

Webinar – Biomarkers in Neuro-Oncology

Wednesday 9 September 2020

Research Workshop – Drug Delivery in Gliomas

in conjunction with the Children's Brain Tumour Drug Delivery Consortium

Thursday 10 September 2020



Welcome from Professor Colin Watts, BNOS President

Dear Colleagues

The British Neuro-Oncology Society continues to adapt in response to the impact of SARS-CoV-2 by providing an exciting series of talks around the theme of 'Biomarkers in Neuro-Oncology' and 'Translational Drug Delivery in Gliomas'. These replace our traditional conference but continue our strategy of providing the latest research insights for clinicians and scientists.

The delivery of clinical care and research requires an integrated approach that is tailored to each patient. Biomarkers will be critical in defining specific patient populations allowing more accurate diagnoses, better prognostication and counselling, and ultimately better treatments. Professor Short has drawn together an exciting cast of scientists & clinicians who will provide an update on advances in this field.

Drug delivery to the brain is a major challenge. Dr Harpreet Hyare, Chair of the BNOS Research Committee has teamed up with Professor David Walker from the Children's Brain Tumour Drug Delivery Consortium to provide an exciting workshop on Translational Drug Delivery. This will explore the use of technologies to circumvent the blood-brain barrier and will be followed by a Q&A session led by Prof Walker.

Together these two programmes provide a diverse and exciting opportunity for our members and the wider community of scientists and clinicians to engage together in a fantastic learning opportunity. My thanks to all those who have worked tirelessly behind the scenes to bring this to fruition and to Prof Short and Dr Hyare for their fantastic leadership.

Do enjoy the first virtual BNOS conference!

Organising Committee

Susan Short, Chair

University of Leeds/St James's University Hospital

Harpreet Hyare

UCLH

Kathreena Kurian

University of Bristol/North Bristol Trust

Laura Yarram-Smith

North Bristol NHS Trust

Samantha Mills

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Silvia Marino

Barts and The London Medical School,
Queen Mary University of London

Research Workshop Committee Members

David Walker

University of Nottingham & Children's Brain Tumour Drug Delivery Consortium

Ruman Rahman

University of Nottingham & Children's Brain Tumour Drug Delivery Consortium



BNOS Webinar

Biomarkers in Neuro-Oncology

Wednesday 9 September 2020, 10.35-14.25 (BST)

10.35 - 10.40	<p>Introduction and welcome Prof Colin Watts BNOS President</p>
10.40 - 11.15	<p>Dr Nina Struve University Medical Center Hamburg-Eppendorf New insights into EGFR and EGFRvIII as a biomarker in GBM Chair: Prof Susan Short</p>
11.20 - 11.55	<p>Prof Norbert Galldiks University Hospital of Cologne; Institute of Neuroscience & Medicine, Germany Translational PET Imaging Biomarkers Chair: Dr Harpreet Hyare</p>
BREAK	
13.00 - 13.35	<p>Prof Cynthia Hawkins University of Toronto; The Hospital for Sick Children Pediatric gliomas: molecular features and clinical implications Chair: Dr Kathreena Kurian</p>
13.40 - 14.15	<p>Dr Farshad Nassiri University of Toronto Application of plasma methylomes as liquid biopsy in brain tumours Chair: Dr Samantha Mills</p>
14.15 - 14.25	<p>Closing comments and thanks Prof Susan Short Chair of Organising Committee; BNOS Council</p>

Speakers

Biomarkers in Neuro-Oncology



Dr Nina Struve

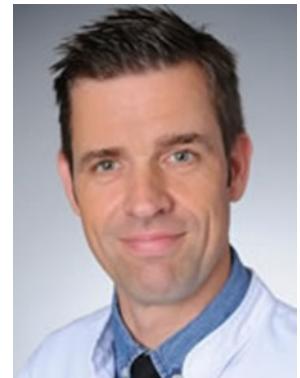
University Medical Center Hamburg-Eppendorf

