M U N I

COMMENTARY TO HABILITATION THESIS[1]

We are currently witnessing great progress across all medical disciplines. The rapid development in the field of molecular biology and genetics has enabled us to understand and describe the process of cancer pathogenesis more accurately. Gliomas and primary glioblastomas as their most common and aggressive form are no exception. The findings were used in the revision of the WHO classification of brain tumours in 2016. Thanks to the concept of the so-called integrated diagnosis, which is based on the histopathological features of the disease and molecular biomarkers, we were able to refine diagnosis, estimate the prognosis more precisely, and make better treatment response predictions. More accurate stratification of patients with glioblastomas into different subgroups according to the profile of biomarkers has been and will continue to be crucial for their inclusion in clinical trials with new drugs.

My habilitation thesis aims to show my contribution to the diagnosis and treatment of glioblastomas. The first part of this habilitation thesis is devoted to the processes of carcinogenesis and molecular classification of glioblastomas. Here, in addition to a summary of basic information on key biomarkers with diagnostic, prognostic and predictive significance, our contributions are mentioned and commented on. These are mainly findings that our group has gained in researching the role of non-coding microRNAs. It is a large group of new promising biomarkers that are involved in the epigenetic regulation of cellular processes and in the pathogenesis of the disease itself. Today, we can use it to estimate the prognosis of glioblastoma, or to predict the response to treatment. However, microRNAs have the potential for therapeutic use. In the second part of the habilitation thesis, a substantial amount of space is devoted to the standard multimodal treatment of glioblastoma, which consists of the maximum possible safe tumour resection followed by concomitant chemoradiotherapy and adjuvant chemotherapy with temozolomide. Unfortunately, despite the acquired knowledge and the huge possibilities of current pathology and laboratory diagnostics, there has been no fundamental change in the therapeutic procedure since 2005. The treatment with alternating electric fields emitted from electrodes affixed to the scalp (Optune) is limited and not suitable for everyone. Clinical trials with targeted therapy and modern immunotherapy have failed. Nevertheless, thanks to general medical progress over the last 10 years, we have managed to extend the lives of our patients by several months. Compared to 10 years ago, our neurosurgeons achieve more radical and safe resections, allowing a larger percentage of patients to undergo intensive postoperative treatment. The supportive and symptomatic treatment has also improved. Thanks to the evaluation of our group of patients, we also confirmed, in agreement with foreign centres, the role of a new negative prognostic factor, which is the rapid early progression of glioblastoma on a planning MR examination before the start of postoperative treatment. This high-risk group of patients is now the subject of research by our cooperation group (the academic study of the 2nd phase GlioMET, grant support from AZV ČR – Czech health research council, principal investigator Radek Lakomý, MD). Despite these partial

[1] The commentary must correspond to standard expectations in the field and must include a brief characteristic of the investigated matter, objectives of the work, employed methodologies, obtained results and, in case of co-authored works, a passage characterising the applicant's contribution in terms of both quality and content.

successes, further research is needed, especially with modern treatment. The concept of clinical trials with glioblastomas is now changing worldwide. Much hope is placed in serial testing of biomarkers using precise targeted treatment and immunotherapy. Scientific teams are currently focused on understanding and overcoming the mechanisms of intrinsic and acquired drug resistance. With this comprehensive approach, it is hopefully possible to change the unfavourable prognosis even in a disease such as glioblastoma.

As part of my habilitation thesis, I selected the 14 most important articles related to the diagnosis and treatment of glioblastoma. My contribution to these articles is summarized in the following tables with special emphasis on experimental work, student supervision, manuscript preparation, and research direction.

[1][2] Sana J, Busek P, Fadrus P, Besse A, Radova L, Vecera M, Reguli S, Stollinova Sromova L, Hilser M, Lipina R, Lakomy R, Kren L, Smrcka M, Sedo A, Slaby O. Identification of microRNAs differentially expressed in glioblastoma stem-like cells and their association with patient survival. Sci Rep. 2018; 8(1): 2836 (IF = 4,011; JCR Category MULTIDISCIPLINARY SCI Q1).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	-	20	10

[2] Besse A, Sana J, Lakomy R, Kren L, Fadrus P, Smrcka M, Hermanova M, Jancalek R, Reguli S, Lipina R, Svoboda M, Slampa P, Slaby O. MiR-338-5p sensitizes glioblastoma cells to radiation through regulation of genes involved in DNA damage response. Tumour Biol. 2016; 37(6): 7719–7727 (IF = 3,650; JCR Category ONCOLOGY Q2).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	-	20	10

[3] Kazda T, Bulik M, Pospisil P, Lakomy R, Smrcka M, Slampa P, Jancalek R. Advanced MRI increases the diagnostic accuracy of recurrent glioblastoma: Single institution thresholds and validation of MR spectroscopy and diffusion weighted MR imaging. Neuroimage Clin. 2016; 11: 316–321 (IF = 4,348; JCR Category NEUROIMAGING Q1).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	-	20	10

[4] Vašina J, Svoboda M, Lakomý R, Kazda T, Adam J, Řehák Z. Využití 11C-methioninu pro PET/CT vyšetření pacientů s tumory mozku – soubor 16 pacientů. NuklMed 2018; 7(4): 62–68.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	20	40	40

[2] Bibliographic record of a published scientific result, which is part of the habilitation thesis.

