



The DCCC Brain Tumor Center

The Research Center is a member of DCCC and supported by The Danish Cancer Society

# Glioblastoma heterogeneity

2nd Annual Meeting  
The DCCC Brain Tumor Center

October 4, 2022





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# Detailed Program

Tuesday October 4

CEST

09.00-10.00	Registration Registration & Coffee	Entrance Auditorium
10.00-10.15	Welcome & Introduction	Auditorium
10.00	Welcome to Aarhus   Morten Høyer	
10.03	Introduction to the DCCC Brain Tumor Center   Ulrik Lassen	
10.08	Introduction to the DCCC Brain Tumor Center 2nd Annual Meeting   Hans Skovgaard Poulsen	
10.15-11.45	<b>Symposium 1 - Tumor Heterogeneity: concepts at a cellular level</b> Chairs: Joachim Weischenfeldt & Webster Cavenee	Auditorium
10.15	TRACERx and Lung Cancer evolution: from tumor initiation through to metastasis, drug resistance and immune evasion   Charles Swanton (Online)	
10.45	Phenotypic heterogeneity and intrinsic plasticity as resistance mechanisms in glioblastoma   Anna Golebiewska	
11.10	Single cell sequencing and glioblastoma evolution   Josephine Deleuran Hendriksen	
11.30	Heterogeneity in GBM is an Active Process   Webster Cavenee	
11.45-13.00	Break - Lunch	Restaurant level 8
13.00-14.40	<b>Symposium 2 - Glioblastoma heterogeneity: targeting by local treatment</b> Chairs: Hans Skovgaard Poulsen & Manfred Westphal	Auditorium
13.00	Do preoperative strategies pave the way to personalized and improved treatment outcomes for Glioblastoma patients   Gerben Borst	

13.35	Heterogeneity & Imaging   Ian Law	Auditorium
14.00	Glioblastoma heterogeneity – neurosurgeon’s perspective   Frantz Rom Poulsen	
14.25	Perspectives & future directions   Manfred Westphal	
14.40-15.10	Break - Coffee + A little walk up in Your Rainbow Panorama	Entrance Auditorium + Galleries
15.10-16.50	<b>Symposium 3 - Glioblastoma heterogeneity: precision medicine</b> Chairs: Ulrik Lassen & Michael Weller	Auditorium
15.10	How to inform about life with a brain tumor? - Danish Brain Tumor Association   Vibeke Vollmer	
15.25	The surfaceome landscape in human glioma is divergent and depends on cellular spatial organization: Implications for immunotherapy target identification   Mattias Belting	
16.00	Identification and validation of novel therapeutic targets in Glioblastoma   Krister Wennerberg	
16.25	Perspectives & future directions   Michael Weller	
16.40-16.50	Closing remarks   Ulrik Lassen	Auditorium
16.50-19.00	Social/Networking Event - Walking dinner	Restaurant level 8

# Welcome to Aarhus

October 4, 2022

Welcome to the DCCC-Brain Tumour Centre 2nd Annual Meeting October 4, 2022. This year, the meeting is held at the ARoS Art Museum in Aarhus. We look forward to sharing the day with you with an exciting scientific program in wonderful environments.

The theme of the meeting is Glioblastoma Heterogeneity. It is a very complex issue, highly important in treatment of cancer in general, and in particular in treatment of glioblastoma. It is obviously of importance in the use of novel biologically targeted therapies where the success of treatment is directly related to the function of tumoral targets and immunological cellular targets, but it is also highly important to the success of neurosurgery, radiation therapy and conventional chemotherapy. This meeting will focus on concepts of tumour cell heterogeneity, on the impact of heterogeneity in imaging and treatment of glioblastoma.

ARoS Art Museum lies at the heart of Aarhus, and is hard to miss due to its iconic look. With about one million visitors each year, ARoS is the most frequented art museum in Scandinavia. Besides four spacious galleries, the museum also features installation art including Your Rainbow Panorama by the world-famous Danish-Icelandic artist Olafur Eliasson. During the 2nd Annual Meeting, we will have the opportunity to visit this 150-metre-long walkway in glass in all the colours of the spectrum, experience the view across the city, alleviate our senses, and gain new perspectives. You are also most welcome at the galleries.

This is an informal event. Engage in the discussions and enjoy the science, the art of ARoS and the nice company of colleagues.

On behalf of the organizing committee and directors of the DCCC-Brain Tumour Centre,

Morten Høyer, Professor, Medical Director Danish Center for Particle Therapy, Board member of the DCCC Brain Tumor Center  
Host of the Brain Tumor Center 2nd Annual Meeting



# Introduction to The DCCC Brain Tumor Center

The DCCC Brain Tumor Center was established in the beginning of 2021. The primary goal is to improve the overall survival and quality of life of patients with brain tumors by joining forces in Denmark and reaching out to international collaborators. Several important research projects within the focus areas have been established and were presented at the first annual meeting in September 2021.