Nina is a postdoctoral fellow working in the Laboratory of Radiobiology & Experimental Radio-oncology at the University Medical Center Hamburg-Eppendorf (Germany). Her research focuses on Glioblastoma Multiforme (GBM), which is an aggressive primary brain tumour, characterized by rapid progression and oncogene activation. One common and frequently expressed oncogene in GBM is the constitutively activated epidermal growth factor receptor deletion mutant EGFRvIII. EGFRvIII represents a typical oncoprotein that activates different signaling pathways altering thereby multiple cellular processes. Therefore, understanding how EGFRvIII impacts therapy relevant processes like DNA repair, replication and cellular signaling are her main research interest.

Prof Norbert Galldiks

University Hospital of Cologne; Institute of Neuroscience and Medicine, Germany

Norbert Galldiks, MD, is a Professor of Neurology, Senior Neurologist and Senior Neuro-Oncologist at the Dept. of Neurology at the University Hospital Cologne in Germany. He studied medicine at the University of Cologne and Cornell University / Memorial Sloan-Kettering Cancer Center, New York. In 2002, he qualified in medicine and received his MD from the University of Cologne, Germany. After a postdoctoral fellowship at the Max-Planck-Institute for Neurological Research in Cologne (PET laboratory) he obtained his training in Neurology at the University Hospital Cologne. Furthermore, he is Senior Research Scientist at the Institute of Neuroscience and Medicine (INM-3) at the Research Center in Juelich, Germany.



Prof Galldiks is also Head of the Outpatient Clinic for Neuro-Oncology at the Dept. of Neurology at the University Hospital Cologne, a Board of Directors member of the Brain Tumor Center at the University Hospital Cologne, and leader of the PET Response Assessment in Neuro-Oncology Working Group (PET/RANO). He developed multiple investigator-initiated neuroimaging studies in brain tumor patients and also served in numerous national and international phase II and III clinical trials for brain tumor therapy. Additionally, he co-authored in collaboration with international major societies in the field (RANO / EANO / EANM / SNMMI) practice guidelines for PET imaging in glioma patients. Currently, he is Associate Editor for the journals *Neuro-Oncology Advances* and *Neuro-Oncology Practice*.

Prof Galldiks has over 230 publications (Web of Science), predominantly focusing on the evaluation of gliomas and brain metastasis using PET, conventional and advanced MRI, hybrid PET/MRI, and Radiomics techniques.

Speakers

Biomarkers in Neuro-Oncology



Prof Cynthia Hawkins

University of Toronto; The Hospital for Sick Children

Prof Cynthia Hawkins obtained her MD/PhD from Western University. She completed her residency training in neuropathology at the University of Toronto, including a post-doctoral fellowship at the University of Zurich. Professor Hawkins joined The Hospital for Sick Children (SickKids) as a neuropathologist in 2002. She is a Senior Scientist at the SickKids Research Institute and a Professor of Laboratory Medicine and Pathobiology at The University of Toronto.

Prof Hawkins' clinical practice includes both surgical and autopsy paediatric neuropathology. She is best known for her expertise in paediatric brain tumours and has a research lab devoted to paediatric glioma. Her research interests include molecular pathogenesis and therapeutics for paediatric glioma and clinical implementation of novel diagnostic, prognostic and therapeutic markers for paediatric brain tumours. The Hawkins laboratory has contributed to the clinical, morphologic and genetic characterization of diffuse intrinsic pontine glioma (DIPG) and paediatric-type glioma as well the clinical and biologic implications of mutant histones.

Dr Farshad Nassiri

University of Toronto

Farshad Nassiri is a senior neurosurgery resident in the Division of Neurosurgery at the University of Toronto. He is completing his PhD concurrent to his clinical training at the University of Toronto, where his work focuses on elucidating biomarkers of clinical outcome for brain tumors. He is the recipient of the prestigious Vanier Scholar award for the Canadian Institute for Health Research, and is a Fellow of the Neurosurgery Research & Education Foundation from the American Association for Neurological Surgeons as well as a Fellow of the Hold'em for Life Oncology chapter.





