1st Net4Brain Annual Meeting, Closing the translational gap in brain cancer treatment

September 4th-6th, 2024

National Institute of Biology (NIB)

BOOK OF ABSTRACTS

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NIB NACIONALNI INŠTITUT ZA BIOLOGIJO
NATIONAL INSTITUTE OF BIOLOGY

Net4Brain
Let's beat brain cancer together

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EUROPEAN COOPERATION
IN SCIENCE & TECHNOLOGY

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Day 1

4 September, Wednesday

08.00 – 9.00 am	**Registration** *NIB registration desk*
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01.00 - 2.00 pm	**Lunch** (only for core group members) *FITO conference room*

Start of Scientific Program (all attendees)

01.00 – 2.00 pm	**Registration** *NIB registration desk*
02.00 – 02.15 pm	**Welcome** *NIB conference room* **Maja Ravnikar**, NIB director **Xinzhong Li**, Net4Brain COST action Chair **Barbara Breznik & Metka Novak**, Chairs of **Organizing** Committee
02.15 – 02.45 pm	**Opening Keynote Lecture, on-line** *NIB conference room* Chair: **Xinzhong Li** **Guohao Dai,** Northeastern University, College of Engineering, USA *Bioengineered perfused human brain microvasculature to model brain tumor and neurodegenerative diseases*
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Talk 2, 20min
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Imaging biomarkers for glioblastoma, including validated AI model for patient stratification in clinical trials

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	Characterizing regulatory heterogeneity and plasticity in glioblastoma through single-cell multi-omics data modelling **Discussion WG3 (30 min)** Bagci-Onder, Kaymaz **Revising and planning WG activities**
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Day 3
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Scientific Program (all attendees)

09.00 – 10.30 am	**Scientific Session 5 – WG5, Clinical Treatment Recommendation** *NIB conference room* Chair: **Oliver Hanemann** **Talk 1, 20 min** **Marija Skoblar Vidmar**, Institute of Oncology Ljubljana, Slovenia *Recurrent glioma: a diagnostic and therapeutic challenge* **Talk 2, 20min** **Johannes Haybäck**, Tyrolpath Obrist Brunhuber GmbH, Austria *Eukaryotic translation initiation factors in brain tumors* **Short talk 1, 7 min** **Catarina Passarinho**, Institute for Systems and Robotics (ISR-Lisboa), Portugal *Optimising Automated Segmentation of High-Grade Gliomas Through Deep Learning Strategies* **Short talk 2, 7 min** **Michal Hendrych**, Department of Pathology, St. Anne's University Hospital and Faculty of Medicine, Masaryk University Brno, Czech Republic *Astrocytoma IDH-mutant with primitive neuronal component is a distinct subtype* **Discussion WG5 (30 min),** Hanemann **Revising and planning WG activities**
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11.00 - 11.30 am	**Coffee break** *NIB gallery*
11.30 - 13.00 pm	**Management Committee Meeting** (only for MC members)
13.00 - 13.30 pm	**Lunch** (only for MC members) *NIB gallery*

WELCOME EXCURSION

Networking, discussion and dinner

Date : September 4th, 2024 **Duration** : 2.00 - 10.30 p.m.

BLED CASTLE

- TRANSPORT FROM LJUBLJANA TO BLED (2:00 - 3:00 p.m.)
- FREE TIME (3:00 - 4:00 p.m.)
- DESCENT (4:00 - 4.30 p.m.)

Meeting point: NIB lobby - ground floor

60 km route from Central Slovenia to Carniola region. Lake Bled is located on the edge of the Triglav National Park, where one can enjoy the Alpine landscape.

Perched atop a cliff towering 130 metres above Lake Bled, the castle with a 1000-year history rewards visitors observing the countryside from its lower courtyard with stunning views of Bled, its lake and the island.

Bled castle offers many options as: The castle chapel, museum, the castle printing works, the wine cellar, the castle wall, gallery STOLP, coffeeshop, Beehouse, observing the view, taking photos, toilet, etc.

Meeting point: Castle entrance

LAKE BLED

- FREE TIME (4:30 - 6:00 p.m.)
- TRANSPORT FROM BLED TO LESCE (6:00 - 6:30 p.m.)

Discover the magic of the lake that attracts travellers from near and far. A tectonic hole made by the Bohinj glacier through the years, was once at the location of the present lake. Its path was obstructed by a huge rock which was so persistently scraped that the only thing that remained was the present island. The ice melted and the basin was filled with water, thus Lake Bled emerged, which is in some places up to 30 metres deep and quite popular amongst divers.

Bled offers stunning nature and viewpoints, taking photos (photopoint: The heart of Bled), Kremšnita (cream cheesecake) at Kavarna Park (Café Park), souvenir shop, shopping, toilet, , etc.

Meeting point: The hearth of Bled

DINNER

- DINNER (6:30 - 9:30 p.m.)
- RETURN TO LJUBLJANA (9:30 - 10.30 p.m.)

Gorenjska is a rugged mountain landscape, where cattle and sheep graze, and cheeses and other dairy products characteristic of the region are obtained from their milk. Farmers sow buckwheat, barley and millet, the flat areas have the best conditions for growing potatoes. Fish scurry in clear alpine rivers, streams and lakes; original Bohinj zlatovčica and trout. The forests are home to game, mushrooms and forest fruits. There are also many high-stemmed orchards with various fruits. We will be able to try some of the locally produced delicious in the guesthouse Tulipan.

Meeting point: Guesthouse Tulipan

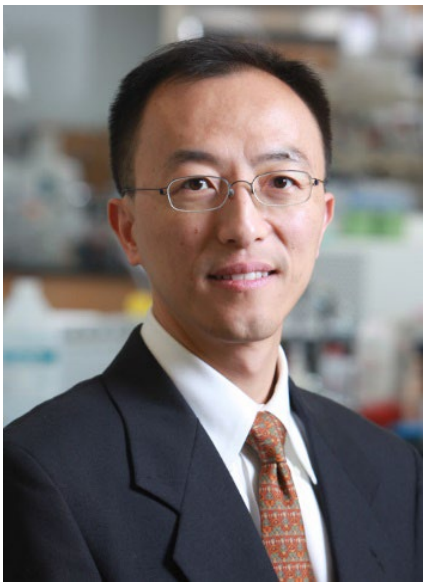
Abstracts of keynote lectures

1. Bioengineered perfused human brain microvasculature to model brain tumor and neurodegenerative diseases

Guohao Dai, PhD, Professor, Fellow AHA AIMBE, BMES, Department of Bioengineering
Northeastern University, Boston, USA

Blood vessels play an increasingly important role in most human tissue and organ systems. Importantly, vascular niche was found to be a key element of many stem cell environments such as neural stem cells and cancer stem cells. Vascular cells not only form conduits to deliver nutrient and oxygen, but also provide instructive signals to control stem cell self-renewal and differentiation, therefore, is critical for tissue regeneration. The mission of Vascular Bioengineering Laboratory is to integrate bioengineering approaches with stem cells and vascular biology to understand blood vessel regeneration and vascular disease processes, and to develop novel therapeutic modalities to treat vascular-related disorders such as cardiovascular, neurovascular and cancer. Toward this goal, our lab has developed the method to bioengineer human brain microvascular network consists of human brain endothelial cells, pericytes and astrocytes. We have shown that interstitial flow promotes lumen formation, interconnectivity and astrocytes association of the bioengineered vasculature and maintains blood brain barrier (BBB) functions. Furthermore, perfused bioengineered vasculature enhances neural stem cell self-renewal and neuronal differentiation and maturation. We have also shown that brain vascular niche supports the infiltrative behavior of glioma stem cells, and glioblastoma dormancy, which contributes to chemo resistance. In this talk, I will present research projects on the bioengineer 3D human brain vascular network and its application in neural stem cell and brain tumor research.

Speaker's Bio:



Dr. Dai is currently a Professor in the Department of Bioengineering at Northeastern University. Dr. Dai received his B.S. in Mechanical Engineering from Peking University, Ph.D. in Biomedical Engineering from MIT's HST Program (Harvard-MIT Division of Health Science and Technology). He completed his Post-doctoral training in Vascular Biology at Harvard Medical School.

Current research in his lab focuses on the 3-D bioprinting technology, stem cells and vascular bioengineering, and are funded by major grants from NSF, NIH, DoD, NASA and American Heart Association. Dr. Dai received the Scientist Development Award from American Heart Association, NSF Career Award, Rising Star Award from Biomedical Engineering Society, Institute's Faculty Career Award (RPI), College of Engineering Faculty Fellow (Northeastern) and CAB Mid-Career Award. Dr. Dai is on the list of World's Top 2% Scientists (by Stanford/Elsevier, 2022, 2023). He is the elected Fellow of American Heart Association (FAHA), and Fellow of American Institute for Medical and Biological Engineering (AIMBE), and Fellow of BMES. He has served as the Chair of BMES's Cellular Molecular Bioengineering Society, and now serves on BMES Board of Directors.

2. Blood-based early diagnosis of brain cancer

James M. Cameron[1†], Paul M. Brennan[2†], Georgios Antoniou[1], Holly J. Butler[1], Ewan Gray[4], David S. Palmer[1], Alexandra Sala[1,7], **Matthew J. Baker[1*]**

[1]Dxcover Ltd.‡, Suite RC534, Royal College Building, 204 George Street, Glasgow, G1 1XW, UK

[2]Translational Neurosurgery, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, EH4 2XU, UK

Background: Diagnostic delays impact the quality of life and survival of patients with brain cancer. Currently, with no blood test to assist them, clinicians must make their referral decision based on symptoms. Existing symptom-based referral guidelines inadequately stratify patients for brain imaging based on suspicion of cancer. A simple, rapid liquid biopsy placed in a primary care setting would enable more efficient triage of patients with non-specific symptoms related to brain cancer.

Methods: The Dxcover Liquid Biopsy is a rapid multi-omic liquid biopsy that interrogates a blood sample with Infrared (IR) radiation and produces a distinctive signature that represents the whole biomolecular profile of the sample. In initial feasibility studies, we recruited 988 patients prospectively with non-specific symptoms associated with a brain tumor, and the algorithm detected 96% of the patients with brain tumors and 100% of glioblastomas (GBM), when tuned for greater sensitivity. The diagnostic models can be tailored towards higher sensitivity (or specificity) depending on clinical priorities and international healthcare markets.

Results: EMBRACE is a prospective, observational, multicenter study, currently recruiting patients across seven sites in the UK and Europe. The targeted population is patients presenting to primary care with non-specific symptoms that are associated with brain cancer, e.g., headaches, seizures, new onset neurological defect etc. Participants will be recruited where the assessing clinician has identified a clinical need to undergo a diagnostic investigation where the differential diagnosis includes a brain tumor, or with a recent new brain cancer diagnosis, prior to instigation of treatment.

Conclusions: This simple, non-invasive liquid biopsy would facilitate the triage of brain tumor patients for rapid imaging. Patients with a true negative result could avoid the radiation from brain imaging and the identification of incidental abnormalities, which can prompt further investigations or treatments. Furthermore, there is potential for cost savings when considering the reduction in unnecessary brain scans, as well as reducing the burden on hospitals and clinicians, and other preventable tests or procedures. By decreasing the time to diagnosis, the quality of life of brain cancer patients can be improved.

Abstracts of invited lectures

1. Epigenetics as biomarkers

Aida Hajdarpasic, Sarajevo Medical School, University Sarajevo School of Science and Technology Bosnia & Herzegovina

Brain cancer development is caused by consistent accumulation of changes which affect structure and function of genes and genome as a whole. When it comes to genetic changes they affect and disrupt the sequence of DNA. On the other hand, epigenetic changes contribute to the acquisition of hallmark tumor capabilities. They do this by regulating gene expression programs that promote tumorigenesis. Changes in DNA methylation and histone modifications significantly contribute to tumor progression and metastasis. However, there is a strong and yet not quite fully explored mechanism of small RNA epigenetic regulation and its contribution to brain cancer development. This presentation introduces all epigenetic mechanisms which contribute to brain cancer development with a special emphasis on the role of small RNAs (e.g. miRNAs).

