA e atua nas áreas de biologia celular e imunologia do câncer.

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Formação acadêmica/titulação

2021 Mestrado em BIOCIÊNCIAS.
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil
Orientador: Elizandra Braganhol

2016 - 2021 Graduação em Biomedicina.
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil
Título: Formulações de base nanotecnológica para o tratamento de melanoma
Orientador: Elizandra Braganhol

2012 - 2016 Ensino Profissional de nível técnico em Curso Técnico em Química.
Instituto Federal de Santa Catarina, IFSC, Florianopolis, Brasil

2012 - 2016 Ensino Médio (2o grau) .
Instituto Federal de Santa Catarina, IFSC, Florianopolis, Brasil

2006 - 2010 Ensino Fundamental (1o grau) .
EEB Prefeito Avelino Muller, EEB%20AM, Brasil, Ano de obtenção: 2010

Formação complementar

2021 - 2021 Extensão universitária em Ação de Testagem de RT-PCR na modalidade Drive Thru. (Carga horária: 48h).
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil

2020 - 2020 Curso de curta duração em XII Curso de Verão de Pesquisa em Oncologia. (Carga horária: 80h).
Instituto Nacional de Câncer, INCA, Rio De Janeiro, Brasil

2019 - 2019 Curso de curta duração em Procedimentos administrativos dos CEPs. (Carga horária: 2h).
Hospital Moinhos de Vento, HMV, Porto Alegre, Brasil

2019 - 2019 Histórico do Sistema CEP/Conep. . (Carga horária: 2h).
Hospital Moinhos de Vento, HMV, Porto Alegre, Brasil

2019 - 2019 Curso de curta duração em Marcos Regulatórios do Sistema CEP/Conep para o processo de análise ética. (Carga horária: 2h).
Hospital Moinhos de Vento, HMV, Porto Alegre, Brasil

2019 - 2019 Curso de curta duração em Como escrever artigos de revisão. (Carga horária: 3h).
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil

2018 - 2018 Curso de curta duração em III Evento de Extensão em Urinálise. (Carga horária: 6h).
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil

2017 - 2017 Curso de curta duração em Liga de Emergência e Trauma da UFCSPA 2017.1- Módulo de Primeiros Socorros. (Carga horária: 8h).
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil

2017 - 2017 Curso de curta duração em Quantificação de imagens. (Carga horária: 3h).
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil

2017 - 2017 Curso de curta duração em Curso para tutores do Museu de Anatomia. (Carga horária: 8h).
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil

2017 - 2017 Extensão universitária em Museu de Anatomia. (Carga horária: 45h).
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil

2017 - 2017 Curso de curta duração em Talks in Clinical Lab. (Carga horária: 4h).
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil

2017 - 2017 Curso de curta duração em Terapêutica do RNA. (Carga horária: 8h).
Sociedade Brasileira de Bioquímica e Biologia Molecular, SBBQ, Sao Paulo, Brasil

2016 - 2016 Extensão universitária em Campanha de Vacinação da gripe/H1N1. (Carga horária: 8h).
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil

2016 - 2016 Curso de curta duração em Introdução aos Equipamentos e Procedimentos Avançados na Biomedicina Estét. (Carga horária: 4h).
Associação Brasileira de Biomedicina, ABBM, Sao Paulo, Brasil

2016 - 2016 Oficina de autorregulação da aprendizagem: Como melhorar meu desempenho?. . (Carga horária: 10h).
Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, Brasil

2016 - 2016 Curso de curta duração em Toxicologia: Técnicas Toxicológicas para uso laboratório clínico. (Carga horária: 4h).
Associação Brasileira de Biomedicina, ABBM, Sao Paulo, Brasil

2015 - 2015 Curso de curta duração em Implantação de sistemas de gestão da qualidade: RDC 48/2013 - cosméticos e. (Carga horária: 8h).
Conselho Regional de Química XIII Região, CRQ XIII, Florianopolis, Brasil

2014 - 2014 Inglês Comunicativo - Intermediário II. . (Carga horária: 144h).
Ways Cursos de Inglês, WAYS, Brasil

Atuação profissional

1. Instituto Federal de Santa Catarina - IFSC

Vínculo institucional

2014 - 2014 Vínculo: Bolsista , Enquadramento funcional: Tratamento de Resíduos de análise de Fosfato , Carga horária: 8, Regime: Parcial
Outras informações:
Bolsa de pesquisa realizada no laboratório de química do Instituto Federal de Santa Catarina. O projeto visou encontrar uma alternativa ao tratamento dos efluentes da análise de fosfato.

