# Professor Sebastian Brandner: the next frontiers of molecular diagnostics of brain tumours—interrogating epigenetic profiles of brain tumours

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## Editor's note

The International Masters Frontier Forum at Sun Yat-sen University was held in the Seventh Affiliated Hospital of Sun Yat-sen University on May 12, 2018. During the forum, Professor Brandner has given a lecture on the topic "Molecular diagnostics of brain tumours: the next frontiers". *Annals of Translational Medicine* (*ATM*) was honored to conduct an interview to conduct an interview with Professor Brandner to share his research focus, research experience and perspective, providing updated knowledge of research on brain tumours among his team and some suggestions for colleagues to translate the advanced knowledge in laboratory into the daily practice and clinical fields.

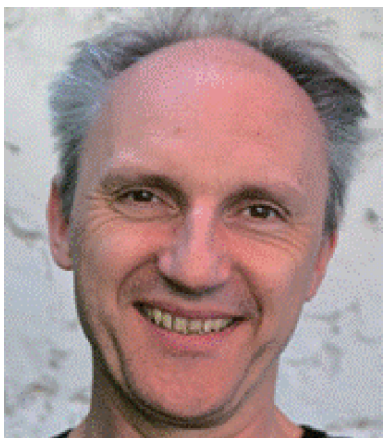

**Figure 1** Professor Sebastian Brandner.

## Expert's introduction

Sebastian Brandner (*Figure 1*) is a Professor of Neuropathology at University College London (UCL) and Head of the Division of Neuropathology at the National Hospital, University College London Hospitals NHS Foundation Trust. He studied medicine in Göttingen, Germany where he obtained his MD degree in experimental neurobiology, at the Max Planck Institute for Biophysical Chemistry. He trained in diagnostic neuropathology in Zürich, Switzerland. In 2001, he was recruited through the Medical Research Council international recruitment scheme and in 2004 he was appointed Professor of Neuropathology.

Professor Brandner and his research team established mouse models for brain tumours. One of their key achievements is the demonstration of genotype-phenotype correlation brain tumours and identifying the cell of origin of gliomas in mice. Molecular profiling of mouse tumours could demonstrate a strong correlation to certain types of human gliomas, thus making it a valuable model for technology development, and biomarker discovery. His group has recently discovered biomarkers (miR-449a and GPR158) that correlate with survival of patients with gliomas, making it a potential druggable target. Results of his research are published in EMBO Journal, Cancer Research, Disease Models and Mechanisms, and Oncogene. Collaborative work published in Cancer Cell oor PNAS. In the field of neurodegeneration, Professor Brandner led two national vCJD surveillance studies, published in BMJ and a study on the human transmission of amyloid beta through medical procedures, published in *Nature* and *Acta Neuropathologica*.

## Interview

***ATM: Your speech topic is Molecular diagnostics of brain tumours: the next frontiers. Would you please introduce what are the main methods of the molecular diagnostics and why they could be the next frontiers?***

**Professor Brandner:** Following an initial histological assessment, we are using mutation specific antibodies to discriminate the most common tumour classes. The next step is the further characterisation with single target

sequencing and copy number assays. The reason for recommending this relatively simple technology is the wide availability, speed and cost effectiveness of this approach. If used in a DNA-based approach (as opposed to fluorescence *in situ* hybridisation, a tissue-based approach) it can be very cost-effective and scalable, and it can be implemented in most molecular biology laboratories associated with pathology departments. The next frontiers that I was referring to are the use of test methods to interrogate epigenetic profiles of brain tumours. This technology is based on the uniqueness of epigenetic modifications that correlate with classes of tumours. The technology that allows the rollout in clinical practice is array-based and the use of "machine learning" has led to the development of algorithms that can discriminate distinct "methylation classes" of brain tumours. This technology was developed at the German Cancer research Centre in Heidelberg and is now available to clinicians and researchers worldwide. In many instances, methylation classes overlap with histological and molecular entities (such as histone mutant gliomas or IDH mutant gliomas), but there is a proportion of tumours where the histology can vary widely, yet these tumours belong to a single methylation class. Conversely, the methylation profiling can also identify distinct methylation classes within a cohort of tumours that look indistinguishable or very similar for the microscope. The next frontiers are therefore the logical and evidence-based implementation of such technologies into clinical practice.

***ATM: You have focused on research of experimental models and their translation to human diseases. What is the up-to-date progress ? How could they help with the clinical treatments in the future?***

**Professor Brandner:** Progress on experimental models and their translation to human diseases is manifold and not restricted to a specific type of model. It is always essential to understand that a good model does not necessarily aim at recapitulating all aspects of human diseases. In fact, the best models may be those which reliably, faithfully, and reproducibly represent a few key features of human disease. Establishing precise models is challenged by the gap of knowledge of the cell of origin, window of opportunity, and matching mutations. Models to assess treatment options may work very differently and may include cellular transplant strategies, genetic editing of human cells and *in vitro* models as a first-line assessment of drug targets.