BNOS and CBTDDC Research Workshop Translational Drug Delivery in Gliomas



Thursday 10 September 2020, 13.00-14.35 (BST)

Introduction and welcome

13.00 - 13.05

Prof David Walker

University of Nottingham & Children's Brain Tumour Drug Delivery Consortium

Assoc Prof Sabine Mueller

University of Zurich

13.05 - 13.25

Convection enhanced delivery drug strategies for pediatric diffuse intrinsic pontine gliomas (DIPG)

Chair: Prof David Walker

Prof Oren Scherman

University of Cambridge

13.25 - 13.45

Overcoming the Blood-Brain Barrier: Post-resection drug delivery to Glioblastoma Multiforme using Supramolecular Hydrogels

Chair: Dr Ruman Rahman

Dr Michael Canney

CarThera

13.45 - 14.05

Ultrasound mediated blood-brain-barrier opening: from concept to high grade glioma clinical trials

Chair: Dr Ruman Rahman

Discussion / Q&A

14.05 - 14.30

Chair: Prof David Walker

Closing comments and thanks

14.30 - 14.35

Dr Harpreet Hyare

Chair of BNOS Research Subcommittee

Speakers

Translational Drug Delivery in Gliomas

Assoc Prof Sabine Mueller

University of Zurich

Sabine Mueller earned her medical degree and Ph.D. in biochemistry and molecular biology from the University of Hamburg, Germany. After a pediatric residency at Massachusetts General Hospital in Boston, she completed a fellowship in child neurology as well as in pediatric neuro-oncology at the University of California, San Francisco (UCSF). She is an Associate Professor in the Department of Neurology, Neurosurgery and Pediatric at UCSF. She is the Project Leader of the Pacific Pediatric Neuro-Oncology consortium (PNOC), a 22-member clinical trial consortium dedicated to develop innovative trials for children with brain tumors with international presence. Since 2019 she directs the Diffuse Midline Center at the University Children's Hospital of Zürich, Switzerland. She has led many clinical trials for children with brain tumors including trials assessing convection enhanced delivery strategies for children with diffuse midline gliomas.



Prof Oren Scherman

University of Cambridge

Oren Scherman is a native of Norman, Oklahoma (USA), he graduated from Cornell University in Ithaca, New York, with a BA in Chemistry in 1999. He then moved to Pasadena, California, where he completed a PhD in 2004 in olefin metathesis and controlled polymerisation, under the supervision of Professor Robert H. Grubbs at the California Institute of Technology (Caltech). After finishing his PhD, Oren moved to the Netherlands to work on supramolecular polymers with Professors E.W. Meijer and Rint P. Sijbesma at the Eindhoven University of Technology. In 2006, he moved to the University of Cambridge to take up an academic appointment as a University Lecturer and Next Generation Fellow in the Melville Laboratory for Polymer Synthesis in the Department of Chemistry. In 2012, he was promoted to Reader in Supramolecular and Polymer Chemistry and in March 2013, he was appointed as the Director of the Melville Laboratory; Oren was promoted to Full Professor in 2015. During the 2013-2014 academic year, Oren was on sabbatical at Tsinghua University as the Xuetang Visiting Professor in Chemistry. His research focuses on dynamic supramolecular self-assembly at interfaces through the application of macrocyclic host-guest chemistry using cucurbit[n]urils in the development of novel supramolecular systems. The Scherman group exploits control over these molecular level interactions to design and fabricate soft materials with integrated function. Current research topics include drug-delivery systems, sensing and catalysis. Of specific interest is the design of functional soft materials including biocompatible hydrogels for drug-delivery applications, tough supramolecular polymer networks and bioinspired supramolecular fibres.

