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Highlights of the inaugural ten – the launch of Neuro-Oncology Advances

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The editorial team of *Neuro-Oncology Advances* is excited to present the inaugural ten papers of the Journal. We selected the first-ten papers to reflect the breadth and scope of the new journal; ranging from basic science, to translational molecular, to biostatistical/epidemiological and imaging studies in the field of neuro-oncology.

"GITRL-armed Delta-24-RGD oncolytic adenovirus prolongs survival and induces anti-glioma immune memory", by Rivera-Molina et al.[1]

Oncolytic viral-based therapies are gaining increasing attention as a promising therapeutic approach for high-grade gliomas. Converging evidence suggests the possibility of an anti-tumoral immune response that is responsible for tumor eradication, leaving room for immune activation as a synergistic treatment option[2–5]. In this issue, Rivera-Molina *et al*. report on the utility of the clinical-trial tested oncolytic Delta-24-RGD virus that is engineered to be armed with a positive activator of the tumor necrosis factor receptor superfamily synapsis: GITRL/GITR[1]. The authors demonstrate increased recruitment and activation of T-cells in tumors of mice treated with the armed oncolytic antivirus, dubbed Delta-24-GREAT, with associated improved survival *in-vivo* in comparison to mice treated with Delta-24-RGD alone. Histopathological examination demonstrated extensive necrosis within Delta-24-GREAT treated tissue. The results of this study highlight an opportunity to overcome the intrinsic lack of co-stimulatory molecules in cancer cells to trigger robust immune responses in high-grade gliomas. The complement of available T-cell activators may be exploited in future studies to achieve synergistic anti-neoplastic effects

in glioblastoma with hopes of rapid translation of armed viruses into controlled clinical trials.

"Differences in spatial distribution between WHO 2016 low-grade glioma molecular subgroups" by Wijnenga et al.[6]

Wijnenga *et al.* use voxel-based methodologies to map the anatomical locations of a robustly annotated cohort of 132 WHO grade II low-grade gliomas that were molecularly characterized using next-generation sequencing approaches[6]. Similar to previous reports in high-grade gliomas. the authors showed that *isocitrate dehydrogenase* (IDH)-mutated WHO grade II gliomas were more frequently located in the anterior extension of the lateral ventricles whereas *IDH*-wildtype WHO grade II gliomas were more commonly found in the basal ganglia[7,8]. The authors did not find distinct regions enriched for *IDH*-mutant astrocytoma or oligodendrogliomas using voxel-cluster based analyses, and although chromosomal alterations are known to have considerable prognostic and biological value in gliomas, the authors did not find any anatomical predilections for specific copy number alterations beyond loss of chromosome 9p which was more frequently located in the left parietal region. The objective quantitative approach to spatially characterizing lower grade gliomas used in this study allows for reliable comparisons of heterogeneity maps between molecular subgroups of gliomas, and further work using standardized imaging-protocols with homogenous imaging acquisition techniques may facilitate further refinement of subtle anatomic distributions.

"Rapid intraoperative molecular genetic classification of gliomas using Raman spectroscopy" by Livermore et al.[9]

Rapid intraoperative identification of molecular subtypes of gliomas has significant implications for both acquisition of diagnostic tissue during biopsy and potentially for guiding extent of tumor resection. In this issue, Livermore and colleagues present evidence for the use of rapid Raman spectroscopy—within 15 minutes—to distinguish among *IDH1* wildtype astrocytomas (all glioblastomas), *IDH1* mutant astrocytomas, and *IDH1* mutant oligodendrogliomas[9]. In their study 62 patients underwent spectroscopic analysis of fresh tissue, cryosections, and formalin-fixed paraffin-embedded (FFPE) sections against the gold standard of histopathology combined with targeted sequencing. Discrimination using Raman spectroscopy among the three groups above with fresh tissue was excellent with sensitivities of 91-95% and specificities of 90-100%, although there was somewhat lower sensitivity (79%) to detect oligodendrogliomas. The sensitivity and specificity to distinguish overall *IDH1* wildtype vs. mutant gliomas were also high, in the range of 91-95%. Although less robust, use of Raman spectroscopy on cryosections and FFPE for molecular classification remained promising. Overall, this study and others[10,11] support the potential for taking this advance in technology to application of surgical care of patients with gliomas and improving the information that can be made available to the surgeons in real-time intraoperatively. Important follow-up questions remain, such as the ability of this technology to distinguish these specific gliomas from non-tumor specimens (i.e. normal brain or gliosis), as well as from gliomas of other molecular subtypes. Additionally, how this technological can be leveraged to practically guide tumor removal particularly in cases where resection is limited by nearby eloquent brain or where gross total or even supramarginal resection is already planned will require thoughtful discussion.