2. Laboratório Controller - CONTROLLER

Vínculo institucional

2014 - 2014 Vínculo: Estagiário , Enquadramento funcional: Controle de qualidade microbiológica , Carga horária: 24, Regime: Parcial
Outras informações:
O estágio envolveu a rotina de controle de qualidade microbiológico (pesquisa de microorganismos patogênicos) de produtos de higiene pessoal, cosméticos, medicamentos, análises de água e ar.

3. Fundação Universidade Federal de Ciências da Saúde de Porto Alegre - UFCSPA

Vínculo institucional

2019 - Atual Vínculo: Bolsista , Enquadramento funcional: Bolsista de Iniciação Científica , Carga horária: 20, Regime: Parcial

2018 - 2019 Vínculo: Bolsista , Enquadramento funcional: Bolsista de iniciação científica , Carga horária: 20, Regime: Parcial

2017 - 2018 Vínculo: Bolsista , Enquadramento funcional: Bolsista de Inovação e Iniciação Tecnológica , Carga horária: 20, Regime: Parcial
Outras informações:
Projeto: Avaliação do potencial terapêutico de formulações lipossomais contendo RNA de interferência para a ecto-5´-nucleotidase/CD73 para o tratamento de gliomas.

2016 - 2017 Vínculo: Bolsista , Enquadramento funcional: Bolsista de Iniciação Científica , Carga horária: 20, Regime: Parcial
Outras informações:
Projeto de Pesquisa: Expressão dos receptores P2X7, P2Y2 e P2Y6 em neutrófilos durante a sepse grave e choque séptico

4. Université Laval - ULAVAL

Vínculo institucional

2018 - 2018 Vínculo: Estagiário , Enquadramento funcional: Research Internship , Carga horária: 40, Regime: Integral
Outras informações:
Project: Identification of novel ectonucleotidase inhibitors Host Professor: Jean Sévigny

5. Novos Tratamentos em Câncer - Centro de Pesquisa Clínica - NTC

Vínculo institucional

2019 - 2021 Vínculo: Celetista , Enquadramento funcional: Assistente de Pesquisa/Coordenadora de Estudo , Carga horária: 40, Regime: Integral

2019 - 2019 Vínculo: Estagiário , Enquadramento funcional: Estagiário , Carga horária: 30, Regime: Parcial

Producão

Produção bibliográfica

Artigos completos publicados em periódicos

1. doi AZAMBUJA, J. H.; **GELSLEICHTER, N. E.**; BECKENKAMP, L. R.; ISER, I. C.; FERNANDES, M. C.; FIGUEIRÓ, F.; BATTASTINI, A. M. O.; SCHOLL, J. N.; DE OLIVEIRA, F. H.; SPANEVELLO, R. M.; SÉVIGNY, JEAN; WINK, M. R.; STEFANI, M. A.; TEIXEIRA, H. F.; BRAGANHOL, ELIZANDRA
CD73 Downregulation Decreases In Vitro and In Vivo Glioblastoma Growth. MOLECULAR NEUROBIOLOGY. JCR, v.56, p.3260 - 3279, 2019.

2. doi AZAMBUJA, J. H.; SCHUH, R. S.; MICHELS, L. R.; **GELSLEICHTER, N. E.**; BECKENKAMP, L. R.; ISER, I. C.; LENZ, G. S.; DE OLIVEIRA, F. H.; VENTURIN, G.; GREGGIO, S.; DACOSTA, J. C.; WINK, M. R.; SEVIGNY, J.; STEFANI, M. A.; BATTASTINI, A. M. O.; TEIXEIRA, H. F.; BRAGANHOL, E.
Nasal Administration of Cationic Nanoemulsions as CD73-siRNA Delivery System for Glioblastoma

Treatment: a New Therapeutical Approach. MOLECULAR NEUROBIOLOGY. JCR, v.01730, p.10.1007/s12035 - , 2019.

3. doi FERREIRA, LUANA MOTA; AZAMBUJA, JULIANA HOFSTATTER; DA SILVEIRA, ELITA FERREIRA; MARCONDES SARI, MARCEL HENRIQUE; DA CRUZ WEBER FULCO, BRUNA; COSTA PRADO, VINICIUS; **GELSLEICHTER, NICOLLY ESPINDOLA**; BECKENKAMP, LIZIANE RAQUEL; DA CRUZ FERNANDES, MARILDA; SPANEVELLO, ROSÉLIA MARIA; WINK, MARCIA ROSÂNGELA; DE CASSIA SANT ANNA ALVES, RITA; NOGUEIRA, CRISTINA WAYNE; BRAGANHOL, ELIZANDRA; CRUZ, LETÍCIA
Antitumor action of diphenyl diselenide nanocapsules: In vitro assessments and preclinical evidence in an animal model of glioblastoma multiforme. JOURNAL OF TRACE ELEMENTS IN MEDICINE AND BIOLOGY. JCR, v.55, p.180 - 189, 2019.