2. Imaging biomarkers for glioblastoma, including validated AI model for patient stratification in clinical trials

Alysha Chelliah , David A. Wood, Liane S. Canas , Haris Shuaib , Stuart Currie , Kavi Fatania, Russell Frood , Chris Rowland-Hill, Stefanie Thust , Stephen J. Wastling , Sean Tenant, Catherine McBain, Karen Foweraker, Matthew Williams, Qiquan Wang, Andrei Roman, Carmen Dragos, Mark MacDonald, Yue Hui Lau , Christian A. Linares , Ahmed Bassiouny , Aysha Luis,ThomasYoung, Juliet Brock, Edward Chandy , Erica Beaumont,Tai-Chung Lam, Liam Welsh, Joanne Lewis , Ryan Mathew , Eric Kerfoot , Richard Brown , Daniel Beasley, Jennifer Glendenning, Lucy Brazil, Angela Swampillai, Keyoumars Ashkan, Sébastien Ourselin , Marc Modat , and **Thomas C. Booth**

School of Biomedical Engineering & Imaging Sciences, King's College London, London, UK (A.C., D.A.W., L.S.C., A.B., A.L., E.K., R.B., D.B., S.O., M.Mo., T.C.B.); Guy's and St. Thomas' NHS Foundation Trust, London, UK (H.S., A.R., M.Ma., C.A.L., T.Y., D.B., L.B., A.S.); Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK (H.S., K.A.); Leeds Teaching Hospitals NHS Trust, Leeds, UK (S.C., K.Fa., R.F., R.M.); Hull University Teaching Hospitals NHS Trust, England, UK (C.R-H.); University College London Hospitals NHS Foundation Trust, London, UK (S.Th., S.J.W.); Institute of Neurology, University College London, London, UK (S.Th., S.J.W.); Nottingham University Hospitals NHS Trust, Nottingham, UK (S.Th., K.Fo.); Precision Imaging Beacon, School of Medicine, University of Nottingham, Nottingham, UK (S.Th.); The Christie NHS Foundation Trust, Withington, Manchester, UK (S.Te., C.M.); Radiotherapy Department, Imperial College Healthcare NHS Trust, London, UK (M.W., Q.W.); Institute for Global Health Improvement, Imperial College London, London, UK (M.W., Q.W.); Oncology Institute Prof. Dr. Ion Chiricuta, Cluj-Napoca, Romania (A.R.); Buckinghamshire Healthcare NHS Trust, Amersham, UK (C.D.); King's College Hospital NHS Foundation Trust, London, UK (Y.H.L., A.L., K.A., T.C.B.); Department of Radiology, Mansoura University, Mansoura, Egypt (A.B.); Brighton and Sussex University Hospitals NHS Trust, England, UK (J.B., E.C.); Lancashire Teaching Hospitals NHS Foundation Trust, England, UK (E.B., T-C.L.); The Royal Marsden NHS Foundation Trust, London, UK (L.W.); Newcastle upon Tyne Hospitals NHS Foundation Trust, England, UK (J.L.); School of Medicine, University of Leeds, Leeds, UK (R.M.); Maidstone and Tunbridge Wells NHS Trust, Kent, UK (J.G.)

Background
The aim was to predict survival of glioblastoma at 8 months after radiotherapy (a period allowing for completing a typical course of adjuvant temozolomide), by applying deep learning to the first brain MRI after radiotherapy completion.

Methods
Retrospective and prospective data were collected from 206 consecutive glioblastoma, isocitrate dehydrogenase -wildtype patients diagnosed between March 2014 and February 2022 across 11 UK centers. Models were trained on 158 retrospective patients from 3 centers. Holdout test sets were retrospective (n = 19; internal validation), and prospective (n = 29; external validation from 8 distinct centers). Neural network branches for T2-weighted and contrast-enhanced T1-weighted inputs were concatenated to predict survival. A nonimaging branch (demographics/MGMT/treatment data) was also combined with the imaging model. We investigated the influence of individual MR sequences; nonimaging features; and weighted dense blocks pretrained for abnormality detection.

Results
The imaging model outperformed the nonimaging model in all test sets (area under the receiver-operating characteristic curve, AUC $P = .038$) and performed similarly to a combined imaging/nonimaging model ($P > .05$). Imaging, nonimaging, and combined models applied to amalgamated test sets gave AUCs of 0.93, 0.79, and 0.91. Initializing the imaging model with pretrained weights from 10 000s of brain MRIs improved performance considerably (amalgamated test sets without pretraining 0.64; $P = .003$).

Conclusions
A deep learning model using MRI images after radiotherapy reliably and accurately determined survival of glioblastoma. The model serves as a prognostic biomarker identifying patients who will not survive beyond a typical course of adjuvant temozolomide, thereby stratifying patients into those who might require early second-line or clinical trial treatment.

3. Preclinical modeling of high-grade glioma – an overview of patient-derived and mouse cell culture models

Lene Uhrbom, Uppsala University, Sweden

At Uppsala University we have a longstanding tradition of establishing, studying and distributing patient-derived cell cultures of high-grade glioma. I will present the background to and development of our HGCC (human glioblastoma cell culture) repository, how we collect, explant, maintain and characterize the cultures and how these can be accessed for research. I will also describe the mouse glioma models we use and cell cultures derived thereof, which serve as a useful complement to HGCC, in particular for functional investigations of developmental and immunological aspects of high-grade glioma.

4. Preclinical modelling expertise and database at NET4Brain consortium

Anna Golebiewska, Luxembourg Institute of Health, Luxembourg

Barbara Breznik, National Institute of Biology, Slovenia

Preclinical models are essential tools for basic research and for preclinical therapeutic interventions. They allow for elucidating the mechanisms involved in tumor onset, progression and treatment resistance. They are fundamental in evaluating therapeutics prior clinical trials. Although numerous clinical trials have been conducted against brain tumors, most fail due to inappropriate selection of the compounds at the preclinical stage. Therefore, advanced models recapitulating closely human disease are crucial for achieving clinical impact.

The Net4Brain consortium aims to provide guidelines for application of diverse preclinical models in research and preclinical efficacy studies, fitting the biological questions and treatment modalities. Net4Brain members are actively collaborating to provide a comprehensive platform to the research community for accessing the well-established and characterized models. Here we will present results of a survey that has been conducted among the Net4Brain members summarizing the expertise in preclinical modelling and available cohorts of patient-derived and experimental models. We will discuss diverse protocols and technologies available for distribution and training.

5. Recent advances in diagnosis of low-grade pediatric gliomas

Ibrahim Kulac, Koç University School of Medicine, Turkey

Pediatric low-grade gliomas are the most common central nervous system tumors in children, characterized by their generally indolent behavior and favorable prognosis. Among these, pilocytic astrocytoma (PA) stands out due to its distinctive pathological features and clinical presentation. PA typically presents in the posterior fossa but can be seen in other regions among neuroaxis in children and young adults. It is pathologically characterized by a biphasic architecture, with more compact and somewhat loose areas including Rosenthal fibers, and eosinophilic granular bodies, although none of them are diagnostic by their own. The majority of PAs harbor alterations in the MAPK pathway and the most commonly seen alteration is *KIAA1549::BRAF* fusion. MAPK pathway alterations can also be seen in many other low (and sometimes high) grade tumors in the central nervous system.

According to the findings we have recently published, none of the so long proposed factors such as molecular findings, patient age, tumor location apart from the extent of surgical resection seem to be an independent prognosticator. In PA gross total resection is strongly associated with improved recurrence-free survival, as we have shown in our cohort of nearly 500 cases. However, the management of PAs poses challenges, particularly in cases where complete resection is not feasible due to the tumor's location or involvement with critical neuroanatomical structures.

Despite advances in molecular characterization, including the identification of MAPK pathway alterations, the precise prognostic implications of these findings remain under investigation.

This talk will primarily focus on the nuances of pilocytic astrocytoma (PA) diagnosis, emphasizing its histological and molecular characteristics. Additionally, it will explore the latest findings on the impact of surgical and adjuvant therapies on patient outcomes. The discussion will also extend to other low-grade glial tumors in pediatric patients, which continue to present diagnostic challenges and other complexities in clinical management.

6. Tumor heterogeneity and therapeutic vulnerabilities in IDH mutant gliomas

Sevin Turcan, Neurology Clinic and National Center for Tumor Diseases, Heidelberg University Hospital and Heidelberg University, Heidelberg, Germany

The isocitrate dehydrogenase (IDH) gene is recurrently mutated in adult diffuse gliomas. IDH-mutant gliomas are categorized into oligodendrogliomas and astrocytomas, each with unique pathological and molecular features. In addition to tumor heterogeneity, IDH-mutant gliomas exhibit differences in their tumor microenvironment. The immune microenvironment of these tumors varies among patients and significantly affects tumor growth and treatment response. The presence of IDH mutations has been identified as a potential therapeutic target, and several drugs targeting the mutant IDH protein are currently in development. However, different tumor sites may respond differently to treatment, and the efficacy of these therapies may be influenced by tumor heterogeneity. Understanding the heterogeneity of IDH-mutant tumors is crucial for the development of effective treatment strategies. This talk will provide an overview of the heterogeneity in IDH-mutant gliomas and summarize potential targets contributing to disease pathology.

7. AI applications in Brain cancer

Robertas Damaševičius, Kaunas University of Technology, Lithuania

8. Non-invasive monitoring to improve glioblastoma follow-up

Margarida Julià-Sapé [1,2, 3]

[1]Departament de Bioquímica i Biologia Molecular, Universitat Autònomade Barcelona (UAB), Carrer de la Vall Moronta, 08193 Bellaterra (Cerdanyola del Vallès), Barcelona, Spain,
[2]Institut de Biotecnologia i Biomedicina (IBB), Edifici MRB. Carrer de la Vinya, s/n. Campus de Bellaterra, 08193 Cerdanyola del Vallès, Barcelona, Spain
[3]Centro de Investigación Biomédica en Red (CIBER), Av. Monforte de Lemos, 3-5. Pabellón 11. Planta 0. 28029 Madrid, Spain

In-vivo magnetic resonance spectroscopy (MRS) is one of several magnetic resonance (MR) modalities. The interest of this technique lies on its ability to provide relevant information about tissue metabolism in a non-invasive and non-radioactive way: in its most used application, 1H-MRS, the technique “sees” the protons of low-molecular weight metabolites in solution, present in the millimolar range of concentration. It is broadly accepted that MRS reveals the drastic differences that appear due to metabolic reprogramming in brain tumours, and that the changes can be observed with the 1.5/3T scanners used in routine clinical practice. Metabolic pattern changes are related to several factors, including the degree of malignancy, the cellular origin of the tumor, or its specific genetic framework. We studied a consecutive cohort of 31 patients at the first follow-up after the Stupp regime to evaluate if the metabolic pattern assessed with MRS was predictive of treatment response two months later. We extracted the underlying metabolic patterns of the contrast-enhancing regions with a blind-source separation method and mapped them over the reference images. We identified a metabolic pattern associated to early response to therapy. This distinctive metabolic response pattern in humans closely resembled the metabolic pattern already observed by us in GL261 tumors induced by intracranial stereotactic injection in C57BL/6 mice. Our findings suggest that MRS may serve as a predictive biomarker for treatment efficacy in brain tumor patients and highlight the potential for translating preclinical research into clinical practice.

