

## COMMENTARY TO HABILITATION THESIS<sup>1</sup>

**BRIEF CHARACTERISTICS OF THE INVESTIGATED MATERIAL:** A quite standard treatments known two decades ago were followed by rapid progress in molecular diagnostics and treatment possibilities in paediatric oncology. New molecular biology methods and new treatments based mainly on theranostics principles are used in daily practice.

**OBJECTIVES:** The objectives of this work are to review how has been the paediatric oncology updated during last two decades and to show this progress in commentary of published papers.

**METHODOLOGIES:** Innovative therapies, diagnostics and treatment of invasive fungal infections and treatment of soft tissue sarcomas are areas covered by published articles. There are a lot of projects on Paediatric Oncology Department of School of Medicine Masaryk University and University Hospital Brno during period 2000-2020, which cover all three topics as metronomic antiangiogenic therapy, tyrosinkinase inhibitors in new therapeutic indications, cell therapies with autologous dendritic cells, new therapeutic strategies of invasive fungal infections and diagnostics and therapeutic approaches in soft tissue sarcomas in children.

**RESULTS:** Many of innovative therapies were used for first time ever or with the best results published. This is the case of human papillomavirus vaccination against recurrent laryngeal papillomatosis or successful management of infantile myofibromatosis in patients with germline mutation of PDGFRB gene with tyrosinkinase inhibitor and treatment of child with fibrodysplasia ossificans progressiva (1,2,3,4). Introduced antiangiogenic metronomic therapy is successfully used in patients with high risk tumours (5,6). Personalised therapies were administered to patients with sometimes surprising results, even curative, which were not anticipated with conventional approach (7,8,9,10). Novel cell therapy with dendritic cells was introduced and this accelerated rapid biotechnology development and proper academic trial administration in era of new and tight law regulations. KDO DC 1311 trial is the only open for children in the Czech Republic, this trial is still active. It generated some new knowledge on monocyte response to anticancer therapies or host immune response against cancer which

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<sup>1</sup> 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.

are used in clinical practice and support further development of such promising method (11,12).

Setting quality of diagnostic and therapeutic tools in patients with invasive fungal infections was substantial for good treatment results and was accompanied by novel therapies used off-label and off-clinical trial as published (13,14,15,16).

Multicentric prospective international clinical trials on diagnostics and treatment of soft tissue sarcomas were essential for generating of standardized therapy across Europe, new treatments such as maintenance chemotherapy in rhabdomyosarcoma which is the first robust evidence about its efficacy in solid tumours, new treatment stratification in alveolar rhabdomyosarcomas with regional nodal involvement, improvement of treatment results of highly aggressive malignant rhabdoid tumours and (17,18,19,20)

CONCLUSIONS: Recent progress in diagnostics and therapies in childhood malignancies are described in published articles with focus to high risk patients without possibility of conventional treatment and to standardization of treatment of invasive fungal diseases and soft tissue sarcomas while participating in international multicentric prospective academic driven clinical trials.

**[1 ] MUDRY P,** Vavrina M, Mazanek P, Machalova M, Litzman J, Sterba J. Recurrent laryngeal papillomatosis: successful treatment with human papillomavirus vaccination. *Arch Dis Child.* 2011;96(5):476-477. doi:10.1136/adc.2010.198184

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
80	20	100	80

**[2] MUDRY, Peter\*(corresponding author)\*,** Ondrej SLABY, Jakub NERADIL, Jana SOUKALOVA, Kristyna MELICHARKOVA, Ondrej ROHLEDER, Marta JEZOVA, Anna SEEHOFNEROVA, Elleni MICHU, Renata VESELSKA a Jaroslav STERBA. Case report: rapid and durable response to PDGFR targeted therapy in a child with refractory multiple infantile myofibromatosis and a heterozygous germline mutation of the PDGFRB gene. *Bmc Cancer* [online]. 2017, 17, 119. ISSN 1471-2407. Dostupné z: doi:[10.1186/s12885-017-3115-x](https://doi.org/10.1186/s12885-017-3115-x).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
70	30	100	100

**[3] SRAMEK, Martin,** Jakub NERADIL, Petra MACIGOVA, **Peter MUDRY,** Kristyna POLASKOVA, Ondrej SLABY, Hana NOSKOVA, Jaroslav STERBA a Renata VESELSKA. Effects of Sunitinib and Other Kinase Inhibitors on Cells Harboring a PDGFRB Mutation

Associated with Infantile Myofibromatosis. *International Journal of Molecular Sciences* [online]. 2018, **19**(9), 2599. ISSN 1422-0067. Dostupné z: doi:[10.3390/ijms19092599](https://doi.org/10.3390/ijms19092599).