Speakers

Translational Drug Delivery in Gliomas

Dr Michael Canney

CarThera

Dr Michael Sean Canney received the B.S. degree in mechanical engineering in 2004 from Boston University and the Ph.D. degree in Bioengineering in 2009 from the University of Washington in Seattle. His doctoral research involved characterization of nonlinear high intensity focused ultrasound fields (HIFU) and the use of shock waves to induce millisecond boiling in tissue. He subsequently conducted post-doctoral research at LabTAU/INSERM U1032 in Lyon, France. He is currently the Scientific Director of CarThera, a startup company that is developing ultrasound-based medical devices for treating brain disorders. The company is a spin-off from AP-HP, Greater Paris University Hospitals, the largest hospital group in Europe, and Sorbonne University. Since 2010, CarThera has been leveraging the inventions of Professor Alexandre Carpentier, a neurosurgeon at AP-HP. CarThera developed the SonoCloud®, an intracranial ultrasound implant that emits ultrasound to temporarily increase the permeability of the blood-brain barrier.



Abstracts

Biomarkers in Neuro-Oncology

New insights into EGFR and EGFRvIII as a biomarker in GBM

Dr Nina Struve, University Medical Center Hamburg-Eppendorf

The oncogene epidermal growth factor receptor variant III (EGFRvIII) is frequently expressed in glioblastomas (GBM) but its impact on therapy response is still under controversial debate. We retrospectively analyzed the survival of 336 GBM patients, demonstrating that under standard treatment, which includes TMZ, EGFRvIII expression is associated with prolonged survival, but only in patients with O6-methylguanine-DNA methyltransferase (MGMT) promoter methylated tumors. Isogenetic GBM cell lines with endogenous EGFRvIII expression displayed increased TMZ sensitivity compared to their EGFRvIII- counterparts. In line with this EGFRvIII+ cells showed enhanced numbers of DNA double-strand breaks and a pronounced S/G2-phase arrest after TMZ treatment. Since TMZ sensitivity in MGMT promoter methylated cells correlates with the expression of DNA mismatch repair (MMR) proteins we analyzed MMR protein expression in vitro and in situ. We observed a higher MMR protein expression in EGFRvIII+ cells and GBM patient tumor samples, which was most pronounced for MSH2 and MSH6. EGFRvIII-specific knockdown reduced MMR protein expression thereby increasing TMZ resistance.

Furthermore, we demonstrate that EGFRvIII expressing cells show typical features of replication stress. EGFRvIII+ cells displayed slower replication forks, increased spontaneous DNA damage, elevated levels of single stranded DNA and an activated replication stress response. Additionally, EGFRvIII expressing cells exhibit elevated RNA synthesis and R-loop formation. Immunohistochemistry analysis confirmed these observations in a panel of EGFRvIII positive GBM patient samples, showing increased expression of RPA, γ H2AX and R-loop accumulation in EGFRvIII+ tumor areas. Targeting EGFRvIII-dependent replication stress by irinotecan resulted in increased sensitivity of EGFRvIII+ cells.

In summary, our results demonstrate that the oncoprotein EGFRvIII sensitizes GBM cells to TMZ and irinotecan by increasing DNA MMR protein expression and replication stress.

Translational PET Imaging Biomarkers

Prof Norbert Galldiks, University Hospital of Cologne; Institute of Neuroscience & Medicine, Germany

In the last years, PET using radiolabelled amino acids has gained increasing interest in the diagnostics of brain tumor patients and has been established in many neurooncological centers in Europe as a complementary diagnostic tool to conventional MRI.

Amino acid PET offers important additional information in the diagnosis of unclear space-occupying brain lesions and an improved delineation of glioma extent, which is helpful for biopsy guidance, planning of resection, and radiotherapy.

Furthermore, amino acid PET biomarkers derived from static and dynamic image acquisition may provide prognostic information in untreated, newly diagnosed glioma patients.