9. Recurrent glioma: a diagnostic and therapeutic challenge

Marija Skoblar Vidmar, Institute of Oncology Ljubljana, Slovenia

Molecular biomarkers have fundamentally changed the understanding of glioma over the last decade. Accordingly, the fifth edition of the World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS5) incorporates numerous molecular biomarkers with clinicopathologic utility that are important for more accurate classification of CNS neoplasms. Molecular biomarkers also improve diagnostic accuracy and influence the course of treatment by changing treatment recommendations. A marker of particular importance is isocitrate dehidrogenase (IDH). Mutations in genes encoding IDH are known to play a crucial role in the classification of gliomas. IDH mutant (IDHm) glioma generally exhibits a better disease outcome than IDH wild type (IDHwt). In adults, diffuse gliomas have been divided into three types according to the new classification: (1) astrocytoma, IDHm; (2) oligodendroglioma, IDHm and 1p/19q-codeleted; and (3) glioblastoma, IDHwt.

The treatment of gliomas includes maximal surgical resection, possibly followed by radiotherapy (RT) and chemotherapy with either procarbazine/lomustine/vincristine (PCV) or temozolomide (TMZ). Due to the proliferative, radioresistant, and chemoresistant nature of the gliomas and high levels of intratumoral heterogeneity, the disease often recurs, and the possibilities of additional treatment are very limited.

The evaluation of treatment response remains a challenge in glioma cases because the neuro oncological therapy can lead to the development of treatment-related changes (TRC) that mimic true progression (TP). Positron emission tomography (PET) using O-(2-[^{18}F] fluoroethyl-)-L-tyrosine (^{18}F-FET) has been shown to be a useful tool for detecting TRC and TP.

The results of our published study indicated that the diagnostic value of static and dynamic biomarkers of ^{18}F-FET PET for discrimination between TRC and TP depends on the IDH mutation status of the tumor. Dynamic ^{18}F-FET PET acquisition proved helpful in the IDHwt subgroup, as opposed to the IDHm subgroup, providing an early indication to discontinue dynamic imaging in the IDHm subgroup.

10. Eukaryotic translation initiation factors in brain tumors

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Glioblastoma (GBM) is a brain tumor with the worst outcome within the group of cerebral neoplasms. Therapies were only able to mildly meliorate the patient's overall survival and disease-free-survival-time. Due to the therapy limitations, new therapeutic options are urgently needed. In many cancer entities, among them gliomas like GBM, eukaryotic initiation factors (eIFs) are altered, particularly many are over- and under-expressed.

The PI3K/AKT/mTOR pathway has an influence on the genesis of gliomas and glioblastomas by affecting the proliferation. Upstream of the pathway, the protein synthesis is performed by eukaryotic translation factors. The group of eIFs consists of about 32 different proteins, with at least 12 strictly necessary for the ribosomal protein machinery. The first step, the translation initiation, could function as a rate-limiting step. Different studies found that mTOR-related proteins and eIFs play a role in glioma (among them astrocytomas of WHO grades I-IV), in particular in GBM samples and cell lines, highlighted by employing immunohistochemistry and immunoblot analyses. mRNA expressions were also analyzed using qRT-PCR among other methods.

In the discussed studies by Krassnig et al, Adamczyk-Grochala et al, Quddusi et al and Otztatlici et al,the results highlight the potential of eIFs as therapeutic targets.

Abstracts of short lectures

1. Circulating Biomarkers: Is There an Ideal One?

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Diagnosing and treating of malignant diseases such as glioblastoma imposes a continuous quest for ideal diagnostic, prognostic, and monitoring biomarkers. Circulating biomarkers secreted by tumor cells into blood circulation and other biofluids and collected by liquid biopsy offer a non-invasive, rapid and accurate approach for early detection and disease progression and treatment effectiveness follow ups. Herein, we provide an overview of cell-free DNA (cfDNAs), circulating proteins, and circulating microRNAs (c-miRNAs), their characteristics, detection methods, applications and limitations as circulating biomarkers. Additionally, potential associations among these three classes of circulating biomarkers have been addressed. Due to their remarkable stability, specificity and sensitivity c-miRNAs have been proposed as superior non-invasive biomarker. Furthermore, future perspectives of combining circulator biomarkers into a multi-analyte liquid biopsy approach should significantly facilitate early identification, reliable prognosis, dynamic monitoring of tumor progression, enhanced prediction of therapeutic responses and improved patient outcomes.

Key words: circulating biomarkers, glioblastoma, cell-free DNA, circulating proteins, circulating microRNAs

2. Intraoperative Precision Sampling of Tumour Microenvironments based on 7T MRSI: A pipeline development.

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Background: 7 Tesla (7T) magnetic resonance spectroscopic imaging (MRSI) can identify neurochemical compounds in the brain at higher resolution. Gliomas are brain tumours that display multiple intratumoural heterogeneities. Our 7T MRSI maps can resolve metabolic heterogeneities to obtain samples from specific intratumoural hotspots. Therefore, the purpose of this study is to develop a pipeline to validate maps that includes MRSI map transfer to neuronavigation, surgical sampling, and sample validation by mass spectrometry (MS).

Method: We acquired and quantified 7T MRSI data of glioma patients. Metabolic maps for choline (Cho), N-acetylaspartate (tNAA), glutamine (Gln), glycine (Gly), and myo-inositol (Ins) were created and transferred together with morphological data to our neuronavigation planning server. Metabolic hotspot regions of interest (ROIs) were contoured by neurosurgeons. During surgery, samples were taken from the ROIs and separated for histopathology, NIO Imaging, and analytical chemistry. Mass spectrometry was used to quantify metabolic profiles of the tumours.

Results: We have applied this pipeline to 6 patients so far. The first patient's metabolic ratio maps show the intratumoural increases of Cho, Gln, Ins and Gly ratios to tNAA. NIO identified tumourous tissue in all 6 patients. Preservation for chemical analysis was successful and preliminary MS results confirm the presence of Cho and Gln.

Conclusions: We successfully tested our proposed pipeline. Preliminary MS and NIO results show that we were able to sample tumour hotspots based on 7T MRSI maps. This indicates that our workflow is feasible for future studies to validate 7T MRSI and to explore heterogeneous glioma metabolism.

3. Excessive nuclear envelope stress blunts the invasive potential of glioblastoma cells

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Glioblastoma (GB) is the most lethal primary brain tumor in adults, infamous for its cellular heterogeneity and extensive tissue infiltration. We hypothesize that the high cell density in the brain imposes significant mechanical load onto GB cells, which may render them vulnerable to nuclear envelope (NE) stress. To investigate this, we have quantified nuclear dynamics in a panel of GB cell lines. We found a significant, but cell-type dependent degree of nuclear dysmorphy, which correlated with the level of nuclear deformation over time. Using live cell imaging, we found that all GB cells experience NE ruptures, which are exacerbated under mechanical confinement. When examining GB cell migration in 3D collagen matrices and human iPSC-derived neurospheres, we discovered an inverse relationship between the level of NE stress and the invasive capacity. A targeted proximity proteomics experiment, using TurboID labelling, allowed identification of a mechanoregulatory circuit that is specifically upregulated in more invasive cells. Thus, we conclude that GB cells experience NE stress, and identified a signaling hub that could represent a new targetable vulnerability in GB disease progression.

4. Advanced 3D Cell Culture Models and Microfluidic Lab-on-Chip Devices for Glioblastoma Therapy Evaluation

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The research project focuses on utilizing advanced cell culture 3D models and microfluidic lab-on-a-chip devices for a comprehensive understanding and pre-clinical treatment evaluation of glioblastoma. The project combines two technologies: 3D cell culture models and lab-on-a-chip microfluidic devices to develop a predictive patient-specific model to evaluate the prospective clinical therapies. Traditional 2D cell cultures often fail to represent the complex tumor microenvironment found in glioblastoma patients accurately. 3D cell culture models, on the other hand, can mimic the 3D architecture and cell-to-cell interactions present in tumors, offering a more realistic platform for studying glioblastoma behavior and drug response. We have developed and utilized 3D cell culture models incorporating glioblastoma cells with other relevant cell types found in the brain tumor microenvironment, such as endothelial cells and immune cells. This approach allowed for a more holistic investigation of glioblastoma growth, invasion, and response to potential therapies.

We are further working to integrate lap-on-a-chip technology. Organ-on-a-chip technologies using patient-specific cells, represent a promising ex-vivo testing platform as they allow for controllable cell culture within an organotypic microarchitectural environment, providing a simple yet more physiologically relevant platform for drug screening than traditional cell culture/animal models. These microfluidic devices can recreate microfluidic environments within a chip, allowing for precise control over factors like flow, pressure, and nutrient delivery. By incorporating 3D glioblastoma cell cultures into lab-on-a-chip devices, we will create an even more sophisticated in vitro 3D model that closely mimics the physiological conditions experienced by glioblastoma cells within the brain.

5. 3D Glioblastoma Cell Culture within Alginate Microfibers for Long-Term Evaluation of Drug Effects

Sofija Jovanović Stojanov[1], Ana Podolski-Renić[1], Jelena Dinć[1], Jasmina Stojkovska[2,3], Bojana Obradović[2,3], Milica Pešić[1], Miodrag Dragoj[1]

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In our study, we aimed to develop a long-term three-dimensional (3D) model for glioblastoma cell culture to facilitate more reliable drug response studies. We cultured human U87 glioblastoma cells in alginate microfibers for a period of 28 days. Throughout this time, we monitored cell growth, viability, morphology, and aggregation in the 3D culture using fluorescent and confocal microscopy. Calcein-AM/propidium iodide staining was performed every seven days.

We validated the glioblastoma 3D model by subjecting the cells to temozolomide (TMZ) treatments for three consecutive days, starting from the 7th day of culturing cells in alginate microfibers. After a recovery period of 18 days, we evaluated cell viability using MTT assays and assessed the expression of resistance-related genes (MGMT and ABCB1) using qPCR. We also applied the same TMZ treatment schedule to cells cultured in a two-dimensional (2D) setting for comparison purposes.

Our results showed that within the long-term 3D model system in alginate fibers, the U87 cells remained viable for the entire 28-day period. Furthermore, on day 7, we observed that the cells formed visible aggregates oriented towards the periphery of the microfibers. Upon TMZ treatment, we observed a reduction in cell growth, as well as an increase in the expression of drug resistance-related genes. This effect was more pronounced in the 3D culture compared to the 2D culture.

In conclusion, we established a novel glioblastoma 3D model system, which could be particularly valuable for conducting long-term drug testing and optimizing treatment strategies.

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6. Bio-Nanomachine Interfaces in Externally Controllable Nanonetworks for Brain Tumour Management

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Resistance to molecular and immunologic therapies in Glioblastoma Multiforme (GBM) is attributed to (i) large genetic and phenotypic spatiotemporal heterogeneity, (ii) lack of successful delivery across the Blood-Brain- Barrier (BBB) and the Tumour Microenvironment , including the extracellular matrix, (iii) ineffective quantification of therapeutics uptake within the tumour and (iv) insufficiency of direct evaluation of treatment effectiveness. Nanosystems have been extensively explored as potential solutions in overcoming biological and mechanical barriers but have not as of yet made it effectively to the clinic. Induced Neural Stem Cells engineered to produce and deliver therapeutic non-encoding nucleic acids epitomised by micro-RNAs have a high potential to home tumour niches and inhibit progression are emerging as highly promising GBM advanced biological therapeutics.
Molecular Communications define a supra-discipline at the interface of Molecular Medicine with Information and Communication Technologies where cellular and sub-cellular units, such as engineered stem cells and tumour exosomes function as information sender and receiver bio-nanomachines propagating through biological and mechanical barriers. Encapsulation of iNSC therapeutic bio-nanomachines in implantable organoids or hybrid sensors comprised by polymeric scaffold membranes – used as host co-polymer (PMMA)-b-(MEBCA), lanthanide-based and aptamer-functionalized nanoparticles – integrated on light emitting diodes (LEDs) and photodiodes (PDs) used for excitation and fluorescence detection of biomarkers, respectively, confer a precision attribute to the theranostic scheme in a close-loop Externally Controllable Molecular Communication (ECMC) system. An ambitious paradigm shift is emerging in Oncology Research, where real-time monitoring of tumour initiation, progression and response to personalized therapy enables the supra-discipline of “bio-nanomachine diagnostics” ushering the emergence of the “Externally Controllable Nanonetwork Therapeutics” field, interfacing the tumour and the therapeutic organoids with actuating nanodevices embodied by wearable metamaterial antennas and multifunctional and multimodal smart biosensors.