***ATM: What do you think are the biggest challenges in brain tumours researches currently?***

**Professor Brandner:** One of the biggest challenges is the identification of druggable targets and subsequently the cost-effective development of drugs that can effectively interact with these targets. Repurposing of drugs has recently been a significant topic of debate, providing potential access to a wide range of tested and proven drugs, and making them available for specifically identified targets.

***ATM: How to better translate the advanced knowledge and technologies in laboratory into the daily practice of pathological diagnosis and clinical fields?***

**Professor Brandner:** There are several factors that need to be considered in introducing advanced knowledge and technologies in laboratories for daily practice. First, a thorough training of pathologists to understand molecular pathways, and their integration into their histology diagnostics. In many fields of pathology, including neuropathology, we are moving away from the histological classification alone, and increasingly integrate the morphological approach with a biomarker-driven diagnostic approach. This approach of course always starts with the recognition of a basic pathology in general (for example inflammation, degeneration, neoplasia) and then (in the context of neuro-oncology) with an assessment of the tumour type (for example, glioma, meningioma, germ-cell tumour, or primitive neuroectodermal tumour, to name a few). The next essential step is the correct choice of molecular markers to be tested. This is of course again in a certain way hypothesis driven, as pathologist needs to understand which of the biomarkers to test for. There are two outcomes: (I) one of the biomarkers is positive and the tumour is molecularly defined. A smaller proportion of tumours may not have informative biomarkers, and (II) these require further testing with advanced technologies, for example methylation arrays for the improved, evidence-based classification according to established methylation classes.

For a cost-effective implementation into clinical practice it is essential to build centres that have sufficiently large catchment areas to serve a substantial population base. This allows for the cost-effective economy of scale, enabling pathologists to see reasonable numbers even of rare tumour types, and laboratory to implement tests even for rare mutations in cost-effective fashion. Finally, it is essential

 

to build up a larger team of specialised pathologists, who can exchange and build up knowledge even in a highly specialised area within pathology (and correspondingly in any other area of medicine).

***ATM: It is said that we are now in the era of precision medicine. What do you think would be the focus or future trend of precision medicine researches on neuropathology in the next 5–10 years?***

**Professor Brandner:** In my opinion we are just entering the era of precision medicine. I think as yet we are far away from the rollout of precision medicine. As for now, neuropathology has just identified diagnostic biomarkers (most developments happened the last 10 years) and it will take another 10 or 15 years for the oncology community to develop drugs that can target these pathways. The advance of epigenetic profiling (see above) will have to be combined with confirmatory testing for druggable targets (single mutations or pathways) and this will form the basis for precision medicine.

***ATM: In retrospect, what do you think motivated/inspired you to study brain tumours?***

**Professor Brandner:** During medical school I worked on the identification of anatomical pathways in the brain, specifically looking at the projection of neurons from the auditory cortex to the thalamus. This was fascinating, but did not help me understanding diseases. After medical school, as a junior doctor I was on a placement in neurosurgery. During the clinical team meetings, I was fascinated, but also confused by the neuropathology terminology, and how pathologists arrived at a diagnosis. These were the times when antibodies against lineage markers such as cytokeratin, GFAP, S 100 or the proliferation marker Ki67 had just been developed and were rolled out into neuropathology diagnostics. At the time, this was revolutionary, as it helped for example discriminating epithelial from glial tumou[redacted]o better understand how brain tumours are diagnosed and classified and ideally also to understand their biology, I joined the Department of Neuropathology at the University of Zürich, where I met my early mentor Professor Kleihues who was at the time the editor of the WHO classification. I was part of an active team , at an Institute that led the field in brain tumour diagnosis and research. Over the next few years, whilst completing my training in neuropathology I developed two interests experimental pathology, neurodegeneration and neuro-oncology. I started building up my own team in brain tumour research and I was fascinated by the opportunities that the mouse models (at the time transgenic mice and conditional knockout mice; the Cre lox system had just been developed) provided us to study the function of genes and their role in causing stem cells to become tumour precursors. Since then I have always enjoyed the combination of diagnostic work, which gave me the opportunity to apply my molecular pathology knowledge to establishing a large molecular test service, and at the same time comparing the human biology with mouse models that are generated myself.

***ATM: What do you think are the most important qualities to be a researcher or scientist?***

**Professor Brandner:** In my view scientific success depends on 3 factors (of course highly simplified): Working at the right time in the right environment, hard work and incredible amount of luck.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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