Recent data show that also amino acid PET radiomics helps to differentiate tumor progression from treatment-related changes (e.g., pseudoprogression, radiation necrosis) in gliomas as well as in brain metastasis and allows to evaluate molecular characteristics non-invasively ("Radiogenomics").

Moreover, amino acid and non-amino acid PET tracers allow to evaluate the response to various brain tumor treatment options, i.e., chemoradiation, alkylating chemotherapy, targeted therapy, and immunotherapy ("Immuno-PET").

Abstracts

Biomarkers in Neuro-Oncology

Pediatric gliomas: molecular features and clinical implications

Prof Cynthia Hawkins, University of Toronto; The Hospital for Sick Children

Our knowledge of the molecular underpinnings of paediatric-type gliomas continues to grow. As neuropathologists we aim to assimilate this information with morphologic features to create an integrated diagnosis, helping to provide prognostic information and guide therapeutic decision making for patients. The upcoming 5th edition of the WHO Classification of CNS Tumours will incorporate many of these principles and introduce several new paediatric-type diagnoses. In this lecture I will review our current understanding of this molecular data and how it impacts prognosis and response to therapy for patients with paediatric-type high and low grade glioma.

Application of plasma methylomes as liquid biopsy in brain tumours

Dr Farshad Nassiri, University of Toronto

The diagnosis of intracranial tumors relies on tissue specimens obtained by invasive surgery. Non-invasive diagnostic approaches, particularly for patients with brain tumours, provide an opportunity to avoid surgery and mitigate unnecessary risk to patients. We reasoned that DNA methylation profiles of circulating tumor DNA in blood can be used as a clinically useful biomarker for patients with brain tumors, given the specificity of DNA methylation profiles for cell-of-origin. To explore this, we generated methylation profiles on the plasma of 608 patients with cancer (219 intracranial, 388 extracranial) and 60 healthy controls using a cell-free methylated DNA immunoprecipitation combined with deep sequencing (cfMeDIP-seq) approach as. Using machine learning approaches, we developed models that could distinguish gliomas from other cancerous and healthy patients with high sensitivity and discriminative capacity (AUC=0.99, 95%CI 0.96-1), with similar performance in IDH mutant and wildtype gliomas as well as in lower- and high-grade gliomas. Moreover, a series of one-versus other regularized generalized linear models showed reliable discrimination of common extra-axial tumors (AUC_{meningioma}=0.89, 95%CI 0.80–0.97; AUC_{hemangiopericytoma}=0.95, 95%CI 0.73-1) as well as intra-axial tumors ranging from low-grade indolent glial-neuronal tumors (AUC 0.93, 95%CI 0.80 – 1) to diffuse intra-axial gliomas with distinct molecular composition (AUC_{IDH-mutant glioma} = 0.82, 95%CI 0.66 -0.98; AUC_{IDH-wildtype-glioma} = 0.71, 95%CI 0.53 – 0.9). Plasma cfMeDIP-seq signals correlated well with corresponding tumor tissue DNA methylation values overall (r=0.37, p<2.2e-16). Altogether, these results demonstrate the potential for cfMeDIP-seq profiles to not only detect circulating tumor DNA, but to accurately discriminate common primary intracranial tumors that share cell-of-origin lineages.

Abstracts

Translational Drug Delivery in Gliomas

Overcoming the Blood-Brain Barrier: Post-resection drug delivery to Glioblastoma Multiforme using Supramolecular Hydrogels

Professor Oren Scherman, University of Cambridge

Glioblastoma multiforme (GBM) is the most common primary cancer in adults and one of the most aggressive cancers with extremely poor survival statistics owing to high rates of disease recurrence. GBM infiltrates the brain tissue diffusely making complete surgical excision impossible. Current standard of care involves surgical resection of the tumour, concomitant radiotherapy and alkylating chemotherapy, followed by adjuvant chemotherapy. Chemotherapeutic choices are limited on account of most drugs' poor propensity to cross the blood brain barrier. Systemic treatment with unspecified concentrations of chemotherapy is ineffective and risks adverse side effects. A localised and sustained delivery of patient-tailored chemotherapy to the resection cavity walls could significantly enhance patient survival opportunities by circumventing the BBB to eradicate the local, residual disease.