7. Characterizing regulatory heterogeneity and plasticity in glioblastoma through single-cell multi-omics data modelling

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In Glioblastoma (GBM), tumor heterogeneity and plasticity are obstacles for effective therapy. Single-cell studies report the presence of several tumor cell states that can transition into one another and offer escape mechanisms. To develop more personalized therapies, a comprehensive understanding of the regulatory programs underlying these cell states and their plasticity is indispensable. This can be studied using Gene Regulatory Networks (GRNs) that model the molecular interactions between transcription factors and their target genes mainly based on transcriptomics and epigenomics data. Besides characterization of single patient and even cell state-specific regulatory programs, including prior knowledge of metabolic pathways enables the reverse engineering of metabolic GBM states. In this way, single-cell multi-omics data modelling allows to identify targetable mechanisms of heterogeneity and plasticity.

On single cell data from primary GBM tumors, we investigated how sequencing technologies, algorithmic choices and cell sampling within an assigned cell state influence accuracy and robustness of GRN inference. Furthermore, we explored cell state-specific regulatory programs in GBM by comparing primary versus recurrent tumors and investigated influential transcription factors for cell-state shifts through in silico perturbation. Finally, we predicted metabolic states in primary GBM tumors.

In conclusion, through single-cell multi-omics data modelling our work provides comprehensive insights into regulatory heterogeneity and plasticity in GBM to aid the development of more effective therapies.

8. Advancing Glioma Research through Multi-Omics Network Discovery and Analysis

Roberta Coletti, Bruno M. Costa, Marta B. Lopes

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Gliomas are primary malignant brain cancers characterised by high heterogeneity. The different glioma types present distinct molecular characteristics, which affect patient prognosis and treatment responses. Our work was developed as part of the "MONET: Multi-Omics Networks in Glioma" project, which aims to explore the molecular diversity of gliomas through multi-omics data analysis to identify possible biomarkers of cancer heterogeneity. In particular, the presented study focuses on network discovery and exploration, which is used to perform additional research tasks such as variable selection, patient clustering, and survival analysis. The data used were retrieved from The Cancer Genome Atlas (TCGA) program, with updated patients' diagnostic labels aligning with the latest glioma classification guidelines. Our results detected promising relations among molecular entities from various omics layers, which might be associated with different glioma-type behaviours or treatment resistance.

9. Towards a deep learning approach for classifying treatment response in glioblastomas

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Glioblastomas (GBM) are the most aggressive type of glioma, having a 5-year survival rate of 6.9%. Treatment typically involves surgery, followed by radiotherapy and chemotherapy, and frequent magnetic resonance imaging (MRI) scans to monitor disease progression. To assess treatment response, radiologists use the Response Assessment in Neuro-Oncology (RANO) criteria to categorize the tumor into one of four labels based on imaging and clinical features: complete response, partial response, stable disease, and progressive disease. This assessment is very complex and time-consuming.
Since deep learning (DL) has been widely used to tackle classification problems, the aim of this work was to systematically study several strategies for the (first-time) development of a DL algorithm capable of classifying RANO criteria using only two consecutive MRI acquisitions. The data used to train and test the models was from the open dataset LUMIERE, and performance metrics analyzed using a five-fold cross-validation approach included balanced accuracy (to address the highly unbalanced dataset), precision, and F1-score.
The best performance was achieved using a densenet considering T1-weighted, T2-weighted, and FLAIR images as input. A mean balanced accuracy of 52% was achieved (reaching 58% in two of the folds) although with mean F1-score and precision of 0.17 and 0.18, respectively. These results highlight not only the complexity of the task, but also the heterogeneity of factors that might be in play when classifying RANO criteria. Furthermore, the inclusion of clinical data might be of benefit and will thus be explored in future work.

10. Optimising Automated Segmentation of High-Grade Gliomas Through Deep Learning Strategies

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Tumour segmentation is essential for precise therapy planning and progression monitoring of high-grade gliomas, the most common and aggressive primary brain tumours. The current gold standard is manual segmentation performed by expert neuroradiologists, which is time-consuming and prone to inter-observer variability. Reliable automated methods can greatly increase the quality and efficiency of patient care. Most proposed approaches are based on supervised learning and have been trained using four MRI modalities – T1, T2, T2 FLAIR and T1CE. This work aimed to assess how the performance of deep learning segmentation models was affected when changing the training conditions by 1) relying on a reduced number of input MRI images during training to simulate missing modalities, 2) employing ensemble learning, where the outputs of different models are combined and 3) using transfer learning, to leverage knowledge from multiple data sources, including pre-operative and post-operative glioma data. Our findings suggest that considering the four modalities and the consequent longer training time required does not contribute significantly to increasing the accuracy of the models. The implication is that shorter acquisition protocols could be used, resulting in shorter network training times, fewer expenses - due to the reduced scanner time and lower computational requirements, and ultimately, increased patient throughput. Ensemble and transfer learning methodologies significantly improve overall segmentation performance, making the models more robust across different datasets and segmentation tasks, and potentially improving treatment of glioma patients.

11. Astrocytoma IDH-mutant with primitive neuronal component is a distinct subtype

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Astrocytoma IDH-mutant is the most common primary brain tumor in young adults, peaking in incidence between the ages of 30 to 40. Astrocytoma IDH-mutant is defined by mutation in IDH1/2 genes with absence of 1p/19q codeletion, frequently also harboring alterations in ATRX and TP53 genes. Only rarely cases of astrocytoma IDH-mutant may possess primitive neuronal differentiation, which is characteristically formed by "small round blue cells" or even large anaplastic cells similar to those of embryonal tumors. Characteristic is also limited or absent expression of GFAP, immunoreaction to neuronal markers and high proliferation rate. Moreover, the primitive neuronal component also possesses distinct epigenetic and copy number variations in comparison to the glial component. All the studied cases were high-grade tumors with high total number of copy number variations.

Abstracts of posters

WG1 Non-invasive Biomarker Discovery

1.Corellation of microRNAs-10b/21 expression levels and tumor size in patients with glioblastoma

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Background. Glioblastoma bigger than 4 cm may be associated with bad outcome. MiR-10b and miR-21 are recognized as some of the most important oncogenic miRNAs. MiR-10b/21 overexpression is usually associated with a larger size of the primary tumor, and presence of metastases in extracranial tumors. The abnormal microRNA regulation and change of their expression levels are observed in cancer and can be measured in body fluids.
Aim. The aim of the study was to find out if there is association between level of expression miR-10b/21 and tumor size.

Methods. Forty-three patients with diagnosed glioblastoma were included in the study. MicroRNA molecules-10b/21 were extracted from the peripheral blood mononuclear cells after surgery and before the treatment with Stupp's regimen. Clinical data on tumor size were obtained from medical records. Patients were divided into 2 groups according to tumor size: < 4 cm and ≥ 4 cm. Results. Patients who had tumor size < 4 cm have significantly higher levels of expression miR-10b ($p = 0.027$), median 214.86 (2.13 - 816.89), and miR-21 ($p = 0.047$), median 81.69 (11.39 - 825.43). No statistical significance was observed in patients who had tumor size ≥ 4 cm.

Conclusions. Higher levels of expression of oncomiRs-10b/21 in glioblastoma size < 4 cm is unexpected. This result may reflect the different biological behavior of glioblastoma compared to extracranial tumors, with different microRNA regulation and expression. Our findings provide insight into the possible role of microRNAs-10b/21 in glioblastoma biological behavior and its correlation to clinical parameters.

2. Impact of Harmonization on Radiomics Features from Longitudinal MRI of Glioblastoma

Marta P. Loureiro[1*], Catarina Passarinho[1], Ana Matoso[1], Rita Reis Nunes[1], José Maria Moreira[2], Pedro Vilela[3], Patrícia Figueiredo[1], Rita G. Nunes[1]

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MRI is an essential tool to diagnose and monitor treatment response in brain tumours, such as glioblastoma (GBM). Recent years have seen a rising interest in the extraction of radiomics features from MRI, used in Machine Learning tools to aid in these tasks. However, the existing literature emphasizes the challenge posed by MRI intensity variations associated with the non-standardization of acquisition and reconstruction protocols, leading to the need for data harmonization. Harmonizing medical imaging data is a growing necessity propelled by clinical research that handles heterogeneous medical imaging datasets and their radiomics features.

Our work aims to assess the performance of ComBat, a harmonization method, and particularly to investigate whether it is more beneficial to apply it before or after radiomics feature extraction on a multi-scanner longitudinal MRI clinical dataset of 24 GBM patients. Images underwent pre-processing: co-registration, lesion segmentation with HD-GLIO and radiomics features extraction with PyRadiomics. ComBat was applied before or after feature extraction. The intraclass correlation coefficient (ICC) was used to evaluate feature differences between different tumoural regions (enhancing tumour and edema) within each acquisition session, to assess which approach better differentiates them. When compared to baseline pre-processed images, ComBat after feature extraction performed better (lower ICC), while ComBat before extraction performed worse than, or similarly to, pre-processing only, depending on the imaging modality. ComBat could not be applied in ~20% of the images, as batches larger than 10 images are required. Results demonstrate the impact of applying ComBat after feature extraction to improve radiomics feature reliability across tumoural regions.

3. Imaging biomarkers of the intracranial tumors

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The poster aims to comprehensively review benign and malignant intracranial tumors and explain the CT and MRI biomarkers for their diagnosis.
The term brain tumors stands for a broad and heterogeneous group of intracranial lesions, arising from different brain structures or the meninges. They can sometimes represent significant diagnostic issues, that require prompt and precise diagnosis to facilitate adequate treatment.
The classification of the intra-axial primary and secondary brain benign and malignant lesions for different age groups is explained in detail, including the childhood tumors and the primary tumors (different grade gliomas, medulloblastomas, lymphomas, meningiomas…) and metastases in adulthood. In addition, the common CT and MRI biomarkers for the diagnosis of most brain tumors are presented, with imaging examples for each radiological sign that can facilitate diagnosis. More recent MRI techniques, including DWI, DTI, SWI, fMRI, and proton MR spectroscopy are also presented and briefly explained.

4. Determination of MGMT promoter methylation status in FFPE samples of glioblastoma

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The methylation status of the MGMT promoter region is one of the most important prognostic factors in patients with glioblastoma. The most commonly used method for analyzing MGMT methylation is Methylation-specific PCR (MSP), which utilizes bisulfite-converted DNA as a template. Formalin Fixed and Paraffin-Embedded (FFPE) samples are essential in glioma diagnostics and sometimes represent the only source of DNA for molecular analyses. However, compromised DNA quality in FFPE samples, primarily due to formalin fixation, can affect the determination of methylation status by MSP, leading to the need to optimize conditions for successful reactions. Our goals were to define the optimal MSP reaction conditions for assessment MGMT promoter methylation status in the FFPE samples and to validate the results by comparing the methylation status of the MGMT promoter obtained from FFPE samples with that from Fresh Frozen (FF) samples of the same patient with glioblastoma. A semi-quantitative approach using additional ImageJ software for gel image analysis was employed to evaluate and compare the methylation status in FF and FFPE samples. Obtained results indicate that for a successful MSP reaction using FFPE DNA isolates, 4U of HotStarTaq polymerase and 125 ng of template DNA were required. Fleiss' Kappa statistical analyses showed moderate overall agreement between FFPE MSP and FF MSP semi-quantitative measurements (Fleiss' Kappa Coefficient = 0.516; 70.0% agreement).