**Document Type: Article; IF = 4,183; median IF BIOCHEMISTRY & MOLECULAR BIOLOGY – SCIE 2,870 + CHEMISTRY, MULTIDISCIPLINARY – SCIE 2,260; dle IF BIOCHEMISTRY & MOLECULAR BIOLOGY Q2 + CHEMISTRY, MULTIDISCIPLINARY Q2; dle AIS BIOCHEMISTRY & MOLECULAR BIOLOGY Q2 + CHEMISTRY, MULTIDISCIPLINARY Q2**

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	30	20	40

**[4]** O Rohleder 1, P Mudry 2, J Neradil 3, H Noskova 4, O Slaby 5, J Sterba 6  
Letter to Editor: F.S. Kaplan, et al., Early clinical observations on the use of imatinibmesylate in FOP: A report of seven cases, *Bone* (2017). *Bone*. 2018 Nov;116:171. doi: 10.1016/j.bone.2018.08.003. Epub 2018 Aug 7.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
70	30	50	70

**[5]** STERBA, Jaroslav, Dalibor VALIK, **Peter MUDRY**, Tomas KEPAK, Zdenek PAVELKA, Viera BAJCIOVA, Karel ZITTERBART, Vera KADLECOVA a Pavel MAZANEK. Combined biodifferentiating and antiangiogenic oral metronomic therapy is feasible and effective in relapsed solid tumors in children: Single-center pilot study. *Onkologie* [online]. 2006, **29**(7), 308–313. ISSN 0378-584X. Dostupné z: doi:[10.1159/000093474](https://doi.org/10.1159/000093474). **Document Type: Article; IF = 1,724; median IF ONCOLOGY – SCIE 2,396; dle IF ONCOLOGY Q3; dle AIS ONCOLOGY Q1**

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	0	20	100

**[6]** ZAPLETALOVA, D., N. ANDRE, L. DEAK, M. KYR, V. BAJCIOVA, **P. MUDRY**, L. DUBSKA, R. DEMLOVA, Z. PAVELKA, K. ZITTERBART, J. SKOTAKOVA, K. HUSEK, A. MARTINCEKOVA, P. MAZANEK, T. KEPAK, M. DOUBEK, L. KUTNIKOVA, D. VALIK a J. STERBA. Metronomic Chemotherapy with the COMBAT Regimen in Advanced Pediatric Malignancies: A Multicenter Experience. *Oncology* [online]. 2012, **82**(5), 249–260. ISSN 0030-2414. Dostupné z: doi:[10.1159/000336483](https://doi.org/10.1159/000336483).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	0	20	100

**[7]** STERBA, Martin, Petra POKORNA, Renata FABEROVA, Blanka PINKOVA, Jarmila SKOTAKOVA, Anna SEEHOFNEROVA, Jan BLATNY, Lucia JANIGOVA, Olga KOSKOVA, Hana PALOVA, Michal MAHDAL, Lukas PAZOUREK, Petr JABANDZIEV, Ondrej SLABY, **Peter MUDRY\*(corresponding author)\*** a Jaroslav STERBA. Targeted treatment of severe vascular malformations harboring PIK3CA and TEK mutations with alpelisib is highly effective with limited toxicity. *Scientific Reports* [online]. 2023, **13**(1), 10499. ISSN 2045-2322. Dostupné z: doi:[10.1038/s41598-023-37468-4](https://doi.org/10.1038/s41598-023-37468-4)