[5] Slaby O*, Lakomy R*, Fadrus P, Hrstka R, Kren L, Lzicarova E, Smrcka M, Svoboda M, Dolezalova H, Novakova J, Valik D, Vyzula R, Michalek J. MicroRNA-181 family predicts response to concomitant chemoradiotherapy with temozolomide in glioblastoma patients. Neoplasma. 2010; 57(3): 264–269 (IF = 1,449; JCR Category ONCOLOGY Q4).
*Both authors contributed equally to this work

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	-	50	20

[6] Lakomy R, Sana J, Hankeova S, Fadrus P, Kren L, Lzicarova E, Svoboda M, Dolezelova H, Smrcka M, Vyzula R, Michalek J, Hajduch M, Slaby O. MiR-195, miR-196b, miR-181c, miR-21 expression levels and O-6-methylguanine-DNA methyltransferase methylation status are associated with clinical outcome in glioblastoma patients. Cancer Sci. 2011; 102(12): 2186–2190 (IF = 3,325; JCR Category ONCOLOGY Q2).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	10	60	30

[7] Sana J, Radova L, Lakomy R, Kren L, Fadrus P, Smrcka M, Besse A, Nekvindova J, Hermanova M, Jancalek R, Svoboda M, Hajduch M, Slampa P, Vyzula R, Slaby O. Risk Score based on microRNA expression signature is independent prognostic classifier of glioblastoma patients. Carcinogenesis. 2014; 35(12): 2756–2762 (IF = 5,334; JCR Category ONCOLOGY Q1).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	-	30	20

[8] Lakomý R, Kazda T, Poprach A. Postavení chemoterapie v léčbě gliomů. In: Lakomý R, Kazda T, Šlampa P a kol. Gliomy. Současná diagnostika a léčba, 2. vydání, Praha: Maxdorf, 2018, s. 177–189.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	-	90	90

[9] Kazda T, Lakomý R, Poprach A, Hendrych M, Knight A, Šlampa P. Multidisciplinární přístup v léčbě gliomů – astrocytomy a oligodendrogliomy. Postgraduální medicína 2020; 22(2): 137–142.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	-	50	50

[10] Lakomý R, Fadrus P, Šlampa P, Svoboda T, Křen L, Lžičařová E, Belanová R, Siková I, Poprach A, Schneiderová M, Procházková M, Šána J, Slabý O, Smrčka M, Vyzula R, Svoboda M. Výsledky multimodální léčby glioblastoma multiforme: Konsekutivní série 86 pacientů diagnostikovaných v letech 2003–2009. Klin Onkol. 2011; 24(2): 112–120.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	10	80	80

[11] Kazda T, Dziacky A, Burkon P, Pospisil P, Slavik M, Rehak Z, Jancalek R, Slampa P, Slaby O, Lakomy R*. Radiotherapy of Glioblastoma 15 Years after the Landmark Stupp's Trial: More Controversies than Standards? Radiol Oncol. 2018; 52(2): 121–128 (IF = 1,846; JCR Category ONCOLOGY Q4 + RADIOLOGY, NUCLEAR MEDICINE Q3).
* corresponding author

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	20	50	40

[12] Lakomy R, Kazda T, Selingerova I, Poprach A, Pospisil P, Belanova R, Fadrus P, Vybihal V, Smrcka M, Jancalek R, Hynkova L, Muckova K, Hendrych M, Sana J, Slaby O, Slampa P. Real-World Evidence in Glioblastoma: Stupp's Regimen After a Decade. Front Oncol. 2020; 10: 840 (IF = 4,848; JCR Category ONCOLOGY Q2 pro rok 2019).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	30	60	50

[13] Lakomy R, Kazda T, Selingerova I, Poprach A, Pospisil P, Belanova R, Fadrus P, Smrcka M, Vybihal V, Jancalek R, Kiss I, Muckova K, Hendrych M, Knight A, Sana J, Slampa P, Slaby O. Pre-Radiotherapy Progression after Surgery of Newly Diagnosed Glioblastoma: Corroboration of New Prognostic Variable. Diagnostics (Basel). 2020;10(9):E676. Published 2020 Sep 5 (IF = 3,110; JCR Category MEDICINE, GENERAL & INTERNAL SCI Q1 pro rok 2019).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	30	50	50

[14] Lakomý R, Kazda T, Poprach A. Klinický výzkum a moderní léčba u gliomů. In: Lakomý R, Kazda T, Šlampa P a kol. Gliomy. Současná diagnostika a léčba, 2. vydání, Praha: Maxdorf, 2018, s. 199–207.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	-	90	90