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5. Unveiling the theragnostic potential of ALDH1A3-targeting agents for glioblastoma multiforme and brain cancers: a journey around potent imidazopyridine ALDH1A3 inhibitors

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Glioblastoma multiforme (GBM) is the most common primary malignant intracranial tumor endowed with a poor median survival rate. Despite significant advancements in GBM treatment, clinically available therapeutics are often ineffective due to GBM intra-tumoral heterogeneity, mostly contributing to drug resistance. In particular, GBM stem cells (GSCs) are able to evade treatment resulting in recurrent tumors or metastases, accounting for most cancer-related deaths. Therefore, GSC-eradicating therapies are urgently needed to improve the diagnosis and prognostication of GBM and enrich the therapeutic pipeline.1 In this context, the Aldehyde Dehydrogenase (ALDH, EC: 1.2.1.3) enzyme family has recently garnered significant attention from the scientific community, with the 1A3 isoform being identified as a GSC biomarker and playing a key role in cancer cell proliferation, invasiveness, and resistance to therapy. Moreover, ALDH1A3 overexpression was found in several brain cancer types, including GBM and neuroblastoma, and was associated with worse outcomes and disease progression.2 Our research group developed a library of imidazo[1,2-a]pyridines as potent and selective ALDH1A3 inhibitors with micro-to-nanomolar EC50s in GBM cell lines.3 Moreover, two compounds, namely GA11 and MF7 showed promising results in in vivo studies in GBM and breast cancer brain metastasis xenograft models by increasing the survival rate of treated mice.4,5 In silico and X-ray crystallography studies guided us to generate theragnostic compounds by conjugating a selected imidazopyridine ALDH1A3-interacting moiety with fluorescent dyes or radioactive labels, in order to develop a valuable tool for guided surgery, being the latter one of the main therapeutic options for brain tumors.6

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6. New semiconductor glyco-biosensors for selective detection of galectin biomarkers of brain cancer

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Malignant cerebrospinal tumors are diagnosed to 300 000 thousand patients every year worldwide, out of which only one third will live longer than five years. High mortality is caused by also by lack of suitable markers for early-stage diagnosis, disease progression and eventually remission. Noninvasive methods are highly appreciated diagnostic tools because they decrease the burden on the patient as well as the cost and duration of the examination. General requirements imposed on every sensor are reliable detection, easy use, robust construction and minimal requirements on the user and sample preparation.

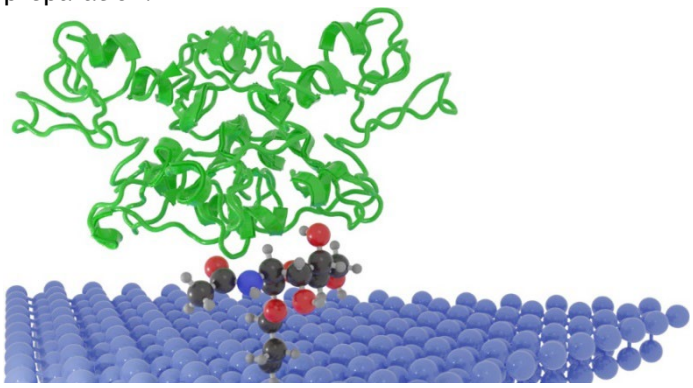

Figure 1 Semiconductor surface is functionalized by specific protein ligands. Galectin binding modulates electrical properties and allows rapid electrical detection

Galectins are a family of proteins binding carbohydrate ligands. They are linked to various (pato)physiological processes, among others in brain cancer. The complexity of their roles in the human body does not allow their use as diagnostic or therapeutic target yet, because every galectin is linked to several diseases and vice versa each disease manifest by a level change of several galectins. Therefore, we must monitor the levels of many galectins at once, *i.e.* to determine the galectin profile.

The primary goal of our project is to develop noninvasive technology for brain cancer early detection by the relative change of galectin levels. Galectins are elusive targets because of the variability of their quaternary, supramolecular and chimeric forms, some of which are uncharted yet. We develop generally applicable electrical sensor of relative levels of galectins in complex clinically relevant media. Electrical detection is ideal, because it can be easily integrated into circuits and is easy to perform and analyze. The sensing layer hence must respond to protein binding by a large change of conductivity, such as in semiconductors. We prepare thin films from metal oxide semiconductors and semiconducting polymers. We graft the semiconductor surface with anchoring molecules bearing functional groups complementary to the immobilization reaction of the carbohydrate ligand. We aim to reach the ultimate selectivity by supramolecular imprinting of the protein's binding sites with ligands into the surface of the sensing layer. This original concept will allow us to determine and monitor elusive biomarker supramolecular constructs of unknown structures.

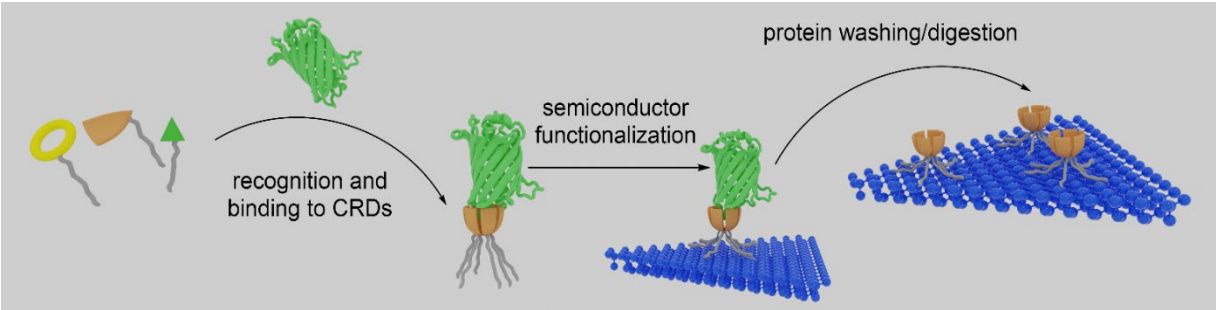

Figure 2 Supramolecular imprinting method for self-assembly of recognition patter for elusive chimeric biomarkers.

7. A Compehensive Liquid Biopsy Method to Uncover Druggable Targets in Glioblastoma

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We collected blood and tumour tissue samples from 25 GBM patients and 25 blood samples from healthy controls. Cell-free DNA (cfDNA) was extracted from the plasma of GBM patients and from healthy controls. Tumour DNA was extracted from fresh tumour samples. Extracted DNA was sequenced using a whole-genome sequencing procedure. We also collected 180 tumour DNA datasets from GBM patients publicly available at the TCGA/PANCANCER project. These data were analysed for mutations and gene-gene fusions that could be potential druggable targets. We found that plasma cfDNA concentrations in GBM patients were significantly elevated (22.6 ± 5 ng·mL-1), as compared to healthy controls (1.4 ± 0.4 ng·mL-1) of the same average age. We identified unique mutations in the cfDNA and tumour DNA of each GBM patient, including some of the most frequently mutated genes in GBM according to the COSMIC database (TP53, 18.75%; EGFR, 37.5%; NF1, 12.5%; LRP1B, 25%; IRS4, 25%). Using our gene-gene fusion database, ChiTaRS 5.0, we identified gene-gene fusions in cfDNA and tumour DNA, such as KDR-PDGFRA and NCDN-PDGFRA, which correspond to previously reported alterations of PDGFRA in GBM (44% of all samples). Interestingly, the PDGFRA protein fusions can be targeted by tyrosine kinase inhibitors such as imatinib, sunitinib, and sorafenib. Moreover, we identified BCR-ABL1 (in 8% of patients), COL1A1-PDGFB (8%), NIN-PDGFRB (8%), and FGFR1-BCR (4%) in cfDNA of patients, which can be targeted by analogues of imatinib.

These results open new avenues for precision medicine in GBM, using noninvasive liquid biopsy diagnostics to assess personalized patient profiles. Moreover, repeated detection of druggable targets over the course of the disease may provide real-time information on the evolving molecular landscape of the tumour.

8. GALECTINS IN BRAIN CANCER - A THERAPEUTIC TARGET OF GLYCODRUGS

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Multivalent presentation of glycans on suitable carriers can multiply the biological potency of synthetic glycoconjugates by several orders of magnitude [1]. Galectins are soluble human b-galactoside-binding lectins associated with tumor growth, angiogenesis, tumor cell migration, and evasion from the host immune system [2]. Selective multivalent glycoconjugates with a high affinity and selectivity can bind and/or inhibit overexpressed galectins, serving as prospective agents for both biomedical research and clinical applications.

To examine the potential of synthetic glycoconjugates to target galectins, we conjugated tailored glycomimetics and poly-LacNAc-type oligosaccharides to multivalent carriers that featured high biocompatibility, non-toxicity, non-immunogenicity, renal clearance, and the ability to penetrate into cells. The prepared library of glycoconjugates exhibited antiproliferative, antimigratory, antiangiogenic, and immunoprotective properties in cell culture assays [2], as well as accummulation in tumors. These results demonstrate the potential of carbohydrate-loaded glycoconjugates as therapeutics of galectin-associated pathologies, such as brain cancer.

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WG2 Preclinical Modelling

9. The effects of gyrophoric acid, a lichen secondary metabolite, during chemically induced brain cancer

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Gyrophoric acid (GA) is a secondary metabolite of various lichens. Our study aimed to reveal the effects of GA on brain structures and related behaviors. The ability of GA to cross the blood-brain barrier (BBB) was analyzed using isolated endothelial cells (BMEC) from two-week-old Wistar rats. The effects of GA on healthy Sprague Dawley animals have been investigated. Furthermore, the potential antitumor effects of GA in Fischer F344 rats with chemically induced brain cancer were analyzed. Our preliminary results indicate that GA crosses BBB and thus could directly affect brain structures. In healthy animals, GA increased rearing ($P<0.01$) in EPM and OFT in both sexes and prolonged time spent in open arms of EPM apparatus ($P<0.01$ and $P<0.001$, respectively). Besides, GA influenced the number of proliferatively active cells in subgranular zone ($P<0.05$) and hilus of hippocampus ($P<0.05$). Moreover, our preliminary results show that GA was not able to influence the occurrence or size of brain tumors. In EPM, time spent in open arms increased significantly ($P<0.001$) compared with untreated group; center crossing and grooming activity remained at the level of healthy animals. Our results are the first evidence that GA could affect some brain structures and influence animal behavior.

10. The effects of gyrophoric acid, a lichen secondary metabolite, during chemically induced brain cancer

Christakis Damianou, Cyprus university of technology, Cyprus

High-intensity focused ultrasound (HIFU) provides an alternative treatment for malignant tumours, with magnetic resonance imaging (MRI) and ultrasound used for monitoring during treatment. An MRI guided robotic system for HIFU treatment of brain cancer was developed, featuring motion in 4 degrees of freedom and equipped with a single element focused ultrasonic transducer. The robotic device was assessed successfully for its MRI compatibility inside a 3 T scanner. The performance of the transducer has been evaluated in a laboratory and MRI environment, on an agar based phantom doped with silica, for its ability to create discrete lesions. MR thermometry data were acquired during sonications providing visualization of the rate of increase of temperature. The MRI compatibility of the system enables its placement on the table of commercial MRI scanners, of any manufacturer, up to 7 T. The proposed robotic system can be utilised in the future for the focal treatment of brain cancer.