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	0	30	80

**[8]** POLASKOVA, Kristyna, Tomas MERTA, Alexandra MARTINCEKOVA, Danica ZAPLETALOVA, Michal KYR, Pavel MAZANEK, Zdenka KRENOVA, Peter MUDRY, Marta JEZOVA, Jiri TUMA, Jarmila SKOTAKOVA, Ivana CERVINKOVA, Dalibor VALIK, Lenka ZDRAZILOVA-DUBSKA, Hana NOSKOVA, Karol PAL, Ondrej SLABY, Pavel FABIAN, Sarka KOZAKOVA, Jakub NERADIL, Renata VESELSKA, Veronika KANDEROVA, Ondrej HRUSAK, Tomas FREIBERGER, Giannoula Lakka KLEMENT a Jaroslav STERBA. Comprehensive Molecular Profiling for Relapsed/Refractory Pediatric Burkitt Lymphomas-Retrospective Analysis of Three Real-Life Clinical Cases-Addressing Issues on Randomization and Customization at the Bedside. *Frontiers in Oncology* [online]. 2020, 9, 1531. ISSN 2234-943X. Dostupné z: doi:10.3389/fonc.2019.01531

Document Type: Article; IF = 6,244; median IF ONCOLOGY – SCIE 4,147; dle IF ONCOLOGY Q2; dle AIS ONCOLOGY Q2

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	0	20	20

**[9]** NOSKOVA, Hana, Michal KYR, Karol PAL, Tomas MERTA, Peter MUDRY, Kristyna POLASKOVA, Tina Catela IVKOVIC, Sona ADAMCOVA, Tekla HORNAKOVA, Marta JEZOVA, Leos KREN, Jaroslav STERBA a Ondrej SLABY. Assessment of Tumor Mutational Burden in Pediatric Tumors by Real-Life Whole-Exome Sequencing and In Silico Simulation of Targeted Gene Panels: How the Choice of Method Could Affect the Clinical Decision? *Cancers* [online]. 2020, 12(1), 230. Dostupné z: doi:10.3390/cancers12010230.

Document Type: Article; IF = 6,639; median IF ONCOLOGY – SCIE 4,147; dle IF ONCOLOGY Q1; dle AIS ONCOLOGY Q2

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	0	20	20

**[10]** Giannoula Lakka Klement, Knarik Arkun, Dalibor Valik<sup>s</sup>, Tina Roffidal, Ali Hashemi, Christos Klement, Paolo Carmassi, Edward Rietman, Ondrej Slaby, Pavel Mazanek, Peter Mudry, Gabor Kovacs, Csongor Kiss, Koen Norga, Dobrin

Konstantinov, Nicolas André, Irene Slavc, Henk van Den Berg, Alexandra Kolenova, Leos Kren, Jiri Tuma, Jarmila Skotakova and Jaroslav Sterba. Future paradigms for precision onkology. *Oncotarget*. 2016 Jul 19;7(29):46813-46831. doi: 10.18632/oncotarget.9488.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	30	30	100

[11] FEDOROVA, Lenka, **Peter MUDRY**, Katerina PILATOVA, Iveta SELINGEROVA, Jana MERHAUTOVA, Zdenek REHAK, Dalibor VALIK, Eva HLAVACKOVA, Dasa CERNA, Lucie FABEROVA, Pavel MAZANEK, Zdenek PAVELKA, Regina DEMLOVA, Jaroslav STERBA a Lenka ZDRAZILOVA-DUBSKA. Assessment of Immune Response Following Dendritic Cell-Based Immunotherapy in Pediatric Patients With Relapsing Sarcoma. *Frontiers in Oncology* [online]. 2019, **9**, 1169. ISSN 2234-943X. Dostupné z: doi:[10.3389/fonc.2019.01169](https://doi.org/10.3389/fonc.2019.01169).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	30	30	100