We are very proud to present a strong scientific program of the 2nd Annual Meeting, focusing on tumor heterogeneity. The DCCC Brain Tumor Center is truly a national center, and we are very happy that Professor Morten Høyer, member of board of the DCCC Brain Tumor Center, and Medical Director of the Danish Center for Particle Therapy, is hosting the meeting in the beautiful surroundings of the ARoS Art Museum.

We are also very happy that our international scientific advisory board once again is supporting the annual meeting. With the presence of Professor Webster Cavenee, Professor Manfred Westphal, and Professor Michael Weller, we have the best opportunities for fruitful scientific discussions.

Ulrik Lassen,  
Director of the DCCC Brain Tumor Center



**Ulrik  
Lassen**

Professor

Ulrik Lassen is Clinical Oncologist, ESMO board certified in Medical Oncology, and head of the Department of Cancer Treatment, Rigshospitalet, Copenhagen. In 2005, he established the Phase 1 Unit at Rigshospitalet and has worked with Phase 1 Oncology trials ever since.

He is a Professor in Clinical Oncology with a special focus on personalized medicine, including early drug development, precision medicine and patient selection based on sequencing platforms, and translational research with identification of predictive markers. In 2013, he established the Copenhagen Prospective Personalized Oncology program (CoPPO) for which he is project leader.

Ulrik is furthermore director of the DCCC Brain Tumor Center, leading this national collaboration in basic, translational, and clinical research in glioblastoma. Ulrik has been awarded several prizes, most recently the Danish Society for Clinical Oncology Honorary Prize 2022.

# 2nd Annual Meeting

October 4, 2022

Dear colleagues and friends,

The Organizing Committee is happy to welcome you to the 2nd Annual Meeting held by the DCCC Brain Tumor Center covering Tumor Heterogeneity.

The center creates new basic and clinical knowledge in adult patients with Glioblastoma which could ultimately lead to increased cure.

The center consists of 20 research groups covering different aspects of five focus areas:

- 1 Tumor heterogeneity
- 2 Dispersal mechanisms and tumor environment
- 3 Treatment resistance
- 4 Local control
- 5 Targeted drug treatment

**Tumor heterogeneity** is a major characteristic of many tumors including glioblastoma. Tumors often consist of a combination of tumor and stromal cells. Tumor cells are genetically and phenotypically heterogeneous which can result in different proliferative and metastatic potential. Moreover, stromal cells can impact the tumorigenic potential, by stimulating or inhibiting the tumor cells. Tumor heterogeneity can impact our ability to provide the optimal diagnosis and therapy, and the existence of tumor heterogeneity is probably one of the major causes to treatment failure as given today. Therefore, a deeper understanding of intra- and intertumor heterogeneity could lead to more effective treatment, providing individual patients with tailored therapy.

In order to discuss this important problem in detail, we are grateful to have brought together a group of highly distinguished national and international scientists who will share their knowledge with us.

We hope the meeting will broaden our understanding of tumor heterogeneity in glioblastoma, and will inspire us to use this new understanding into our daily and future work.

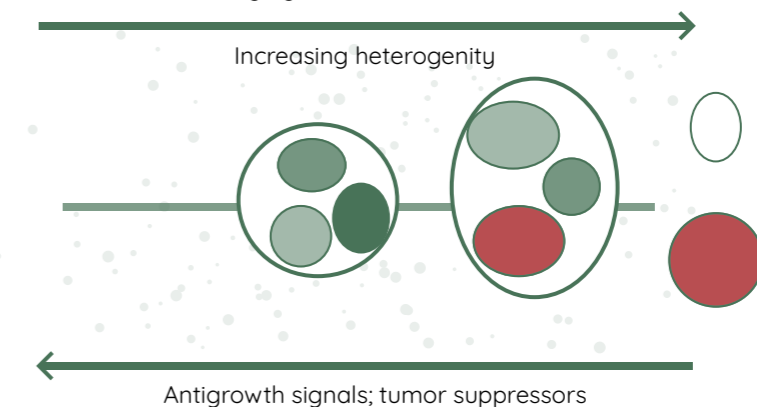
We look forward to your participation and we warmly welcome you to the Brain Tumor Center 2nd Annual Meeting 2022.

## The Organizing Committee,

Alice Mary Clarke, Anouk Kirsten Trip, Camilla Skinnerup Byskov, Kim Møller Hochreuter, Morten Høyer, Ulrik Lassen, Joachim Weischenfeldt, Rikke Hedegaard Dahlrot, Charlotte Aaquist Haslund, Anne-Marie Bach & Hans Skovgaard Poulsen

## Cancer Development

Growth signals; evading apoptosis; unlimited replication;  
sustained angiogenesis; invasion and metastasis



## Symposium 1

# Tumor Heterogeneity: concepts at a cellular level

Charles Swanton

TRACERx and Lung Cancer evolution: from tumor initiation through to metastasis, drug resistance and immune evasion

Anna Golebiewska

Phenotypic heterogeneity and intrinsic plasticity as resistance mechanisms in glioblastoma

Josephine Deleuran Hendriksen

Single cell sequencing and glioblastoma evolution

Webster Cavenee

Heterogeneity in GBM is an Active Process

## Charles Swanton

### Molecular characterization and identification of clonal evolution



Charles  
Swanton

Professor

Charles completed his MBPhD training in 1999 at the Imperial Cancer Research Fund Laboratories and Cancer Research UK clinician scientist/medical oncology training in 2008. Charles is a senior group leader of the Cancer Evolution and Genome Instability Laboratory at the Francis Crick Institute and combines his research with clinical duties at UCLH, as a thoracic oncologist, focussed on how tumours evolve over space and time.