11. Lichen secondary metabolites in chemically induced brain cancer

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Lichens produce a plethora of primary and secondary metabolites. Secondary metabolites have several biological functions that can be used for human health. Recent studies have described their antioxidant, anti-inflammatory, antimycotic, or antibiotic/antiviral activities. Most of those studies are carried out in *in vitro* conditions. None of them described their effects during brain cancer. The aim of our studies was to test the effects of atranorin (10mg/kg), one of the lichen secondary metabolites, during chemically induced brain cancer in Sprague-Dawley rats. Brain cancer was induced prenatally by Ethyl-NitrosoUrea (ENU) as one intraperitoneal dose (100mg/kg b.w.). The progeny was divided into six groups per sex. Atranorin (ATR) was administered daily freshly prepared in ethanol in the dose of 10mg/kg for one month. Temostad (TMZ) was administered in the dose of 100mg/kg per os in the same schema as atranorin. Our preliminary results show that the incidence was decreased significantly after TMZ and the combination TMZ+ATR, but only slightly after ATR. We observed a significant increase in the number of red or white blood cells as well as other parameters in ENU animals. The combination of TMZ+ATR was able to return the observed blood parameters, such as white blood cell count, to the level of healthy animals. Thus, we can assume that the combination of these drugs is suitable for further testing of various cancer types.

12. Co-cultures of cerebral organoids with Glioblastoma cell line spheroids and Patient-derived tumoroids for investigating crosstalk with tumor microenvironment ex vivo

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Glioblastoma multiforme (GBM) is the most aggressive type of brain tumor, with a median survival time of just 15 months. Unfortunately, this figure has not changed in the past 30 years.The lack of progress is largely due to the high resistance of glioblastoma cells to current treatments. Therefore, there is an urgent need to develop new approaches to study GBM and improve treatment outcomes. Specifically, it is crucial to create better preclinical models that mimic the relationship between human brain tissue and the tumor. These models can help in understanding how glioblastoma cells resist treatment and in identifying new drugs to target GBM. Our project aims to develop a 3D in vitro model using human cerebral organoids (CO) combined with glioblastoma cell line spheroids (GLICO) or patient-derived tumoroids. We have successfully developed the GLICO model using four GBM cell lines: U87, U3013, U3047, and U3118. We have performed analysis of migrating cells in these GLICO models and analysed gene expression of U87 spheroids co-cultivated with CO demonstrating that mature CO supports growth and migration of GBM cells. The study on patient-derived tumoroids is currently ongoing. We have optimized cultivation and co-cultivation conditions, as well as the migration analysis protocol. This procedure will enable us to focus on studying the mechanisms of GBM formation and evaluating the biological activity of potential therapeutic substances.

13. Drug-loaded hybrid layer composite nanofibers offer a new approach to suppress recurrence in the local treatment of Glioblastoma

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Total resection of glioblastoma (GB) tumor is almost impossible. Additionally, systemic administration of the chemotherapy drug temozolomide (TMZ) is inadequate. In this study, we designed hybrid layered composite nanofiber networks (LHN) for local use in a GB tumor bed. The LHN consisted of a polyvinyl alcohol (PVA) layer and a core-shell PLA layer. Each layer was encapsulated with chemotherapy drug and bioactive compound, which were also loaded between the layers. After characterization, behavioral changes of T98G cells were analyzed in vitro. Tumor invasion and the presence of cancer stem cells were examined at both functional and RNA levels. Proteomics clarified the protein network. The feasibility of LHN was tested using the orthotopic C6-derived GB model. Magnetic resonance imaging and immunocytochemistry confirmed the tumor. Mitochondrial structure and PARP1 expression of the tumors were evaluated. Serum AST, ALT, creatine, urea levels, and splenocyte IFNg/IL4 ratio proved biosafety. Chemotherapy drug and bioactive compound-loaded LHNs slowed EMT and GSC, and treatment with loaded LHNs significantly reduced sphere size compared to untreated cell spheres ($p<0.0001$). Notably, the tumor-reducing effect was more pronounced in combination therapy than in chemotherapy-only. Based on tumor volumes determined by H&E staining, the combination treatment reduced tumor size compared to untreated GB rats ($p<0.005$). The local treatment application of LHNs in the GB-rat model detected a mitigating effect on GB's aggressive features. Additionally, loaded LHNs did not cause local tissue inflammation or negatively affect essential markers in the liver and kidneys. Our findings indicate that this nanoproduct is a promising biocompatible model for the local treatment of GB.

14. Mimicking brain-tumor interactions using cerebral organoids and glioblastoma spheroids to study the migration of glioblastoma cells

Veronika Fedorová[1], Jana Slováčková[1,2], **Kateřina Amruz Černá**[1], Veronika Pospíšilová[1], Jiří Sedmík[1], Soňa Cesnáriková[1], Martin Barák[3], Michal Hendrych[4], Radim Jančálek[3], Dáša Bohačiaková[1,2]

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Glioblastoma IDH-wildtype is the most aggressive and lethal form of brain tumor characterized by significant heterogeneity and a poor prognosis. To advance treatment strategies, better models that replicate the in vivo behavior of glioblastoma cells are essential. In our laboratory, we established a glioblastoma spheroid-cerebral organoid (GLICO) co-culture model and optimized analytical tools to monitor the migration of glioblastoma cells into the healthy tissue to study the aggressivity of four glioblastoma cell lines U87, U3013, U3118, and U3047. Importantly, mRNA sequencing of U87 glioblastoma cells after co-cultivation with cerebral organoids revealed dramatic changes in their expression profile, indicating that the cerebral organoid microenvironment significantly affects tumor cell phenotype. We are now applying this knowledge to explore the interaction between patient-derived glioblastoma tumoroids and healthy cerebral organoids. This model will also be beneficial for drug testing experiments to study their effect on glioblastoma cell migration.

WG3 Pathogenesis and Tumour Profiling

15. m6A modified lncRNA profile of glioblastoma and healthy brain

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Interest in long-non-coding RNAs (lncRNAs) during oncogenesis is constantly increasing. lncRNA plays an important role in gene regulation via chromatin remodelling, RNA processing, transcriptional activation, in protein function and activity alteration via direct interaction with proteins etc. Recently developed methods for RNA chemical modification identification, promoted interest in human epi-transcriptome. N6-methyladenosine (m6A) is the most prominent and widely studied RNA modification, which affects RNA stability, location, and translation. However, information on m6A effect to lncRNAs and other non-coding RNAs (ncRNAs) is lacking. Here we compare transcriptome wide m6A modifications of lncRNAs in human glioblastoma and healthy brain samples applying direct RNA sequencing method from Oxford Nanopore Technology (ONT dRNA-seq). The analysis of ONT dRNA-seq identified lncRNA targets that are differentially modified between glioblastoma and healthy human brain specimen. Previously reported glioma associated lncRNAs like NEAT1, SOX2-OT, SNGH6, OIP5-AS1, etc. in present study showed decreased levels of m6A modification in glioblastoma specimens compared to healthy brain samples indicating that m6A demethylation of lncRNAs transcripts might be characteristic during gliomagenesis.

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16. ELK1 TRANSCRIPTION FACTOR AS A NEW MITOTIC TARGET IN BRAIN TUMORS

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Brain tumors, particularly gliomas and glioblastomas of glial origin, can invade brain tissue quite rapidly and in later stages both show extreme rates of proliferation and exhibit resistance to therapy. Therefore, elucidating molecular mechanisms of mitotic proliferation in brain tumor will be an important step towards development of new therapies. The ternary complex factor Ets-like transcription factor 1 (Elk1) has been implicated in protecting cells from apoptosis and downregulating apoptosis-associated genes thereby mediating cell survival, and Akt-dependent phosphorylation of Elk-1 has been shown to be important for proliferation of glioblastoma cells. In addition to this, through various projects in our laboratory, we have identified a different mitotic role of the mitogenic transcription factor Elk-1 belonging to the ETS domain superfamily in various brain tumor model cell lines such as glioma, glioblastoma and neuroblastoma. Confocal microscopy analyses revealed that serine 383 phosphorylated Elk-1 is found at the nucleus during interphase and through prophase to metaphase predominantly localizes to the spindle poles. In anaphase, Elk-1 accumulates both at the spindle poles and midzone and Elk-1 relocates to the spindle midbody when cells proceed to the cytokinesis. The interaciton of Elk-1 with dynein and kinesin motors indicates that this mobility of Elk-1 during mitosis is realized through motor proteins. In addition to microtubule motor proteins, Elk-1 also interacts with the cell cycle kinase Aurora-A and when Aurora inhibitors are used, P-S383-Elk-1 fails to localize to the poles and remains associated with DNA. The mitotic spindle localization of a transcription factor and its interaction with motor proteins and mitotic kinase Aurora-A is particularly interesting. We analyzed Elk-1 protein sequence in terms of potential kinase phosphorylation motif and several residues were found to be putative sites for phosphorylation by cell cycle related kinases, such as Cdks, Plks and Aurora kinases. Mitotic kinases have pivotal roles during regulation of cell cycle progression, centrosome maturation and microtubule dynamics and any abnormalities in these processes resulted in the formation and progression of tumors. Investigation of the interaction between Elk-1 and such mitotic kinases is supposed to help to understand the possible mitotic role of Elk-1 and its effects in brain tumors.

17. Clinical Implications of Intratumoral Heterogeneity in Glioblastoma

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Keywords: glioblastoma, intratumoral heterogeneity, neurosurgery

Glioblastoma, IDH-wildtype, WHO G4 (GB), is the most common primary malignant tumor of the central nervous system. Despite significant advancements in surgical techniques allowing for a greater extent of resection, the use of targeted radiotherapy along with the application of new anticancer drugs, GB remains an incurable disease with a median survival of 16 months. One of the key factors contributing to the development of therapeutic resistance and recurrence is the intratumoral heterogeneity of GB. Although surgical therapy aims at gross-total tumor resection (GTR), a considerable residual heterogeneous tumor population remains at the resection margin. These residual tumor populations encompass various genomic, epigenetic, and microenvironmental variations, creating a pool from which treatment-resistant clones can emerge and subsequently become a source of GB recurrence. The ability to identify and target therapy towards these high-risk cell populations could improve patient prognosis and treatment outcomes.

18. Investigating hypoxia and the glial reaction at the infiltrative margin of brain tumours

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Aim
To characterise astrocytes/microglia populations and hypoxia marker expression in the brain tumour infiltrative margin.
Methods
Dual immunostaining of astrocyte (GFAP) and microglia (Iba-1) populations, on FFPE human tissue sections from high grade glioma (HGG; n=5), low grade glioma (LGG; n=5) and brain metastasis (BrM; n=3). RNA-ISH was performed for hypoxia markers, HIF-1α and CAIX, alongside NF-κB on adjacent tissue sections. Stained tissue sections were digitally scanned and analysed using QuPath. Regions of interest were identified by a consultant histopathologist.
Results
Microglia were significantly more abundant in BrM (unpaired t-tests; p=0.0007, p=0.0409), and were more abundant in HGG compared to LGG (Dunn's test; p<0.0001). Activated and resting microglia were observed across all brain tumours. GFAP expression was significantly increased at the glioma core compared to the edge (Dunn's test, LGG; p=0.0118, HGG; p=0.0005). Astrocyte morphology also varied across tumours, with reactive astrocytes significantly more abundant at the glioma core compared to the edge (Dunn's test, LGG; p=0.0229, HGG; p=0.0021).
There was no significant difference in NF-κB or CAIX expression between tumour type or regions (Kruskal-Wallis test; p-value>0.05). However, HIF-1α was significantly upregulated at the HGG edge compared to the core (Dunn's test; p=0.0462).
Conclusions
Reactive astrocytes and microglia are associated with worse prognosis. Their presence, coupled with upregulated hypoxia marker expression, poses a challenge against effective treatment response of infiltrating brain tumours. Future investigation of the inflammatory profile at the infiltrative margin will improve our understanding of the mechanisms of brain tumour pathogenesis and treatment resistance.