We describe the utilisation of a peptide-functionalised hyaluronic acid hydrogel cross-linked by the host-guest interactions of cucurbit[8]uril (CB[8]) as a drug-delivery vehicle for the treatment of GBM. The resulting material (98 wt% water) exhibits extraordinary tailorability and biocompatibility and can be produced to closely match the rheological properties of GBM tumour tissue.[1-3] The shear-thinning and self-healing capability of the hydrogel is successfully achieved through the use of CB[8] as a supramolecular cross-linker,[4] allowing the hydrogel to mold itself to an ex vivo resection cavity, maintaining tight apposition whilst releasing therapeutic compounds up to 950 μm in 1 h. The hyaluronic acid cysteine-phenylalanine (HA-CF) hydrogel shows no toxicity towards in vitro cell lines, with up-regulation of inflammatory markers seen only in samples loaded with chemotherapeutics. Importantly, these supramolecular hydrogels demonstrate superior release properties compared to conventional carmustine-impregnated wafers, GliadelTM. HA-CF supramolecular hydrogels represent a class of physically cross-linked biocompatible materials that open a crucial window into post-operative treatment for glioma resection patients.

In vitro release studies of various drug compounds encapsulated in the hydrogel have been performed and efficacy against multiple patient-derived human GBM cell lines determined. In vivo experiments with a mouse model are currently underway. We envisage that access to such drug-delivery technology will lead to clinical studies in the near future with an overall goal to prevent disease recurrence and improve patient survival rates.

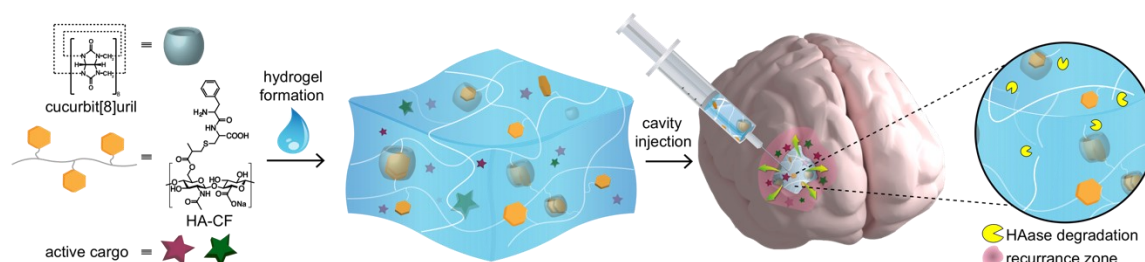


Figure 1. The hydrogel (blue) may be implanted in a tumour resection cavity via a syringe/needle. The hydrogel acts as a drug reservoir, delivering active chemotherapies through the cavity wall into the recurrence zone. The hydrogel consists of a hyaluronic acid functionalised with phenylalanine terminated peptides that bind in a 2:1 fashion with the CB[8] host providing shear-responsive crosslinks that allow for injection.

Abstracts

Translational Drug Delivery in Gliomas

Convection enhanced delivery drug strategies for pediatric diffuse intrinsic pontine gliomas (DIPG)