Charles research branched evolutionary histories of solid tumours, processes that drive cancer cell-to-cell variation in the form of new cancer mutations or chromosomal instabilities, and the impact of such cancer diversity on effective immune surveillance and clinical outcome. Charles is chief investigator of TRACERx, a lung cancer evolutionary study and the national PEACE autopsy program. Charles has been awarded several prizes including the ESMO Award for Translational Cancer Research (2019) and the Memorial Sloan Kettering Paul Marks Memorial Prize (2021).



## Anna Golebiewska

### Phenotypic heterogeneity and intrinsic plasticity as resistance mechanisms in glioblastoma

Glioblastomas create a dynamic ecosystem, where phenotypically heterogeneous tumor cells interact with the tumor microenvironment to establish different niches. Upon tumor growth, glioblastoma cells manifest remarkable plasticity and respond flexibly to selective pressures by transiting towards states favorable to the new tumor microenvironment. How this phenotypic plasticity contributes to treatment resistance is currently less clear.

Further studies at the single cell level are needed to reveal transient and long-term signatures of the resistant states. I will present how we apply patient-derived organoids and orthotopic xenografts to investigate phenotypic adaptation of tumor cells and adjacent microenvironment upon treatment by single cell transcriptomics.

I will discuss how advanced computational algorithms, including reference-free deconvolution methods can be applied to reveal treatment resistance signatures and master regulators of the identified treatment-resistant subpopulations. Key molecular regulators of tumor cell plasticity towards treatment resistance states may represent novel targets for future combinatory treatments.



Anna  
Golebiewska

Group Leader

Anna Golebiewska is a molecular biologist and group leader at NORLUX Neuro-Oncology Laboratory, Luxembourg Institute of Health. She obtained her PhD in Stem Cell Biology at the University of Newcastle, United Kingdom. In 2008, she started postdoctoral research at NORLUX Neuro-Oncology Laboratory and in 2019, she became group leader.

Her work focuses on understanding brain tumor biology and development of clinically relevant animal models. She is particularly interested in the various aspects of tumor heterogeneity and the cancer stem cell hypothesis. Her current projects aim to tackle intrinsic plasticity allowing brain tumour cells to adapt and survive external pressures from microenvironmental cues and treatment.

Her lab developed a large collection of glioma patient-derived organoids and orthotopic xenografts for preclinical research and drug testing. Anna has been awarded several prizes, including best pre-clinical abstract at EANO 2019 and the Luxembourg National Research Fund Award for Outstanding Scientific Achievement 2021.

## Josephine Deleuran Hendriksen

### Single cell sequencing and glioblastoma evolution

Glioblastoma is the most aggressive cancer originating in the brain with an average survival of 15 months. One of the characteristics of glioblastoma is the high level of intra-tumour heterogeneity, but the composition and complexity at the single-cell level is poorly understood, as are the longitudinal consequences of this.

Here, we aimed to trace the genomic, single-cell transcriptional and chromatin conformation evolution of a glioblastoma patient case at primary, first and second relapse surgeries. We achieved this through the integration of three complementary data types: single cell RNA-sequencing, Hi-C analysis and whole genome sequencing, all obtained at each surgical time point.

We identified mutational alterations driving early disease including early trunk chromothripsis and seeding extrachromosomal DNA events, while the later disease stages were characterised by selection of rare populations from the primary tumour.

Through integrative analyses we identified regulatory changes affecting key transcription factor networks associated with gene expression changes in the relapse tumours. An example of this was the gradual opening of chromatin surrounding the glioma stem cell-associated receptor PTPRZ1, accompanied by gene upregulation and increased interaction between cancer-associated fibroblasts and tumour cells.

In conclusion, we identified a previously underappreciated impact of the interplay between genetics, chromatin conformation and gene regulation in this disease and demonstrate the utility and knowledge gained from integrating different levels of molecular information.



**Josephine  
Deleuran  
Hendriksen**

PhD, Postdoc

Dr. Josephine Deleuran Hendriksen is a Postdoc in the lab of Joachim Weischenfeldt at Biotech Research & Innovation Centre (BRIC), University of Copenhagen, and has a background in molecular biomedicine. In her PhD thesis, she has used single cell RNA sequencing to investigate glioblastoma evolution and found signs of an early mutation-driven evolution, while later disease stages were dependent on chromatin changes and tumor microenvironment.