[12] HLAVACKOVA, Eva, Katerina PILATOVA, Dasa CERNA, Iveta SELINGEROVA, **Peter MUDRY**, Pavel MAZANEK, Lenka FEDOROVA, Jana MERHAUTOVA, Lucie JURECKOVA, Lukas SEMERAD, Rita PACASOVA, Lucie FLAJSAROVA, Lenka SOUCKOVA, Regina DEMLOVA, Jaroslav STERBA, Dalibor VALIK a Lenka ZDRAZILOVA-DUBSKA. Dendritic Cell-Based Immunotherapy in Advanced Sarcoma and Neuroblastoma Pediatric Patients: Anti-cancer Treatment Preceding Monocyte Harvest Impairs the Immunostimulatory and Antigen-Presenting Behavior of DCs and Manufacturing Process Outcome. *Frontiers in Oncology* [online]. 2019, **9**, 1034. ISSN 2234-943X. Dostupné z: doi:[10.3389/fonc.2019.01034](https://doi.org/10.3389/fonc.2019.01034).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	30	30	100

[13] KRENOVA, Zdenka, Zdenek PAVELKA, Petr LOKAJ, Jarmila SKOTAKOVA, Ivana KOČMANOVA, Otakar TEYSCHL, Leos KREN, **Peter MUDRY** a Jaroslav STERBA. Successful Treatment of Life-threatening Candida Peritonitis in a Child With Abdominal Non-Hodgkin Lymphoma Using Efungumab and Amphotericin B Colloid Dispersion. *Journal of Pediatric Hematology Oncology* [online]. 2010, **32**(2), 128–130. ISSN 1077-4114. Dostupné z: doi:[10.1097/MPH.0b013e3181cb49a8](https://doi.org/10.1097/MPH.0b013e3181cb49a8).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	40	20	90

**[14]** RACIL, Zdenek, Barbora WEINBERGEROVA, Iva KOCCMANOVA, Jan MUZIK, Michal KOUBA, Lubos DRGONA, Lucia MASAROVA, Tomas GUMANG, Elena TOTHOVA, Kristina FORSTEROVA, Jan HABER, Barbora ZIAKOVA, Eva BOJTAROVA, Jan VYDRA, **Peter MUDRY**, Renata FORALOVA, Daniela SEJNOVA, Nada MALLATOVA, Vit KANDRNAL, Petr CETKOVSKY a Jiri MAYER. Invasive aspergillosis in patients with hematological malignancies in the Czech and Slovak republics: Fungal InfectioN Database (FIND) analysis, 2005-2009. *International Journal of Infectious Diseases* [online]. 2013, **17**(2), E101–E109. ISSN 1201-9712. Dostupné z: doi:[10.1016/j.ijid.2012.09.004](https://doi.org/10.1016/j.ijid.2012.09.004).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	0	10	70

**[15]** MARTIN, Judith M., Mercedes MACIAS-PARRA, Peter MUDRY, Umberto CONTE, Jean L. YAN, Ping LIU, M. Rita CAPPARELLA a Jalal A. ARAM. Safety, Efficacy, and Exposure-Response of Voriconazole in Pediatric Patients With Invasive Aspergillosis, Invasive Candidiasis or Esophageal Candidiasis. *Pediatric Infectious Disease Journal* [online]. 2017, **36**(1), E1–E13. ISSN 0891-3668. Dostupné z: doi:10.1097/INF.0000000000001339. Document Type: Article; IF = 2,305; median IF IMMUNOLOGY – SCIE 3,187 + INFECTIOUS DISEASES – SCIE 2,616 + PEDIATRICS – SCIE 1,695; dle IF IMMUNOLOGY Q3 + INFECTIOUS DISEASES Q3 + PEDIATRICS Q2; dle AIS IMMUNOLOGY Q2 + INFECTIOUS DISEASES Q2 + PEDIATRICS Q1

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	0	20	70

**[16]** STERBA, J., J. PROCHAZKA, J. VENTRUBA, L. KREN, D. VALIK, D. BURGETOVA, **P. MUDRY**, J. SKOTAKOVA a J. BLATNY. Successful treatment of aspergillus brain abscess in a child with acute lymphoblastic leukemia and liver failure. *Pediatric Hematology and Oncology* [online]. 2005, **22**(8), 649–655. ISSN 0888-0018. Dostupné z: doi:[10.1080/08880010500278665](https://doi.org/10.1080/08880010500278665). Document Type: Article; IF = 0,532; median IF ONCOLOGY – SCIE 2,371 + HEMATOLOGY – SCIE 2,008 + PEDIATRICS – SCIE 1,102; dle IF ONCOLOGY Q4 + HEMATOLOGY Q4 + PEDIATRICS Q4; dle AIS ONCOLOGY Q1 + HEMATOLOGY Q1 + PEDIATRICS Q1