19. Metabolic mapping with tissue water referencing using proton density maps

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Magnetic resonance spectroscopic imaging with concentric ring trajectories (CRT) at 7T has been previously shown to rapidly produce mapping of 5 metabolites with inter-subject coefficients of variation (CV) under 11% on avarage for 44 brain regions of interests (ROI). This used water referencing based on gray matter (GM)/white matter (WM) segmentation and normalizing it to the literature values. However, in pathologies where the compartmentalization of the brain is not reliable e.g. gliomas, this strategy is less reliable.
This study investigates the integration of proton density (PD) mapping for tissue water referencing, and compare it with the aforementioned strategy in healthy volunteers. hMRI-toolbox has been utilized for obtaining quantitative PD images by processing GRE multi-echo (ME) T1-weighted and PD-weighted images. Following are evaluated: water content (WC) maps of both approaches including three different resolution and excitation mode of ME-GRE sequences, the concentration estimate maps of 4 metabolites from these two WC maps.
We found that minimum of 128x128 is needed to get satisfactory seperation of GM/WM peaks, as increasing it further decreased the partial volume effects and also reduce the impact of ringing artifacts. Excitation mode match with of the B1 maps improved the results. Both water content maps are in high agreement. The ratio of both maps shows variance as low as 10%. Consequently, the concentration maps for both present good correspondance.
While preliminary results are promising, increasing study cohort is essential for thorough analysis of robustness. Upon confirming the next objective to move on glioma patients.

20. To Explore the Potential Role of Circular RNAs in Brain Tumor Progression

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Dr Vasileios Lenis - Institute of Cancer and Genomic Sciences, University of Birmingham United Kingdom.
Jamie Bojko - School of Health and Life Sciences, Teesside University United Kingdom.
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Circular RNAs (circRNAs) are recognized to play crucial roles in most malignant cancers, with many displaying tissue-specific expression patterns. They arise from linear precursor RNAs in which 5' and 3' ends become covalently ligated through back splicing. We investigate the role of circRNAs in brain tumor progression, aiming to elucidate their potential as biomarkers and therapeutic targets. A comprehensive profile of circRNAs was identified from the brain tissue of astrocytoma grade II-IV IDH mutant patient sample, and healthy control, 4 groups with 7 samples each. We used the circRNA identification and quantification tool DCC to detect circRNAs from chimeric BSJ reads using STAR. A relative circRNA abundance of 11.21% was recorded for the Glioma group and 0.96% for the Control samples. Circular – Linear ratio tests were conducted to quantify the variation of circRNAs to host genes with CircTest. Preliminary bioinformatics analyses revealed differential expression patterns, with several circRNAs regulations in tumors. A differentially expressed circRNA-miRNA network was further constructed. Ongoing analyses are focused on validating these findings and further explicating the molecular mechanisms underlying circRNA-protein complexes and their functional interactions.

WG4 Mathematical & Computational Modelling

21. To Explore the Potential Role of Circular RNAs in Brain Tumor Progression

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In the field of mixed models, this paper examines a novel estimation method designed to handle mixtures of distributions and controlled heteroscedasticity. By departing from traditional assumptions of normality and homoscedasticity, we present a more adaptable approach to data analysis., particularly in brain cancer research. The proposed methods include techniques for estimating variance components, estimable vectors, and cumulants, alongside developing prediction intervals and prediction ellipsoids for future observations. A numerical example is employed to illustrate the method and compare it with traditional ANOVA and Bayesian estimation methods. The results demonstrate the superior flexibility and broader applicability of the proposed methods in diverse contexts, enhancing the accuracy and robustness of statistical inference in mixed models. This study advances the effort to bridge the translational gap in brain cancer treatment by offering more flexible and accurate analytical tools.

22. Detection and Classification of Brain Cancer Using Generative AI

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This research aims to explore the potential of using generative AI in the diagnosis and classification of brain cancer, offering a significant innovation by providing more accurate and faster diagnoses compared to current medical methods. Early detection of aggressive brain tumors, such as glioblastoma, can significantly improve patients' lifespan and quality of life. By learning from large datasets, generative AI can better understand the biological and genetic diversity of tumors, thus providing more accurate diagnoses. Data Collection and Preprocessing: Medical imaging data such as MRI and CT scans will be combined with genomic, proteomic, and metabolomic data to create a comprehensive dataset. Model Training and Development: Deep learning models like Convolutional Neural Networks (CNNs) and Generative Adversarial Networks (GANs) will be trained for tumor segmentation and classification. GANs will be used to augment training data and provide additional data for rare tumor types. Simulation and Validation: The developed models will be validated using preclinical and clinical data to ensure their applicability in diagnosis and treatment planning. Accuracy and reliability tests will be conducted throughout this process. The project will be managed by a multidisciplinary team of data scientists, bioinformatics experts, oncologists, and radiologists. Detailed planning and coordination will be ensured for each phase of the project, with data security and confidentiality maintained at the highest level. Adherence to ethical guidelines will be a fundamental principle of the project. The results of this research have the potential for widespread application in the diagnosis and treatment of brain cancer. Generative AI-based approaches will enable faster and more accurate diagnosis of tumors, aiding in the development of personalized treatment plans. This will enhance patient quality of life and improve the efficiency of healthcare services. Additionally, the data obtained and models developed could be applied to the diagnosis and treatment of other cancer types, offering broad innovation potential in the field of healthcare.

Keywords: Brain Cancer Diagnosi,Generative AI,Deep Learning,Medical Imaging,Convolutional Neural Networks (CNNs),Generative Adversarial Networks (GANs)

23. Exploring transcriptomic profiling of glioblastoma patient-derived primary tumor cell lines through computational analysis

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Glioblastoma multiforme (GBM) is a highly aggressive primary brain cancer marked by significant transcriptomic heterogeneity among patients, posing substantial challenges to effective treatment. Herein, an advanced computational analysis of bulk RNA-sequencing data from primary tumor cell lines derived from GBM patients is presented, complemented by transcriptomic profiles of normal brain tissue obtained from matched controls. For both datasets, a series of preprocessing steps, including quality control checks, trimming of adapter sequences, and alignment to the reference human genome using the STAR aligner was implemented. Following alignment, featureCounts was used to quantify gene expression levels, which were then normalized to account for differences in sequencing depth and gene length. Additionally, the ComBat function from the sva package was applied to correct for batch effects. Differential expression analysis was conducted using the DESeq2 package, allowing the identification of differentially expressed genes between GBM and normal brain tissues. Further validation was performed through cross-referencing with established databases and advanced bioinformatics tools. Hierarchical clustering and principal component analysis were executed to visualize the overall differences between diseased and healthy tissues while gene set enrichment analysis was executed to identify significantly enriched biological pathways and molecular functions associated with GBM. Our findings indicate that comprehensive transcriptomic profiling can significantly enhance our understanding of GBM complexity, highlighting key molecular targets for potential therapeutic intervention.

24. Quality analysis for the detection of Brain Injuries with Deep Learning

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Accurate and timely detection of brain injuries is crucial for effective patient care and treatment planning. This study conducts a thorough quality analysis of deep learning models for brain injury detection from medical imaging. We assess a variety of state-of-the-art deep learning architectures, including convolutional neural networks (CNNs), recurrent neural networks (RNNs), and hybrid models, using an extensive dataset of MRI and CT scans. Performance metrics such as accuracy, sensitivity, specificity, precision, and F1-score are employed to evaluate each model's efficacy. The robustness of these models is further examined under different imaging conditions, including the presence of noise and artifacts. Our analysis reveals significant insights into the strengths and limitations of each model, highlighting the practical implications for clinical use. Additionally, we explore the benefits of transfer learning and ensemble methods in enhancing detection performance. The results demonstrate that advanced deep learning models, particularly those incorporating sophisticated architectures and fine-tuning techniques, achieve high levels of accuracy and reliability in detecting brain injuries. This study underscores the potential of deep learning to revolutionize diagnostic procedures, advocating for its integration into automated diagnostic systems to improve patient outcomes. Future research will aim to expand the dataset and refine the models to cover a broader range of brain injury types and severities, further advancing the field of medical imaging diagnostics.

25. Improving Flexibility in Distributions: A Novel Generalization of the Half-Logistic Distribution

Sandra Ferreira. Mathematics Department, Center of Mathematics and Applications, University of Beira Interior, Portugal

Over time, various adaptations of the half-logistic distribution have been proposed to expand its scope of use and efficiency. This discussion seeks to present a fresh approach to generalizing this distribution, highlighting its potential benefits and consequences. Additionally, this exposition explores the applied aspects of this novel generalization, scrutinizing its practical importance and relevance.
One application of this distribution will be made related to brain cancer developments, showcasing its versatility in addressing complex real-world problems.

26. Bioactive phytocompounds of Allium ursinum L. leaves as potential inhibitors of acetyl-CoA synthase 2 and monoamine oxidase: a preliminary docking study

Oskar Szczepaniak, Department of Biochemistry and Biotechnology, Poznań University of Life Sciences, Poznań, Poland

Wild garlic (Allium ursinum L.) is a Middle-European plant with documented anti-oxidant and anti-inflammatory effects due to high content of phenolic compounds and organosulfur compounds. The secondary plant metabolites present in wild garlic may also act as anti-tumor agents. In this work the literature analysis was done to select the predominant phenolic compounds and organosulfur compounds in the Allium ursinum leaves. Then, the model of the compounds were subjected to docking analysis against acetyl-coA synthase 2 (ACSS2) and monoamine oxidase (MAO) - enzymes which overactivity follows and induces the brain cancer progression. The results of this study help find which individual compounds of wild garlic has anti-tumor properties and also may be an input to further in vitro experiments.

27. Mathematical Simulation of Brain Tumor Progression via an Intelligent Markov Chain Monte Carlo Method

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The recent necessity for reliable and cost-effective approaches to action against the brain tumor progression has prompted a challenging interest in the computational biomedical engineering. Rising interest in mathematical models in oncology enhances inference and prediction, complementing experimental biomedical models. The intrinsic stochasticity of tumor progression dynamics is a major consideration for clinical decision-making. Markov processes and Monte Carlo estimation method are powerful tools to capture this stochasticity and render effective treatment decisions. While the current methodologies focus on deterministic and stochastic modelling approaches, this paper propose an intelligent Markov Chain Monte Carlo (MCMC) method because of its robustness in handling uncertainties and complex probabilistic progression dynamics. This paper proposes integrating the introduced MCMC method with real-time imaging data to enable dynamic treatment adjustments, enhancing the precision of individualized radiotherapy protocols. The key algorithm introduced and used in this paper is the intelligent MCMC algorithm, which is employed for Bayesian inference and parameter estimation in the tumor growth modeling framework. Indeed, the sensitivity analysis is conducted to assess the uncertainty of parameters with the aid of Artificial Intelligence-Markov Chain Monte Carlo (AI-MCMC) method. The authors developed a Bayesian AI-MCMC framework that integrates MRI and FET-PET scans to infer patient-specific tumor cell density, accounting for uncertainties. So, personalized radiotherapy plans from inferred tumor cell density maps spare more healthy tissue while maintaining accuracy comparable to standard protocols. This paper uses experimental studies to estimate uncertain model parameters applicable to the survivability and costs of major cancer metastases.

Keywords
Brain tumor progression, Markov chain Monte Carlo method, Artificial Intelligence, Cancer metastasis, Mathematical modelling, Stochastic simulation-based optimization.

28. A Novel Label Propagation Approach for Cancer Subtype Identification

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Cancer is a disease in which abnormal cells grow uncontrollably and invade other tissues. Several types of cancer have various subtypes with different clinical and biological implications. Based on these differences, treatment methods need to be customized. The identification of distinct cancer subtypes is an important problem in bioinformatics, since it can guide future precision medicine applications. In order to design targeted treatments, bioinformatics methods attempt to discover common molecular pathology of different cancer subtypes. Along this line, several computational methods have been proposed to discover cancer subtypes or to stratify cancer into informative subtypes. However, existing works do not consider the sparseness of data (genes having low degrees) and result in an ill-conditioned solution. To address this shortcoming, we propose an alternative unsupervised method to stratify cancer patients into subtypes using applied numerical algebra techniques. More specifically, we applied a label propagation based approach to stratify somatic mutation profiles of different cancer types. We evaluated the performance of our method by comparing it to the baseline methods. Extensive experiments demonstrate that our approach highly renders tumor classification tasks by largely outperforming the state-of-the-art unsupervised and supervised approaches.