As part of her PhD training, Josephine joined the Computational Oncology lab of Naveed Ishaque, Berlin Institute of Health, Charité for an exchange and performed trajectory analysis on single-cell RNA sequencing data, allowing the estimation of each patient's evolutionary transcription state selection between primary and relapse tumor.

After obtaining her PhD in September 2022, she started her Postdoc continuing the work on single cell derived evolution of glioblastoma in the Weischenfeldt lab. As such, Josephine is affiliated to work packages 1 and 3 of the DCCC Brain Tumor Center.

## Webster Cavenee

### Heterogeneity in GBM is an Active Process

GBM is characterized by heterogeneity, both within and among tumors. The variability of cell-intrinsic genomic alterations that drive tumor behavior is thought to result in phenotypic variation that manifests as tumor heterogeneity. Most targeted therapeutic approaches have primarily been directed at cell-intrinsic tumor cell features and have proven ineffective. I will briefly use two examples that involve a prototypical GBM alteration, the amplification and mutation of the epidermal growth factor receptor gene (EGFR) that results in the common and oncogenic EGFRvIII ( $\Delta$ EGFR) variant, to illustrate that tumor heterogeneity is actually a complicated active intercellular process and has substantial consequences for therapy.

The first example addresses the paradoxical observation that, despite its greater intrinsic biological activity than wildtype EGFR (wtEGFR), only a minority of cancer cells in primary tumors carry the hallmark  $\Delta$ EGFR lesion, while the remainder express wtEGFR. We discovered that the  $\Delta$ EGFR-expressing subpopulation has an extrinsic activity-- involving cytokine secretion and aberrant

receptor utilization-- that provides actively enhanced tumorigenicity to the entire tumor. The second example is the discovery that tumor cells reversibly upregulate or suppress oncogene expression, conferring distinct cellular phenotypes to reach an optimal equilibrium for growth. This leads to acquired resistance to EGFR tyrosine kinase inhibitors being mediated by elimination of EGFR from extrachromosomal DNA. After drug withdrawal, re-emergence of clonal EGFR mutations on extrachromosomal DNA follows providing a highly specific, dynamic, and adaptive means by which cancers can evade targeted therapies.

These findings demonstrate that the heterogeneity that characterizes GBM, and perhaps other tumors with this feature, does not occur stochastically. Instead, it results from both intrinsic and extrinsic activities of driver mutations and can be an actively maintained feature. This illuminates that heterotypic cancer cell interactions might be of potential therapeutic significance.



Webster  
Cavenee

Professor

Dr. Cavenee is global director emeritus of Strategic Alliances in Central Nervous System Cancers, Ludwig Institute for Cancer Research and distinguished professor emeritus, University of California, San Diego. Web has a background in microbial/human genetics and biochemistry and has worked at several other renowned universities, including the Massachusetts Institute of Technology, the Jackson Laboratory, the University of Cincinnati and McGill University.

He is on the editorial boards of several scientific journals and, among dozens of external advisory boards in academia and business, has served on the Board of Scientific Counselors for the US National Cancer Institute and the US National Institute of Environmental Health Sciences as well as President of the American Association for Cancer Research. He also serves on the Board of Directors of the Global Coalition for Adaptive Research which sponsors GBM AGILE, a revolutionary global collaboration to test and develop new brain cancer treatments.

He has published more than 400 publications and has been recognized with more than 100 honors and awards. He is an elected member of the US National Academies of Science and Medicine, the German Leopoldina Academy of Science and the Chinese Academy of Engineering. His genetic evidence of the existence of tumor suppressor genes has fundamentally changed the way scientists now think about the onset of cancer and its progression.



## Symposium 2

# Glioblastoma heterogeneity: targeting by local treatment

Gerben Borst

Do preoperative strategies pave the way to personalized and improved treatment outcomes for Glioblastoma patients?

Ian Law

Heterogeneity & Imaging

Frantz Rom Poulsen

Glioblastoma heterogeneity - neurosurgeon's perspective

Manfred Westphal

Perspectives & future directions

## Gerben Borst

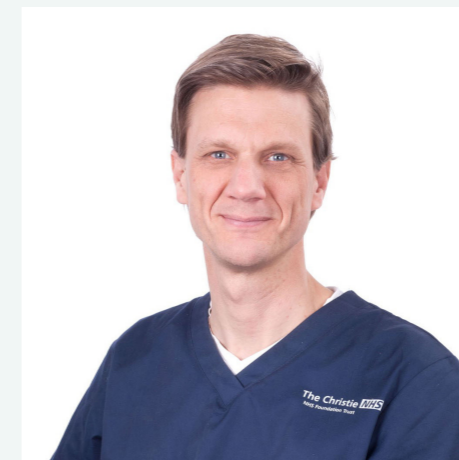
### Do preoperative strategies pave the way to personalized and improved treatment outcomes for Glioblastoma patients?

Glioblastoma is the most common and aggressive type of brain tumor, with a median survival of 15 months, and its incidence is increasing. The devastating prognosis, the physical and emotional consequences and the socio-economic cost are among the highest in oncology.