4. doi MICHELS, LUANA R.; FACHEL, FLÁVIA N.S.; AZAMBUJA, JULIANA H.; **GELSLEICHTER, NICOLLY E.**; BRAGANHOL, ELIZANDRA; TEIXEIRA, HELDER F.
HPLC-UV method for temozolomide determination in complex biological matrices: Application for *in vitro* , *ex vivo* and *in vivo* studies. BIOMEDICAL CHROMATOGRAPHY. JCR, v.4615, p.e4615 - , 2019.

5. doi AZAMBUJA, J. H.; SCHUH, R. S.; MICHELS, L. R.; **GELSLEICHTER, N. E.**; BECKENKAMP, L. R.; LENZ, G. S.; DE OLIVEIRA, F. H.; WINK, M. R.; STEFANI, M. A.; BATTASTINI, A. M. O.; TEIXEIRA, H. F.; BRAGANHOL, E.
CD73 as a target to improve temozolomide chemotherapy effect in glioblastoma preclinical model. CANCER CHEMOTHERAPY AND PHARMACOLOGY. JCR, v.85, p.1177 - 1182, 2020.

6. doi FACHEL, FLÁVIA NATHIELY SILVEIRA; MICHELS, LUANA ROBERTA; AZAMBUJA, JULIANA HOFSTÄTTER; LENZ, GABRIELA SPIES; **GELSLEICHTER, NICOLLY ESPINDOLA**; ENDRES, MARCELO; SCHOLL, JULIETE NATHALI; SCHUH, ROSELENA SILVESTRI; BARSCHAK, ALETHEA GATTO; FIGUEIRÓ, FABRÍCIO; BASSANI, VALQUÍRIA LINCK; HENRIQUES, AMELIA TERESINHA; KOESTER, LETÍCIA SCHERER; TEIXEIRA, HELDER FERREIRA; BRAGANHOL, ELIZANDRA
Chitosan-coated rosmarinic acid nanoemulsion nasal administration protects against LPS-induced memory deficit, neuroinflammation, and oxidative stress in Wistar rats. NEUROCHEMISTRY INTERNATIONAL. JCR, v.141, p.104875 - , 2020.

7. doi VARANO, FLAVIA; CATARZI, DANIELA; VINCENZI, FABRIZIO; PASQUINI, SILVIA; PELLETIER, JULIE; LOPES RANGEL FIETTO, JULIANA; **ESPINDOLA GELSLEICHTER, NICOLLY**; SARLANDIE, MARINE; GUILBAUD, AUDREY; SÉVIGNY, JEAN; VARANI, KATIA; COLOTTA, VITTORIA
Structural investigation on thiazolo[5,4-d]pyrimidines to obtain dual-acting blockers of CD73 and adenosine A2A receptor as potential antitumor agents. BIOORGANIC & MEDICINAL CHEMISTRY LETTERS. JCR, v.30, p.127067 - , 2020.

8. doi BONA, NATÁLIA P.; PEDRA, NATHALIA S.; AZAMBUJA, JULIANA H.; SOARES, MAYARA S. P.; SPOHR, LUÍZA; **GELSLEICHTER, NICOLLY E.**; DE M. MEINE, BERNARDO; SEKINE, FERNANDA G.; MENDONÇA, LORENÇO T.; DE OLIVEIRA, FRANCINE H.; BRAGANHOL, ELIZANDRA; SPANEVELLO, ROSELIA M.; DA SILVEIRA, ELITA F.; STEFANELLO, FRANCIELI MORO
Tannic acid elicits selective antitumoral activity in vitro and inhibits cancer cell growth in a preclinical model of glioblastoma multiforme. METABOLIC BRAIN DISEASE. JCR, v.35, p.283 - 293, 2020.

Trabalhos publicados em anais de eventos (resumo)

1. Lenz, G.S; AZAMBUJA, J. H.; MICHELS, LUANA R.; **GELSLEICHTER, NICOLLY E.**; Wink, MR; BRAGANHOL, E.
Investigação da participação dos glicocorticóides no desenvolvimento de quimiorresistência em gliomas In: Jornada Acadêmica do curso de medicina da UFCSPA 2019, 2019, Porto alegre.
Jornada Acadêmica do curso de medicina da UFCSPA 2019. , 2019.