"Efficacy of Ruthenium coordination complex based Rutherrin in a pre-clinical rat glioblastoma model", by Munegowda et al.[12]

There are numerous factors recognized to influence the challenges of successful therapy for glioblastoma. High among these are the infiltrative nature of the disease and the ability to adequately deliver agents to the tumor. The work by Munegowda *et al.* in this issue explores the use of a novel Ruthenium-based photosensitizer, TLD-1433, in a rat model of glioblastoma[12]. By taking advantage of the transferrin receptor upregulation in glioma, TLD-1433 bound to transferrin (Rutherrin) allows for tissue-selective delivery of therapies. The use of light activated photodynamic therapy provides a new dimension in overcoming the challenges related to an invasive disease like glioblastoma. In this study, the authors demonstrated both safety and improved survival in rodent models which the authors attribute to the enhanced ability of Rutherrin to enter the CNS, the more favorable photophysical and photochemical properties, and the induction of glioma specific immune responses. The observed CD8+ T-cell tumor infiltration is encouraging and provides a rationale for a more extensive and rigorous immune evaluation after photodynamic therapy. The results from this study also suggest less post-treatment edema with Rutherrin compared to 5-aminolevulinic acid based therapy, which is important given the challenges treatment-induced brain edema and inflammation generate when it comes to the interpretation of disease response to therapy. Overall, this study provides an exciting direction with a potential for a new dimension of photodynamic therapy for gliomas and provides a strong basis for additional studies in other models of glioma particularly in an immunocompetent background.

"An independently validated nomogram for IDH-wildtype glioblastoma patient survival", by Gittleman et al.[13]

With an increasing understanding of the heterogenous biology in glioma, there has been an evolving appreciation that outcomes for glioma patients are also

"multiforme"[4,14]. In order to further refine outcome predictions in isocitrate dehydrogenase (IDH)-wildtype glioblastoma, Gittleman and colleagues have expanded on their previous work[15] in this issue by developing a nomogram to predict individual 12-month, 18-month, and 24-month survival probabilities in newly diagnosed patients with IDH-wildtype glioblastoma using a set of six commonly known clinic-molecular variables: age, sex, extent of resection, adjuvant treatment protocol, Karnofsky performance status, and *O6-methylguanin DNA-methyltransferase* (MGMT) methylation status[13]. When applied to an external cohort from an independent institution, the nomogram was able to reliably discriminate 12-month survival (concordance index 0.756). The authors have made their software publicly available for broad implementation which the neuro-oncology community will hopefully be able to adopt and promote its value. This work lays the foundation for moving beyond stratified medicine in gliomas, demonstrating how readily available clinical and molecular factors can be integrated to provide disease outcome predictions that are tailored to a given patient. Future incorporation of additional molecular layers into the authors' nomogram may offer an avenue to further refine prognostication estimates in IDH-wildtype glioblastomas.

"Combined Targeting of PI3K and MEK Effector Pathways via CED for DIPG Therapy", by Chang et al.[16]

Although nearly 50% of diffuse intrinsic pontine gliomas (DIPGs) demonstrate alterations in the PI3K signaling pathway, monotherapies with PI3K inhibitors have been largely ineffective with nominally favourable outcomes at best [17]. In this issue, Chang *et al.* demonstrate that dual inhibition of the PI3K and MEK signalling pathways results in potent synergism against DIPG cell viability *in-vitro*[16]. To facilitate clinical translation and to overcome the limiting penetration of the blood-brain barrier, the authors further build on their previous experience[18] by delivering these drugs via convection-enhanced delivery in an intracranial model of DIPG and demonstrate both survival benefit and safety of their approach. Further pharmacokinetic/pharmacodynamic evaluation will help translate these findings into clinical trials to determine whether this approach will be clinically applicable and impactful for an otherwise deadly disease.