Surgery followed by chemoradiotherapy is the standard-of-care treatment, but it fails to cure patients. Therefore, it is well accepted that a paradigm shift is needed. In our work, we focus on clinically applicable tools (e.g. MRI imaging) to characterize the tumor in an early stage after diagnosis supporting the development of better and individualized treatment strategies.

We propose that preoperative treatment strategies lead to fundamental improvements in treatment outcomes as they target the tumor in a more treatment-sensitive period. Such procedures will also mitigate the early progression of residual tumor that is inevitably left behind after surgery.

There is a growing interest in this early progression that occurs between surgery and administration of postoperative radiotherapy, and more research is needed to understand this early progression to develop individualized and effective strategies targeting this. In my talk, I will share how we try to advance our understanding of the early tumor progression and develop new treatment strategies that will hopefully lead to better treatment outcomes for glioblastoma patients.



Gerben  
Borst

Senior Lecturer

Dr Gerben Borst is senior lecturer at the University of Manchester and honorary consultant clinical oncologist at The Christie NHS Foundation Trust. Gerben obtained his MD at the University of Antwerp Medical School in Belgium and his PhD at the University of Amsterdam in the Netherlands. He combined his PhD with a residency at the Department of Radiation Oncology, the Netherlands Cancer Institute (NKI).

Gerben's speciality training has taken him to Hokkaido University in Japan under the supervision of Professor Shirato, and the Institute of Cancer Research in London, under the supervision of Professor Kevin Harrington. After completing his speciality training, he worked with Professor Rob Bristow at the Princess Margaret Cancer Centre, Toronto (Dutch Cancer Society fellow), and did the Ladislau and Melita Steiner Radiosurgery Fellowship at UCSF. As a consultant radiation oncologist and Assistant Professor at the NKI, he started his own research group investigating novel insights in radiation treatment response to develop innovative treatment strategies. Dr Borst has a passion for developing the next generation of scientists and since 2018, he has supported PhD students as a primary supervisor. In 2020, Gerben moved to The University of Manchester and The Christie NHS Foundation Trust, continuing his research into implementing better and innovative treatment strategies for patients with brain tumors. His goal is to contribute to the paradigm shift that is needed to improve the prognosis of glioblastoma patients.

## Ian Law

### Molecular Imaging of glioma heterogeneity

PET and advanced MRI imaging may visualize the spatial distribution of tumor physiology and molecular profile. Within modality heterogeneity may be caused by limitations in methodology (expression of target in multiple tissues, off-target binding, molecular target polymorphism, binding thresholds, kinetic modeling) that need to be understood before biological variability in tumor or environment can be addressed. The primary methodological limitation of PET tracers is limited transport across the blood brain barrier (BBB), that exclude the possibility of imaging the physiology of tumor infiltration behind an intact BBB.

For clinical amino acid PET tracers such as O-(2-[<sup>18</sup>F]-fluoroethyl)-L-tyrosine ([<sup>18</sup>F]FET) heterogeneity in uptake may be associated with cellular and vascular density and post treatment damage related uptake in astrogliosis.

Between modality heterogeneity has been found between [<sup>18</sup>F]FET PET and blood volume measurements with advanced MRI, but does not robustly translate into improved diagnostic accuracy.

Small patient series have been published showing between modality heterogeneity in late stage GBM between [<sup>18</sup>F]FET PET and [<sup>123</sup>I]CLINDE SPECT. [<sup>123</sup>I]CLINDE targets the TSPO site in activated microglia and the results suggest that [<sup>123</sup>I]CLINDE could predict the direction of tumor growth.



Ian  
Law

Professor

Dr. Ian Law has worked as a research fellow at Akita, Japan (1990), and at the Neurobiology Research Unit, Rigshospitalet. He has received both his PhD (1997) and habilitation thesis, DMSc (2007), in neuroscience from the University of Copenhagen using PET scanning techniques.

Ian was appointed Chief Physician at Rigshospitalet, Copenhagen in Clinical Physiology and Nuclear Medicine in 2007, and Full Professor at the University of Copenhagen in 2014. Professor Law's work has focused on cerebral perfusion measures and the practical translational clinical application of multimodality imaging (PET/CT, LAFOV PET/CT, PET/MRI) with emphasis on dementia and neuro-oncology.

Besides, he was the previous chairman of the Neuroimaging Committee, European Association of Nuclear Medicine (EANM) and has published over 170 articles in peer reviewed international journals.



## Frantz Rom Poulsen

### Glioblastoma heterogeneity – neurosurgeon’s perspective

Glioblastomas are notoriously known for their macroscopic and microscopic heterogeneity. In the operating theater, this is easily appreciated during surgery where tumor consists of central necrosis and thrombosed vessels are intermingled with viable bleeding-prone areas.