Keywords: Cancer subtype identification, label propagation, personalized medicine, machine learning, numerical algebra

29. OPTIMIZING 3D MEDICAL IMAGE SEGMENTATION MODELS THROUGH ARCHITECTURE TUNING AND QUANTIZATION TECHNIQUES: BALANCING MODEL EFFICIENCY AND ACCURACY

Kevin Hoxhalli, **Arban Uka**, Florenc Skuka

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Medical image analysis using computational techniques constitutes an essential area in providing precise quantitative results in a short time to deduce patient condition. The detection, segmentation and shape parameters of tumors (including volume, area, eccentricity etc) is now being implemented using deep learning techniques. Optimization of resources have to be considered during the dataset preparation, the training steps, and the testing steps. Models that are trained based on a manually labelled datasets can be used by medical practitioners to evaluate new patient data. Here in this work we report brain tumor segmentation on BraTS 2020 dataset using different architectures and then we use quantization to reduce the size of the trained models. A comprehensive evaluation framework was utilized to assess segmentation performance across whole tumor (WT), tumor core (TC), and enhancing tumor (ET) regions. Results demonstrated the robust performance of the baseline 3D U-Net, achieving high accuracy (91.19%) across all tumor regions. However, Att_EquiUnet, using the CBAM attention module, showed improvements in boundary localization as evidenced by reduced Hausdorff distances. 16-bit quantization emerged as an optimal compromise, achieving a 75% reduction in model size while maintaining accuracy and even slightly improving sensitivity in some cases. 8-bit quantization, while further reducing model size (to 6.4%), incurred a more pronounced accuracy loss, raising concerns about its suitability for clinical use.

30. BRAIN TUMOR DETECTION AND CLASSIFICATION USING DEEP LEARNING

Florenc SKUKA, Arban UKA
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Brain tumors are a significant health challenge due to their nature and potential for fast growth. Diagnosing brain tumors accurately and fast is very essential for effective treatment and enhancing patient survival rates. Traditional methods which rely on manual analysis of medical images are time-consuming and liable to human faults. Machine Learning (ML) and Deep Learning (DL) techniques have been used for many years as tools to enhance tumor diagnostics accurately and efficiently. In Magnetic Resonance Imaging (MRI), DL techniques, particularly Convolutional Neural Networks (CNNs), have shown outstanding achievement in automating the detection and classification of brain tumors. These methods significantly reduce the diagnostic workload on radiologists while improving accuracy. This study analyzes machine learning techniques such as Random Forest, K-Nearest Neighbor, Naive Bayes, and Support Vector Machine, alongside CNN-based methods. The methods are assessed and analyzed based on different evaluation metrics like accuracy, recall, loss and running time, aiming to determine the most effective approach for the rapid and precise detection of brain tumors. The implementation of advanced DL algorithms shows potential for transforming brain tumor diagnostics, offering a robust solution to the challenges of traditional methods.

WG5 Clinical Treatment Recommendation

31. Nanoparticle and Implantable 3D-printed Scaffold-Based Approaches for Enhanced Cancer Treatment via Radiotherapy

Yavuz Nuri Ertaş, Erciyes University, Türkiye

Radiotherapy is a common cancer treatment in medical practice that utilizes high-energy X-rays to administer radiation doses to cancerous tissues. However, the therapeutic use of radiotherapy is constrained by its low radiosensitivity, inaccurate tumor localization and poor differentiation between lesions, and the adverse effects of irradiation in healthy tissues. Hence, it is crucial to develop methods to enhance the radiosensitivity of malignancies while reducing their systemic side effects. Combining nanotechnology with radiation improves therapeutic results. Using high-atomic-number (high-Z) nanoparticles as radiosensitizers can greatly enhance the effectiveness of breast cancer treatment when exposed to X-ray radiation, as evidenced by studies evaluating cell viability, proliferation, reactive oxygen species production, and in vivo antitumor effects. Implementation of chemotherapy along with radiotherapy, known as synchronous chemoradiotherapy, can further augment the treatment efficacy. Tumor targeted and anticancer drug loaded nanoparticles will be discussed within this concept. Further, radiotherapy enhanced local cancer therapy via surgical implantation of 3D-printed nanoparticle-containing scaffolds will be discussed to address the chronic problem of metastasis after surgical removal of tumors. Biocompatible and biodegradable scaffolds may potentially lower the recurrence and metastasis rates in breast cancer patients by inhibiting residual tumor cells following post-surgery, as well as exhibit anticancer properties in other solid tumors. In short, this talk will focus on the utilization of nanoparticle and 3D-printed scaffold strategies for cancer treatment through the use of radiotherapy.

32. Advanced Imaging Techniques in Brain Cancer

Safiye KAFADAR, Harran University, Faculty of Medicine, Radiology Department, 63100, Sanliurfa, Türkiye

Thanks to the advances in the imaging of brain tumors, great progress has been made in the early diagnosis, treatment, and close follow-up of this disease group. Imaging characterizations may change with the oncological chemotherapy of patients, treatments applied in radiation oncology, and surgical methods applied.
Evaluation of regression, progression and pseudoprogression in the tumor area is very important in the follow-up of the patient. These techniques are divided into three groups. The first is the techniques used for tumor characterization. These are precontrast and postcontrast T1WI, T2WI, and FLAIR images, DWI, and calculated ADC, MRS, and SWI. The second group includes perfusion imaging. These are DCS, DCE, ASL, PET, FDG PET, and AA PET. The third group includes preoperative and intraoperative applied methods, and these methods are DTI and calculated FA, fMRI, and BOLD. In this study, the advantages and disadvantages of these methods in the diagnosis and treatment of the patient will be discussed.

33. Bioethical and human security approaches in the treatment of brain tumors

Serghei SPRINCEAN, doctor habilitate, professor, Institute of Legal, Political and Sociological Research of Moldova State University, Academiei str. 3/2, MD-2028, Chisinau, the Republic of Moldova.

Bioethics and human security are one of the newest and most important methodological perspectives, defending human dignity, social resilience and equity, human rights and personal safety, and advocating for the elimination of human risks in the context of health changes and individual transformations.
Brain cancer patients, being one of the most vulnerable citizens in a contemporary society concentrated on individualistic and liberal values and practices, also have to be treated from the bioethical and human security perspective as well. Bioethics and human security as civilizationist perspectives, offer for patients with brain tumors a chance to be treated with dignity and respect in the social environments, including in those hostile. The imperative necessity of counteracting contemporary threats at the level of protection of human person can be fulfilled through re-conceptualization at local, regional and global scales, in methodological and bioethical ways, of the perspectives of strengthening human security [1].

RERERENCES
1. Sprincean S. Securitatea umana si bioetica. Chisinau: Tipogr. Centrală, 2017.

List of invited lecturers

Number of talks	Name	Surname	Institution	Country	WG
1	Aida	Hajdarpasic	Sarajevo Medical School, University Sarajevo School of Science and Technology	Bosnia & Herzegovina	1
2	Thomas	Booth	King's College London	United Kingdom	1
3	Lene	Uhrbom	Uppsala University	Sweden	2
4	Anna	Golebiewska	Luxembourg Institute of Health	Luxembourg	2
4	Barbara	Breznik	National institute of Biology	Slovenia	2
5	Ibrahim	Kulac	Koç University School of Medicine.	Turkey	3
6	Sevin	Turcan	Ruprecht-Karls-Uxniversitaet Heidelberg	Germany	3
7	Robertas	Damaševičius	Kaunas University of Technology	Lithuania	4
8	Margarida	Julià-Sapé	Universitat Autònoma de Barcelona	Spain	4
9	Marija	Skoblar Vidmar	Institute of Oncology	Slovenia	5
10	Johannes	Haybäck	Tyrolpath Obrist Brunhuber GmbH	Austria	5

List of short lecturers

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2	Sagar	Acharya	Medical University of Vienna	Austria	1
3	Winnok	De Vos	University of Antwerp	Belgium	2
4	Bilal	Javed	Technological University Dublin	Ireland	2
5	Sofija	Jovanović Stojanov	Institute for Biological Research "Siniša Stanković" - National Institute of the Republic of Serbia	Serbia	3
6	Andreani	Odysseos	EPOS-IASIS	Cyprus	3
7	Vanessa	Vermeirssen	Ghent University	Belgium	4
8	Roberta	Coletti	NOVA Math, Nova School of Science and Technology	Portugal	4
9	Ana	Matoso	Institute for Systems and Robotics	Portugal	4
10	Catarina	Passarinho	Institute for Systems and Robotics (ISR-Lisboa)	Portugal	5
11	Michal	Hendrych	First Department of Pathology, St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Brno	Czech Republic	5

List of posters

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1	Aleksandar	Stepanovic	Institute for Oncology and Radiology of Serbia	Serbia	1
2	Marta	Padrela Loureiro	Institute for Systems and Robotics (ISR) - Instituto Superior Técnico	Portugal	1
3	Slavcho	Ivanoski	St. Erasmo Hospital for Orthopedic Surgery and Traumatology	North Macedonia	1
4	Jelena	Vitorović	Faculty of Sciences and Mathematics, Department of Biology and Ecology, University of Niš	Serbia	1
5	Fabio	Scianò	University of Pisa	Italy	1
6	Petr	Kovaricek	University of Chemistry and Technology Prague	Czech Republic	1
7	Milana	Frenkel-Morgenstern	Reichman University	Israel	1
8	Pavla	Bojarová	Institute of Microbiology of the Czech Academy of Sciences	Czech Republic	1
9	Patrik	Simko	Pavol Jozef Safarik University in Kosice	Slovakia	2
10	Christakis	Damianou	Cyprus University of Technology	Cyprus	2
11	Terezia	Kiskova	University of Pavol Jozef Safarik	Slovakia	2
12	Jana	Slovackova	Department of Histology and Embryology, Faculty of Medicine, Masaryk University	Czech Republic	2
13	Berrin	Tunca	Bursa Uludag University	Türkiye	2
14	Veronika Kateřina	Fedorova Amruz Černá	Masaryk University	Czech Republic	2
15	Daina	Skiriute	Lithuanian University of Health Sciences	Lithuania	3
16	Oya	Ari Uyar	TUBIRAK MRC	Türkiye	3
17	Martin	Barak	Department of Neurosurgery, St. Anne's University Hospital Brno and Faculty of Medicine, Masaryk University, Czech Republic	Czech Republic	3
18	Vinton	Cheng	University of Birmingham	United Kingdom	3
19	Ahmet	Azgın	Medical University of Vienna	Austria	3
20	Uchenna	Ngameduru	Teesside University	United Kingdom	3
21	Dário	Ferreira	University of Beira Interior	Portugal	4
22	Abdulsamet	Haşıloğlu	Department of Computer Engineering, Faculty of Engineering and Architecture, Istanbul Gelişim University	Türkiye	4
23	Marios	Krokidis	Ionian Univeristy Department of Informatics	Greece	4
24	Jewel	Sengupta	Kaunas University of Technology	Lithuania	4
25	Sandra	Ferreira	University of Beira Interior	Portugal	4
26	Oskar	Szczepaniak	Poznań University of Life Sciences	Poland	4
27	Abdulsamet	Haşıoğlu	Department of Computer Engineering, Faculty of Engineering and Architecture, Istanbul Gelişim University	Türkiye	4
28	Burcu	Bakir-Gungor	Abdullah Gul University	Türkiye	4
29	Arban	Uka	Epoka University	Albania	4
30	Florenc	Skuka	EPOKA University	Albania	4
31	Yavuz Nuri	Ertas	Erciyes University	Türkiye	5

32	Safiye	KAFADAR	Harran University	Türkiye	5
33	Serghei	Sprincean	Moldova State University	Moldova	5

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