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	0	20	50

**[17]** BISOGNO, Gianni, Gian Luca DE SALVO, Christophe BERGERON, Soledad GALLEGO MELCON, Johannes H. MERKS, Anna KELSEY, Helene MARTELLI, Veronique MINARD-COLIN, Daniel ORBACH, Heidi GLOSLI, Julia CHISHOLM, Michela CASANOVA, Ilaria ZANETTI, Christine DEVALCK, Myriam BEN-ARUSH, **Peter MUDRY**, Sima FERMAN, Meriel

JENNEY a Andrea FERRARI. Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncology* [online]. 2019, **20**(11), 1566–1575. ISSN 1470-2045. Dostupné z: doi:[10.1016/S1470-2045\(19\)30617-5](https://doi.org/10.1016/S1470-2045(19)30617-5).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
80	0	10	60

[18] GALLEGO, Soledad, Ilaria ZANETTI, Daniel ORBACH, Dominique RANCHERE, Janet SHIPLEY, Angelica ZIN, Christophe BERGERON, Gian Luca DE SALVO, Julia CHISHOLM, Andrea FERRARI, Meriel JENNEY, Henry C. MANDEVILLE, Timothy ROGERS, Johannes H. M. MERKS, **Peter MUDRY**, Heidi GLOSLI, Giuseppe Maria MILANO, Sima FERMAN a Gianni BISOGNO. Fusion Status in Patients With Lymph Node-Positive (N1) Alveolar Rhabdomyosarcoma Is a Powerful Predictor of Prognosis: Experience of the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). *Cancer* [online]. 2018, **124**(15), 3201–3209. ISSN 0008-543X. Dostupné z: doi:[10.1002/cncr.31553](https://doi.org/10.1002/cncr.31553).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
80	0	10	60

[19] BRENNAN, Bernadette, Gian Luca DE SALVO, Daniel ORBACH, Angela DE PAOLI, Anna KELSEY, **Peter MUDRY**, Nadine FRANCOITTE, Max VAN NOESEL, Gianni BISOGNO, Michela CASANOVA a Andrea FERRARI. Outcome of extracranial malignant rhabdoid tumours in children registered in the European Paediatric Soft Tissue Sarcoma Study Group Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study EpSSG NRSTS 2005. *European Journal of Cancer* [online]. 2016, **60**, 69–82. ISSN 0959-8049. Dostupné z: doi:[10.1016/j.ejca.2016.02.027](https://doi.org/10.1016/j.ejca.2016.02.027).

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
80	0	10	60

[20] ORBACH, Daniel, Bernadette BRENNAN, Angela DE PAOLI, Soledad GALLEGO, Peter MUDRY, Nadine FRANCOITTE, Max VAN NOESEL, Anna KELSEY, Rita ALAGGIO, Dominique RANCHERE, Gian Luca DE SALVO, Michela CASANOVA, Christophe BERGERON, Johannes H. M. MERKS, Meriel JENNEY, Michael C. G. STEVENS, Gianni BISOGNO a Andrea FERRARI. Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience. *European Journal of Cancer* [online]. 2016, **57**, 1–9. ISSN 0959-8049. Dostupné z: doi:[10.1016/j.ejca.2015.12.028](https://doi.org/10.1016/j.ejca.2015.12.028). Document Type: Article; IF = 6,029; median IF ONCOLOGY – SCIE 2,993; dle IF ONCOLOGY Q1; dle AIS ONCOLOGY Q1

<b>Experimental work (%)</b>	<b>Supervision (%)</b>	<b>Manuscript (%)</b>	<b>Research direction (%)</b>
30	0	20	60