The tumor heterogeneity is proposed as the main reason for glioblastoma recurrence after optimal radio-chemotherapy. MRI, amino-acid and FDG PET are often used to identify tumor areas with increased metabolism/turnover, and high MRI perfusion as well as high PET values are considered an indication of aggressiveness.

Detailed knowledge of the association between MRI and PET imaging and tumor characteristics is, however lacking. The purpose of the present study was to investigate glioblastoma heterogeneity using selective and neuronavigation guided biopsies based on MRI and PET hot and cold spots and correlate with tumor pathology.



Frantz Rom  
Poulsen

Professor

Professor Frantz Rom Poulsen is neurosurgeon and head of research at the Department of Neurosurgery, Odense University Hospital. In 2003, he obtained his PhD in experimental neurobiology at the University of Southern Denmark, and in 2010, he completed his training as neurosurgeon at Odense and Aarhus University hospitals.

His research interests include the treatment of primary brain tumors, skull base tumors and pituitary tumors, molecular mechanisms in malignant gliomas and pituitary tumors, chronic subdural hematomas, cerebral metabolism and MR guided focused ultrasound.

He has previously been head of Brain Research – Inter-Disciplinary-Guided-Excellence (BRIDGE), a translational collaboration focused on brain diseases. Frantz is furthermore co-PI for work package 7 ‘Nanocarrier-based drug delivery for next generation glioblastoma therapy’ of the DCCC Brain Tumor Center.

## Manfred Westphal

### Glioblastoma heterogeneity – neurosurgeon’s perspective

Therapy for intrinsic brain tumors is hampered by inadequate drug delivery to the brain. Local drug delivery strategies show improved local control but only delay progression. Targeting larger disease affected areas is evaluated in the context of interstitial drug delivery by enhanced convection and lately by temporary areal blood brain barrier opening with focused ultrasound, both allowing large molecules to enter brain parenchyma.

Resistance to current therapies is in a large part regulated by the interaction with the host environment, in particular by manipulating the brain intrinsic immune system. Another major component supporting tumor cell tolerance in the brain which is coming into focus of attention is the neuro-glial interaction.

By being embedded into the brain’s circuitry with synaptic connections, tight junctions or even syncytial relationships, protection appears to be conveyed against a broad spectrum of therapeutic strategies. The tumor biology and the reaction of the environment to the tumor is reflected in extracellular vesicles which are shed by all cells of that composite compartment.

By being shed into the circulation, these particles could serve as biomarkers before surgery and during therapy once the sufficient selective purification from blood or csf is mastered. The analysis of methylation patterns of the DNA in these vesicles so far only allows for the most current tumor classification but more refined gene regulatory analyses of enhancer regions in cell free DNA may even allow for the analysis of specific gene activation programs and specific therapeutic options.



Manfred  
Westphal

Professor

Professor Manfred Westphal is neurosurgeon and clinical director of the Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Germany. Manfred obtained both his MD and PhD in 1981 at the University of Hamburg. He continued his research as Postdoctoral Research Fellow in the Hormone Research Laboratory at UCSF Medical Center in San Francisco (USA), Director C.H.Li, PhD.

After 2 years, he returned to Hamburg and founded the Laboratory for Brain Tumor Biology. He then started his residency in neurosurgery and developed into professor and director of the neurosurgical department. His research interests include glioblastoma, intracerebroventricular drug administration, aneurysm neurosurgery and oncologic spine neurosurgery.

Besides, he is a former board member of the European Brain Council (2004-2021), President of the German Academy of Neurosurgery (2013-2014), President of the European Congress for Neurosurgery, EANS (2021), and current Director of the European Brain Foundation. Manfred has been highly distinguished for his work, including the Milam E Leavens Distinguished Lectureship MD Anderson Cancer Center, and the Warner Prize for Cancer Research, and has been involved in the completion of numerous glioblastoma landmark trials, establishing the current standard-of-care.

## Symposium 3

# Glioblastoma heterogeneity: precision medicine

Vibeke Vollmer

How to inform about life with a brain tumor? -  
Danish Brain Tumor Association

Mattias Belting

The surfaceome landscape in human glioma  
is divergent and depends on cellular spatial  
organization: Implications for immunotherapy  
target identification

Krister Wennerberg

Identification and validation of novel therapeutic  
targets in Glioblastoma

Michael Weller

Perspectives & future directions



## Vibeke Vollmer

### How to inform about life with a brain tumor?

In our communication we seek to enhance understanding and recognition, to promote dialogue, and to support relations – both in families and in society.

In a video project of nine small fictive sequences, developed in cooperation with film professionals, we follow a family, where the mother is diagnosed with a brain tumor.

A writing project, supervised by a professional writing coach, included 23 brain tumor patients and relatives, who through coaching were encouraged to write their story. The very courageous, personal, and touching stories were published in the book “Hjernetumorfortællinger” (“Brain Tumor Tales”).



**HJERNETUMORFORENINGEN**  
hjernetumorforeningen.dk



Vibeke  
Vollmer

Danish Brain Tumor  
Association

Vibeke Vollmer has studied in Copenhagen and Berlin and has a master’s degree in German language. After a few years of teaching, she changed into business and was the founder of an awarded Danish kitchen design brand.