"Histomolecular Characterization of Intracranial Meningiomas Developed in Patients Exposed to High-Dose Cyproterone Acetate, an Antiandrogen Treatment", by Portet et al.[19]

The link between compounds with progestogenic effects and meningiomagenesis has been previously explored[20], however, the underlying mechanisms are so far not fully understood. In this issue, Portet *et al.* report on a cohort of meningioma patients with a history of treatment with the anti-androgenic drug cyproterone acetate (CPA). A third of these cases harboured mutations in *PIK3CA* or *AKT1*, which are otherwise less frequent in meningioma (e.g. 10.7% in the control cohort of this study). Meningiomas arising after CPA treatment were also mainly located at the skull base further supporting the association of *AKT1* and *PIK3CA* mutations with this localization[21–23]. The authors' findings expand on previous reports that also identified high rates of *PIK3CA* mutations and a predominant skull base location in their cohort of patients developing meningiomas after use of different progestins[24]. The exact mechanisms rendering development of meningiomas under treatment with CPA and similar compounds remains to be elucidated. However, these data already have implications for our understanding of the molecular subgroups of meningioma. Besides the accumulation of structural rearrangements in meningioma arising after radiation[25,26], this enrichment of *PIK3CA* and *AKT1* mutations in hormone treatment-related cases represents another example for correlation of genomic findings and exposure to exogenous factors putatively involved in oncogenesis. For meningiomas in which cessation of hormone treatment and surgery are not sufficient, the PIK3CA/AKT1 pathway may offer a potential target for therapy.

"Integrated models incorporating radiologic and radiomic features predict meningioma grade, local failure and overall survival", by Morin et al.[27]

Although traditional classifications in meningioma modestly risk-stratify patients for risk of recurrence, considerable variability remains in clinical behaviour that is unexplained. Given that nearly all patients with meningiomas will have MRI prior to surgical resection, quantitative features from high-resolution pre-operative imaging that may not be appreciable to humans may be a promising avenue to identify additional information to refine the unexplained variability in clinical outcomes in meningioma. In this issue, Morin *et al.* used machine-learning approaches to generate radiologic-based strata of meningiomas with distinct clinical behaviour[27]. The authors found that tumors within the high-risk radiologic strata harboured known aggressive molecular alterations such as increased tumor mutation burden and a hypermethylation phenotype. Using feature reduction strategies, the authors identified Apparent Diffusion Coefficient (ADC) hypointensity and low sphericity as features that were independently associated with tumor grade on an external validation cohort. Further integration of radiologic characteristics together with clinical parameters resulted in general improvement of risk estimations with integrated models in comparison to clinical models alone. In sum, the authors demonstrated that pre-operative MRI radiologic features have added value in identifying aggressive meningiomas providing rationale and justification for further layering of molecular data into integrated radiologic-clinical models.

"Current Status of PET Imaging in Neuro-Oncology", by Galldiks et al.[28]

Although MRI has become cemented as the gold-standard imaging technique in neuro-oncology owing to its substantial soft-tissue contrast and high resolution with relatively common availability, there are clear challenges particularly with delineating subtle changes in biology using conventional MRI. PET using radiolabelled aminoacids provides an opportunity to overcome these limitations[29,30]. In this issue, Galldiks *et al.* review the utility of PET imaging particularly for disease delineation, response assessment and differentiation of treatment-changes from neoplastic biological alterations in gliomas, meningiomas, and brain metastases[28]. The authors describe how amino acid PET may represent a highly promising approach owing to efforts to standardize imaging acquisition. Hybrid PET-MR systems that allow for simultaneous capturing of high-resolution MRI with PET hold considerable promise as the next generation of imaging advances that can offer complementary information about tumor biology that would not otherwise be captured using a single modality.

"Efficacy and pharmacodynamics of niraparib in BRCA-mutant and wildtype intracranial triple negative breast cancer murine models", by Sambade et al.[31]

Brain metastases from triple negative breast cancer are associated with a terrible prognosis. Unfortunately, there are no approved systemic therapies for patients with negative breast cancer (TNBC) brain metastases. The frequent alterations in *BRCA* and genomic instability of these tumors renders them deficient in homologous recombination DNA repair and possibly sensitive to poly (ADP-ribose) polymerase (PARP) inhibitor therapy[32]. In this issue, Sambade *et al.* evaluated the efficacy of brain-permeable PARP-inhibitor niraparib in *BRCA*-mutant and wildtype murine models of TNBC[31]. The authors found that niraparib reduced tumor burden, was well tolerated, and improved survival in one of two intracranial *BRCA*-mutant TNBC models. Interestingly, both *BRCA*-mutant TNBC models had detectable levels of niraparib with resultant significant reduction in PAR levels in tumor tissue suggesting factors beyond pharmacokinectics and dynamics being responsible for heterogeneity in response to niraparib monotherapy. Using RNA sequencing data from the TCGA, the authors showed considerable heterogeneity in DNA-damage signatures in *BRCA*-mutant tumors including DNA combination repair and homologous recombination that correlated with *RAD51* gene expression. RAD51 inhibition using B02 was found to sensitize both *BRCA*-wildtype and *BRCA*-mutant cell lines to niraparib-mediated PARP inhibition. Previous clinical trials testing PARP inhibitors for metastatic BRCA1/2 associated breast cancer has routinely excluded patients with active brain metastases. These exciting results support the development of PARP-inhibition, either as monotherapy or perhaps in combinatorial therapy with PARP-sensitizers, in *BRCA*-mutant TNBC brain metastases, a disease entity in urgent need of better therapeutics.