Assoc Prof Sabine Mueller, University of Zurich

Children diagnosed with DIPG continue to have dismal outcomes and almost all children succumb to their disease within a relative short time period from diagnosis. One key issue for more effective therapy development for DIPGs is to assure adequate exposure of the tumor cells to the chosen therapeutic. Many agents show great promise in the preclinical setting but due to lack of sufficient blood brain barrier (BBB) fail clinically. One strategy to forego the issue of insufficient CNS penetration is to utilize CNS directed delivery strategies such as convection enhanced delivery (CED). A recently reported phase 1 clinical trial assessed the safety and feasibility using a one-time CED of ^{124}I labeled 8H9 antibody. This study showed that this approach was well tolerated and might lead to clinical benefit in a subset of children. We have assessed repeated CED of MTX110, an aqueous form of Panobinostat, as well as repeated CED of liposomal CPT11 using real time image guidance for children and young adults with DIPG. Our phase 1 clinical trials are ongoing and designed to assess the safety of repeated CED in children with DIPG and to determine distribution of these agents by co-infusion with gadolinium. To date we have been able to demonstrate that repeated CED of these agents is feasible and relatively well tolerated. Infusion to distribution volume ratio was approximately 1:3.5. Further, we were able to show that there were no significant changes in self-reported quality of life measures. In summary our results to date show that repeated CED delivery is feasible and reasonably well tolerated. The next step of this therapeutic strategy is to use implantable catheter systems that make repeated delivery more practical and might allow more frequent dosing.

Ultrasound mediated blood-brain-barrier opening: from concept to high grade glioma clinical trials

Dr Michael Canney, CarThera

Low intensity pulsed ultrasound (LIPU), in combination with systemic injection of microbubbles, can be used to transiently disrupt the blood-brain barrier (BBB) and increase brain-drug concentrations. In pre-clinical models, chemotherapy agents such as carboplatin has been shown to be enhanced in the brain using LIPU and to increase survival of glioma-bearing mice. In clinical studies, a single emitter, implantable ultrasound device (SonoCloud-1) was used to disrupt the BBB in 19 patients with recurrent glioblastoma (rGBM) prior to carboplatin chemotherapy (NCT02253212). The feasibility of the approach was demonstrated, and safe acoustic parameters were determined. Currently, a multicenter, international, Phase 1/2a study (NCT03744026) is being performed to demonstrate the safety of BBB disruption over a larger volume, including the tumor and surrounding peritumoral region in rGBM patients using a nine-emitter version of the device (SonoCloud-9). This current and planned future clinical studies using this emerging technique for brain drug delivery will be discussed.

Sponsors

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Brainlab, Children with Cancer UK, Codman Specialty Surgical, Orbus Therapeutics, Medac Pharma, and UCB Pharma.

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Brainlab is a digital medical technology pioneer founded in 1989 and headquartered in Munich. The company employs more than 1500 people in 20 offices around the globe. Brainlab serves physicians, medical professionals and their patients in over 5600 hospitals in 116 countries.

Brainlab creates software-driven medical solutions that digitize, automate and optimize clinical workflows for neurosurgery, spine, trauma, craniomaxillofacial (CMF), general and vascular surgery as well as radiotherapy and radiosurgery. Core products center around surgical navigation, radiotherapy, digital operating room integration, and information and knowledge exchange. The Brainlab open framework operating system will allow third parties to develop medical applications to further advance the field of spatial computing and mixed reality.

Brainlab is dedicated to creating an impact in healthcare. The company connects opportunities from emerging digital technologies to transform healthcare at scale and help improve the lives of patients worldwide.

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Children with Cancer UK is the leading national children's charity dedicated to the fight against childhood cancer. Every day 12 children and young people are diagnosed with cancer in the UK. 2 of the 12 won't survive. Our vision is a world where every child survives cancer.

Our mission is to improve survival rates and the quality of survival in young cancer patients and to find ways to prevent cancer in the future. We actively raise and invest money for vital specialist research to help save the life of every child with cancer and keep their family together.

For more information about Children with Cancer UK, please visit us at

www.childrenwithcancer.org.uk

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Orbus Therapeutics is happy to announce the opening of The STELLAR Study, a phase 3 clinical trial. Patients with anaplastic astrocytoma that has recurred or progressed after surgery or biopsy, radiation therapy and chemotherapy may be eligible.

The STELLAR trial is now recruiting participants at selected medical centers in Canada, the United States, Belgium, Germany, Italy, the Netherlands, France and UK.

For more information about the STELLAR Study, please visit us at www.stellarstudy.com

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