In 2010, Vibeke was diagnosed with meningioma, which eventually led to early retirement in 2021. Vibeke Vollmer became a member of the board of the Danish Brain Tumor Association in 2018, where she is in charge of finances and communication strategies.

Besides the financial responsibilities, her focus is information on diagnoses, treatment and life with a brain tumor, both for patients, relatives and the public. Primarily through newsletters and social media, but also in printed media.

Vibeke had an important role in designing a video project in 2021 and was the initiator of a writing project for patients and relatives, resulting in a book release in 2022.

## Mattias Belting

### The surfaceome landscape in human glioma is divergent and depends on cellular spatial organization: Implications for immunotherapy target identification

Cell-surface proteins have a key role in drug development, and the tumor surfaceome (TS) has attracted considerable attention as targets for immunotherapies. Checkpoint inhibitor blocking antibodies, antibody drug conjugates (ADCs), and CAR-T cells are all directed at the TS. However, a remaining challenge is the lack of strategies to comprehensively map TS antigens for the design of rational, individualized treatments.

TS proteins that functionally engage in endocytosis as targets for ADC and other intracellular drug delivery strategies are of specific interest. With the aim to address these challenges, we have developed a versatile technology for TS mapping (TS-MAP). As proof-of-concept, we focused on primary brain tumors that remain among the most aggressive forms of cancer, and for which attempts to conquer the most common variant, glioblastoma (GBM), have failed so far. TS-MAP is compatible with 3D cultures and patient tumors with preserved tissue architecture, and specifically identifies proteins capable of endocytosis as tractable targets for toxic payload internalization.

Moreover, a TS classifier (SURFME) was curated for categorization of bona fide membrane proteins. We reveal how cellular spatial organization transforms the TS with general implications for target screening approaches. We found a highly diverse TS repertoire between patient tumors, not directly associated with grade and histology, which highlights the need for individualized approaches.

Our findings provide new layers of understanding for the future development of immunotherapy strategies, as well as new procedures for proteomics-based target identification aimed at a better understanding of how to harness the TS for personalized immunotherapy.



**Mattias  
Belting**

Professor

Mattias Belting earned his MD in 1997 and PhD in 1999, followed by postdoctoral studies at UCSD and the Scripps Research Institute, La Jolla, USA. He is currently Professor in clinical oncology at Lund University, Consultant of neuro-oncology at Skåne University Hospital, Lund, and Visiting Professor at Uppsala University, Sweden.

With a research background in preclinical tumor biology, Dr. Belting and his team have successfully translated original research findings into clinical intervention studies with publications in broad audience journals (e.g. Nature Med., JCO, PNAS, and Nature Comm.).

His current research interests focus on how stress adaptive mechanisms in the tumor microenvironment and the tumor surfaceome can be harnessed for therapeutic development.

## Krister Wennerberg

### Identification and validation of novel therapeutic targets in Glioblastoma

Glioblastoma (GBM) growth and relapse is thought to be driven by a small subpopulation of glioblastoma stem cells (GSCs) that display self-renewal and tumor-initiating capacities. Importantly, following surgery that removes the tumor bulk, and adjuvant chemo-radio therapy, this population can be reactivated and drive relapse. In this context, there is a need to develop approaches aiming at understanding and targeting the biology mechanisms driving survival and self-renewal of this cell subpopulation.

To address this, we are searching for novel stratified vulnerabilities in GSCs. Starting from public pooled CRISPR screening data on GSC-driven neurosphere cultures, we have identified 1654 putative GSC-selective genetic vulnerabilities in one or more of the publicly profiled GSC models. Among the genes are multiple well-known GBM/GSC gene dependencies (such as EGFR, AKT1, PIK3CA), arguing for the relevance of the approach. However, most genes have not previously been explored as drug targets in GBM. The roles of these genes are now explored, knocking out one gene at a time with high throughput arrayed CRISPR screening in neurosphere and organoid

culture models of a panel of diverse GBMs to validate key novel selective genetic vulnerabilities in GSCs. Selective vulnerabilities will be compared to the genetic alterations in the GBMs with the aim of finding predictive genetic biomarkers for response. Finally, to convert the genetic vulnerabilities to novel therapeutic vulnerabilities, we are building collections of drugs and drug candidates that directly target the dependency genes as well as the pathways that they control. These drug sets will be tested on relevant in vitro GBM models. Together, we expect that these studies will identify new therapeutic targets that can be explored in animal models and eventually in clinical trials.



**Krister  
Wennerberg**

Professor, Biosketch

Krister Wennerberg, PhD, is a professor at the Biotech Research and Innovation Centre (BRIC) at University of Copenhagen. He received his PhD at Uppsala University, Sweden and his postdoctoral training at the University of North Carolina at Chapel Hill, USA. After his postdoc, he first worked as an R&D scientist at Cytoskeleton, Inc, Denver, CO, USA and then as a Research Biologist at Southern Research Institute, Birmingham, AL, USA. Before moving his group to BRIC in 2018, he was also a FIMM-EMBL group leader for 8 years at the Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Finland.