2. Lenz, G.S; AZAMBUJA, J. H.; SCHUH, RS; MICHELS, LUANA R.; **GELSLEICHTER, NICOLLY E.**; BECKENKAMP, L. R.; Wink, MR; STEFANI, M. A.; TEIXEIRA, H. F.; BRAGANHOL, E.
Análise da citotoxicidade de nanoemulsões catiônicas contendo RNA de interferência para o silenciamento da CD73 via administração intranasal em um modelo pré clínico de glioblastoma In: 38ª semana científica do HCPA, 2018, Porto alegre.
38ª semana científica do HCPA. , 2018.

3. Lenz, G.S; AZAMBUJA, J. H.; SCHUH, RS; **GELSLEICHTER, NICOLLY E.**; MICHELS, LUANA R.; BECKENKAMP, L. R.; Wink, MR; STEFANI, M. A.; TEIXEIRA, H. F.; BATTASTINI, A. M. O.; BRAGANHOL, E.
CD73 KNOCKDOWN REDUCES TUMOR VOLUME IN A PRECLINICAL GLIOBLASTOMA MODEL: A COMPARISON WITH STANDARD THERAPY In: IV Mostra de Trabalhos de Ensino, Pesquisa e Extensão da Universidade Federal de Ciências da Saúde de Porto Alegre, 2018, Porto Alegre.
IV Mostra de Trabalhos de Ensino, Pesquisa e Extensão da Universidade Federal de Ciências da Saúde de Porto Alegre. , 2018.

4. Lenz, G.S; AZAMBUJA, J. H.; **GELSLEICHTER, NICOLLY E.**; BECKENKAMP, L. R.; ISER, I. C.; DA CRUZ FERNANDES, MARILDA; BATTASTINI, A. M. O.; OLIVEIRA, FH; WINK, M. R.; STEFANI, M. A.; BRAGANHOL, E.
THERAPEUTIC IMPLICATIONS OF CD73-SIRNA DELIVERY ON GLIOBLASTOMA SURGICAL TREATMENT: A HISTOPATHOLOGICAL APPROACH In: XXXII Congresso Brasileiro de Neurocirurgia, 2018, Porto Alegre.
XXXII Congresso Brasileiro de Neurocirurgia. , 2018.

5. Cruz, LP; PRA, M. D.; **GELSLEICHTER, N. E.**; AZAMBUJA, J. H.; Wink, MR; BRAGANHOL, E.
Avaliação da quimioresistência desenvolvida por gliomas de camundongos e sua relação com a proliferação e expressão dos receptores do tipo toll-like In: II Encontro do PPG Biociências da UFCSPA e Encontro de Pesquisa em Fisiologia do RS, 2017, Porto Alegre.
Avaliação da quimioresistência desenvolvida por gliomas de camundongos e sua relação com a proliferação e expressão dos receptores do tipo toll-like. , 2017.

6. Cruz, LP; PRA, M. D.; AZAMBUJA, J. H.; **GELSLEICHTER, N. E.**; Wink, MR; BRAGANHOL, E.
Envolvimento da Sinalização Purinérgica na interação entre gliomas e astrócitos no microambiente tumoral In: III Mostra de Trabalhos de Ensino, Pesquisa e Extensão da UFCSPA, 2017, Porto Alegre.
Envolvimento da Sinalização Purinérgica na interação entre gliomas e astrócitos no microambiente tumoral. , 2017.

7. AZAMBUJA, J. H.; Carvalho, R.T; **GELSLEICHTER, N. E.**; SILVEIRA, E. F.; Spavanello, RM; BRAGANHOL, E.
Glioma and Macrophagues: The role os chemoresistance to temozolomide in modulation of immunosuppressive tumor environment In: 46ª Reunião Anual da Sociedade Brasileira de Bioquímica e Biologia Molecular, 2017, Águas de Lindoia.
Glioma and Macrophagues: The role os chemoresistance to temozolomide in modulation of immunosuppressive tumor environment. , 2017.

8. Lenz, G.S; AZAMBUJA, J. H.; Cruz, LP; **GELSLEICHTER, N. E.**; Roliano, G; BRAGANHOL, E.
Implicações Terapêuticas do sinergismo entre P2X7, P2Y6 e TLR4 na liberação de IL-8 em glioblastomas via ativação de p38 e ERK1/2 In: II Encontro do PPG Biociências da UFSCPA e Encontro de Pesquisa em Fisiologia do RS, 2017, Porto Alegre.
Implicações Terapêuticas do sinergismo entre P2X7, P2Y6 e TLR4 na liberação de IL-8 em glioblastomas via ativação de p38 e ERK1/2. , 2017.

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