These inaugural 10 papers promise an exciting first year of publications for *Neuro-Oncology Advances* and set the pace for the Journal that we hope the readership, investigators, clinicians and patients will find to be of value to the field of neuro-oncology. The authors of the first-ten papers should be commended for their support to launch the new Journal in the field.

Reference

1. Rivera-Molina Y, Jiang H, Fueyo J, et al. GITRL-armed Delta-24-RGD oncolytic adenovirus prolongs survival and induces anti-glioma immune memory. *Neuro-Oncology Adv.* 2019;1(1). doi:10.1093/noajnl/vdz009.
2. Chiocca EA, Abbed KM, Tatter S, et al. A Phase I Open-Label, Dose-Escalation, Multi-Institutional Trial of Injection with an E1B-Attenuated Adenovirus, ONYX-015, into the Peritumoral Region of Recurrent Malignant Gliomas, in the Adjuvant Setting. *Mol Ther.* 2004;10(5):958-966. doi:10.1016/j.ymthe.2004.07.021.
3. Desjardins A, Gromeier M, Herndon JE, et al. Recurrent Glioblastoma Treated with Recombinant Poliovirus. *N Engl J Med.* 2018;379(2):150-161. doi:10.1056/NEJMoa1716435.
4. Chiocca EA, Nassiri F, Wang J, Peruzzi P, Zadeh G. Viral and other therapies for recurrent glioblastoma: is a 24-month durable response unusual? *Neuro Oncol.* 2019;21(1):14-25. doi:10.1093/neuonc/noy170.
5. Lang FF, Conrad C, Gomez-Manzano C, et al. Phase I Study of DNX-2401 (Delta-24-RGD) Oncolytic Adenovirus: Replication and Immunotherapeutic Effects in Recurrent Malignant Glioma. *J Clin Oncol.* 2018;36(14):1419-1427. doi:10.1200/JCO.2017.75.8219.
6. Wijnenga MMJ, van der Voort SR, French PJ, et al. Differences in spatial distribution between WHO 2016 low-grade glioma molecular subgroups. *Neuro-Oncology Adv.* 2019;1(1). doi:10.1093/noajnl/vdz001.
7. Lai A, Kharbanda S, Pope WB, et al. Evidence for sequenced molecular evolution of IDH1 mutant glioblastoma from a distinct cell of origin. *J Clin Oncol.* 2011;29(34):4482-4490. doi:10.1200/JCO.2010.33.8715.
8. Tejada Neyra MA, Neuberger U, Reinhardt A, et al. Voxel-wise radiogenomic mapping of tumor location with key molecular alterations in patients with glioma. *Neuro Oncol.* 2018;20(11):1517-1524. doi:10.1093/neuonc/noy134.
9. Livermore LJ, Isabelle M, Bell IM, et al. Rapid intraoperative molecular genetic classification of gliomas using Raman spectroscopy. *Neuro-Oncology Adv.* 2019;1(1). doi:10.1093/noajnl/vdz008.
10. Longuespée R, Wefers AK, De Vita E, et al. Rapid detection of 2-hydroxyglutarate in frozen sections of IDH mutant tumors by MALDI-TOF mass spectrometry. *Acta Neuropathol Commun.* 2018;6(1):21. doi:10.1186/s40478-018-0523-3.
11. Sim H-W, Nejad R, Zhang W, et al. Tissue 2-Hydroxyglutarate as a Biomarker for Isocitrate Dehydrogenase Mutations in Gliomas. *Clin Cancer Res.* 2019;25(11):3366-3373. doi:10.1158/1078-0432.CCR-18–3205.
12. Munegowda MA, Fisher C, Molehuis D, et al. Efficacy of Ruthenium coordination complex based Rutherrin in a pre-clinical rat glioblastoma(GBM) model. *Neuro-Oncology Adv.* May 2019. doi:10.1093/noajnl/vdz006.
13. Gittleman H, Cioffi G, Chunduru P, et al. An independently validated nomogram for IDH-wildtype glioblastoma patient survival. *Neuro-Oncology Adv.* 2019;1(1). doi:10.1093/noajnl/vdz007.