The research focus in Professor Wennerberg's group is to functionally and therapeutically stratify individual cancers to a) identify the underlying signals that drive each individual cancer, b) understand how drug responses relate to the molecular features of the cancer, and c) identify effective personalized drug combinations overcoming drug resistance. This is done by using high throughput approaches to study primary and early passage cancer cells, their drug responses as well as genetic dependencies, and relate that to their molecular characteristics.

In the DCCC Brain Tumor Center, Professor Wennerberg leads work packages 2 (Ex vivo high-throughput Drug screening) and 5 (Identification and validation of novel therapeutic targets).



## Michael Weller

### Perspectives and future directions

Glioblastoma is a highly malignant brain tumor thought to be derived from neuroglial progenitor cells. The current standard of care for glioblastoma of neurosurgical resection as feasible followed by involved-field radiotherapy and concomitant and maintenance temozolomide alkylating agent chemotherapy prolongs survival to a median of 16 months in clinical trial populations, but survival with glioblastoma is still in the range of one year on a population level.

The options for targeted therapy are limited because glioblastoma is very rarely a single pathway disease. Immunosuppression is one of the hallmarks of the glioblastoma microenvironment, prompting the clinical development of various immunotherapeutic strategies that are currently being studied in clinical trials of phase I, II or III. Efforts focusing on the antagonism of glioma-associated immunosuppression alone, e.g., blocking the transforming growth factor- $\beta$  pathway or programmed cell death ligand-1, have not been successful. Similarly, counteracting inhibitory signaling to T cells at the target cell level via cytotoxic

T lymphocyte-associated protein 4 or programmed death 1 using various neutralizing antibodies has not been demonstrated to improve outcome yet. Various vaccination approaches have also been tested, including dendritic cell-based vaccines, without proof of efficacy. Thus, alleviating the immunosuppression generated by glioma cells remains a prime goal for better treatment successes in glioblastoma, but attention should at the same time be directed to render immune effectors more active against target cells, and more resistant to inhibition, e.g., by generating CAR T cells refractory to immune inhibitory signaling.



Michael  
Weller

Professor

He received his training in clinical neurology at the Department of General Neurology, University Hospital Tübingen, Germany, where he was appointed Chairman in 2005. Michael has been involved in major practice-changing clinical trials including the registration trial for temozolomide in glioblastoma and served as Principle Investigator on a.o. the NOA-03, NOA-04, NOA-08, ACT IV, CheckMate 143, 498 and 548 trials.

The Laboratory of Molecular Neuro-Oncology at the University Hospital and University of Zurich led by Michael has a major research focus on the development of innovative treatment approaches to brain tumors, including immunocytokines and CAR T cells, and molecular pathways of constitutive and acquired resistance to current therapies. In addition, Michael has received several awards in recognition of his contributions to cancer research, including the German Cancer Award in 2007.

Professor Michael Weller is neurologist and chairman of the Department of Neurology, University Hospital Zurich, Switzerland since 2008. He qualified in medicine in Cologne, Germany. A postdoctoral fellowship at the Department of Clinical Immunology, University Hospital Zurich, followed where he identified death receptor targeting as a potential treatment strategy for glioblastoma.

He furthermore served as Chairman of the Neuro-Oncology Group of the German Cancer Society (2001-2008), as President of EANO (2014-2016), and as Chairman of the Brain Tumor Group of the EORTC (2015-2021). He is the current Chairman of the German Glioma Network of the German Cancer Council.

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Rikke Hedegaard Dahlrot

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# Practical information

## For whom?

The DCCC Brain Tumor Center Annual Meeting is intended for all those interested in the field of primary brain cancer.

We thus kindly ask you to forward this to those who are affiliated with one of the WPs, for example PhD-students and Postdocs, and others.

## Registration

Registration is free of charge (Anne-Marie Bach, [anne-marie.bach@regionh.dk](mailto:anne-marie.bach@regionh.dk)). Your registration is final after September 1.

In case of no show, we take the liberty of invoicing you the cost of your seat. In case you know you are not able to join, kindly let us know a.s.a.p.

We will accommodate you for the entire event including catering and access to the ARoS galleries. However, drinks with alcohol are at your own expense. Furthermore, travel costs are at your own expenses.

## Location

We would love to see you among us at ARoS Art Museum

Aros Allé 2  
8000 Aarhus C  
Denmark  
[aros.dk](http://aros.dk)

Please note that ARoS is currently only accessible via the entrance at Aros Alle. The museum can be entered via stairs or elevator.

The galleries are accessible free-of-charge for participants to the meeting and open from 10.00 - 21.00 (CEST).

## Contact information

Please direct your questions to: Anne-Marie Bach, [anne-marie.bach@regionh.dk](mailto:anne-marie.bach@regionh.dk)







∞ Kræftens Bekæmpelse