14. Aibaidula A, Chan AK-Y, Shi Z, et al. Adult IDH wild-type lower-grade gliomas should be further stratified. *Neuro Oncol*. 2017;19(10):1327-1337. doi:10.1093/neuonc/nox078.
15. Gittleman H, Lim D, Kattan MW, et al. An independently validated nomogram for individualized estimation of survival among patients with newly diagnosed glioblastoma: NRG Oncology RTOG 0525 and 0825. *Neuro Oncol*. 2017;19(5):669-677. doi:10.1093/neuonc/now208.
16. Chang R, Tosi U, Voronina J, et al. Combined Targeting of PI3K and MEK Effector Pathways via CED for DIPG Therapy. *Neuro-Oncology Adv*. 2019;1(1). doi:10.1093/noajnl/vdz004.
17. Pollack IF, Stewart CF, Kocak M, et al. A phase II study of gefitinib and irradiation in children with newly diagnosed brainstem gliomas: A report from the Pediatric Brain Tumor Consortium. *Neuro Oncol*. 2011;13(3):290-297. doi:10.1093/neuonc/noq199.
18. Souweidane MM, Kramer K, Pandit-Taskar N, et al. Convection-enhanced delivery for diffuse intrinsic pontine glioma: a single-centre, dose-escalation, phase 1 trial. *Lancet Oncol*. 2018;19(8):1040-1050. doi:10.1016/S1470-2045(18)30322-X.
19. Portet S, Naoufal R, Tachon G, et al. Histo-molecular characterization of intracranial meningiomas developed in patients exposed to high-dose cyproterone acetate: an antiandrogen treatment. *Neuro-Oncology Adv*. 2019;1(1). doi:10.1093/noajnl/vdz003.
20. Gil M, Oliva B, Timoner J, Maciá MA, Bryant V, de Abajo FJ. Risk of meningioma among users of high doses of cyproterone acetate as compared with the general population: evidence from a population-based cohort study. *Br J Clin Pharmacol*. 2011;72(6):965-968. doi:10.1111/j.1365-2125.2011.04031.x.
21. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat Genet*. 2013;45(3):285-289. doi:10.1038/ng.2526.
22. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. *Science*. 2013;339(6123):1077-1080. doi:10.1126/science.1233009.
23. Abedalthagafi M, Bi WL, Aizer AA, et al. Oncogenic PI3K mutations are as common as AKT1 and SMO mutations in meningioma. *Neuro Oncol*. 2016;18(5):649-655. doi:10.1093/neuonc/nov316.
24. Peyre M, Gaillard S, de Marcellus C, et al. Progestin-associated shift of meningioma mutational landscape. *Ann Oncol Off J Eur Soc Med Oncol*. 2018;29(3):681-686. doi:10.1093/annonc/mdx763.
25. Agnihotri S, Suppiah S, Tonge PD, et al. Therapeutic radiation for childhood cancer drives structural aberrations of NF2 in meningiomas. *Nat Commun*. 2017;8(1):186. doi:10.1038/s41467-017-00174-7.
26. Sahm F, Toprak UH, Hübschmann D, et al. Meningiomas induced by low-dose radiation carry structural variants of NF2 and a distinct mutational signature. *Acta Neuropathol*. 2017;134(1):155-158. doi:10.1007/s00401-017-1715-9.
27. Morin O, Chen WC, Nassiri F, et al. Integrated models incorporating radiologic and radiomic features predict meningioma grade, local failure and overall survival. *Neuro-Oncology Adv*. 2019;1(1). doi:10.1093/noajnl/vdz011.
28. Galldiks N, Lohmann P, Albert NL, Tonn JC, Langen K-J. Current Status of PET Imaging in Neuro-Oncology. *Neuro-Oncology Adv*. 2019;1(1). doi:10.1093/noajnl/vdz010.
29. Albert NL, Weller M, Suchorska B, et al. Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas. *Neuro Oncol*. 2016;18(9):1199-1208. doi:10.1093/neuonc/now058.
30. Langen K-J, Watts C. Amino acid PET for brain tumours — ready for the clinic? *Nat Rev Neurol*. 2016;12(7):375-376. doi:10.1038/nrneurol.2016.80.
31. Sambade MJ, Van Swearingen AED, McClure MB, et al. Efficacy and pharmacodynamics of niraparib in BRCA-mutant and wildtype intracranial triple negative breast cancer murine models. *Neuro-Oncology Adv*. 2019;1(1). doi:10.1093/noajnl/vdz005.
32. Diossy M, Reiniger L, Sztupinszki Z, et al. Breast cancer brain metastases show increased levels of genomic aberration-based homologous recombination deficiency scores relative to their corresponding primary tumors. *Ann Oncol*. 2018;29(9):1948-1954. doi:10.1093/annonc/mdy216.