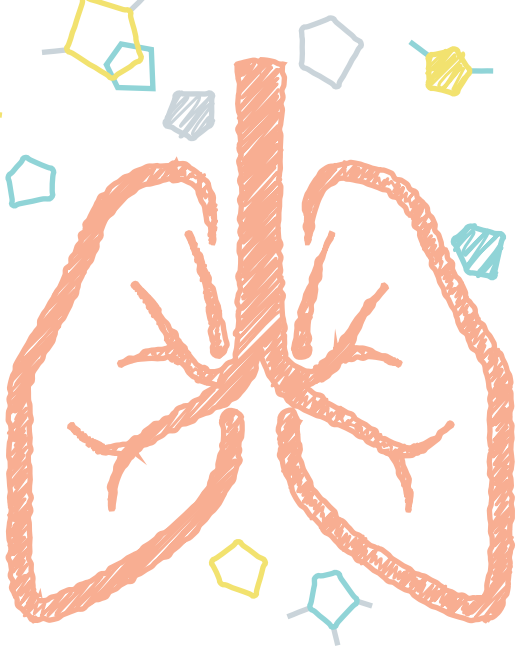
Cutting-edge cancer diagnostics



Professor Reinhard Büttner discusses how his research into lung cancer is fuelling the translation of large-scale molecular tumour diagnostics and personalised treatment strategies into clinical practice

Can you outline your particular area of interest in oncology and describe how your professional career has developed to date?

It has always been my belief that a comprehensive molecular understanding of genomic changes in cancer cells will pave the way for better therapies. I therefore went into pathology, after which I sought training in a professional research environment as a postdoctoral researcher at the Gene Center in the University of Munich, Germany, and later at the University of Texas MD Anderson Cancer Center in Houston, USA. At that time, we believed that the 'differentiation' of cancer cells would prevent tumour growth. This inspired me to study genes in cancer cells that are being regulated by differentiation under treatment with retinoic acid – an approach that is applied today in some types of leukaemia. Later, we recognised that some mutations and molecular pathways are highly characteristic for certain tumours. For instance, some show specific defects in DNA repair mechanisms.

Could you provide some background into your current research on the pathology of lung cancer?

When I started to work as Professor of Pathology at the Universities of Aachen and Bonn, Germany, I became the reference pathologist in the German consortia for hereditary colon and breast cancers, and I helped perform genomic testing of tumour samples on a large scale. Later, I met some highly motivated lung cancer specialists, oncologists and molecular biologists at the University of Cologne. Together with Roman Thomas and Jürgen Wolf, I envisioned the Network Genomic Medicine (NGM) to translate large-scale molecular tumour diagnostics and individualised therapies into clinical practice. I decided to move to Cologne, and we founded the Network in 2010. It has grown rapidly since then and is now being supported by long-term cancer survivors.

Could you outline your role within the Lung Cancer Group Cologne, Germany, and explain its goals?

I work as part of a multidisciplinary team, together with bioinformatics, pathologists, medical and radiation oncologists and molecular biologists. We review all the histological, genomic and clinical data of the patients and make comprehensive therapeutic recommendations. My specific role involves leading and steering all tasks related to histopathological and genomic diagnostics. I act as a bridge between the genomics scientists in the lab and the clinicians by interpreting the data into a clinically useful diagnostic context.

How are you concentrating your diagnostic efforts to screen for informative genomic lesions?

We avoid whole-genome analysis because this is currently not amenable to very deep sequencing. Instead, we multiplex all informative genes for a specific tumour diagnosis, such as lung cancer and melanoma. Following this, we then multiplex these genes from very small biopsies using a deep parallel-sequencing approach. This type of sequencing allows us to detect a few mutated cancer alleles within a mixture of normal cells and many normal, non-mutated alleles. Thus, the pathologists prepare the groundwork for the development of therapeutic strategies by identifying the biomarkers that enable them to predict which therapies are likely to be effective in specific patients.

Through NGM, you currently work with many collaborators across Germany. What approaches have you taken to facilitate these collaborations?

The NGM functions both as a service network for genomic tumour diagnostics and as a communication structure. As members of the Network, we regularly meet to come up with ideas for new studies, communicate our goals and address requests from our collaborators. Additionally, we are currently extending NGM's structure to support clinical studies at the sites of our various partners.

What have been your most significant findings to date? How do you hope your work will progress in the future?

For the first time, the NGM has demonstrated the feasibility of personalised cancer medicine in practice. We have been able to comprehensively analyse genomic alterations at a large scale for lung cancer patients. We have also shown that novel, targeted therapies do make a difference to patient outcomes, as they significantly increase survival rates and pave the way for their more widespread implementation in routine clinical practice. Looking to the future, our goal is essentially very simple: we want to make lung cancer a curable disease.

Targeted treatments

As part of the **Network Genomic Medicine** at the **Centre for Integrated Oncology** in Cologne, Germany, researchers are studying the molecular alterations that drive tumour progression. They are using this information to develop specific and individualised cancer therapies with the goal of long-term patient survival

ONE OF THE most common and aggressive cancers, lung cancer is a devastating disease with a poor prognosis. According to Cancer Research UK, only 32 per cent of lung cancer patients will live for one year following diagnosis and just 10 per cent will live for five years. Unfortunately, the disease is notoriously difficult to diagnose, meaning it is often not noticed until the later stages of its pathogenesis. There is therefore an urgent need to develop more robust diagnostic strategies that can detect lung cancer in its earliest stages. Equally, more effective and less toxic therapies are needed for patients in the late stage of the disease.

In response, as part of the Network Genomic Medicine (NGM), researchers in the Centre for Integrated Oncology, Cologne, Germany, are conducting innovative research into lung cancer. The multidisciplinary team is studying the molecular mechanisms that underpin genomic changes in cancer cells, with an overall focus on histopathological and genomic diagnostics. Composed of lung cancer specialists, oncologists and molecular biologists, the NGM is aiming to advance clinical approaches to lung cancer and make therapies more effective, less toxic and personalised to individual patients.

Motivated by the exciting possibilities that personalised cancer treatment offers, renowned pathologist and co-founder of the NGM Professor Reinhard Büttner is leading Germany's largest and most prominent screening effort for cancer patients. Through the use of next-generation sequencing (NGS) technologies, Büttner and his team are generating new insights into genomic alterations in cancer biopsies: "Integrating genomic information and histopathology will substantially change the practice of tumour diagnostics, leading to more selective and individualised cancer treatment," he asserts.

DRIVING DIAGNOSTICS

Moving towards treating tumours in a more comprehensive and targeted way, Büttner and his colleagues are concentrating on developing diagnostics that screen for all informative genomic lesions. For example, in a study conducted in collaboration with the Clinical Lung Cancer Genome Project, the NGM researchers aimed to pinpoint genetically defined and clinically relevant subtypes of lung tumours. They characterised clinically annotated lung tumours from all histological subtypes. Their analyses revealed that in over half of all cases, at least one oncogenic genome alteration would be potentially responsive to targeted therapeutic strategies, including some personalised interventions that are currently being clinically evaluated.

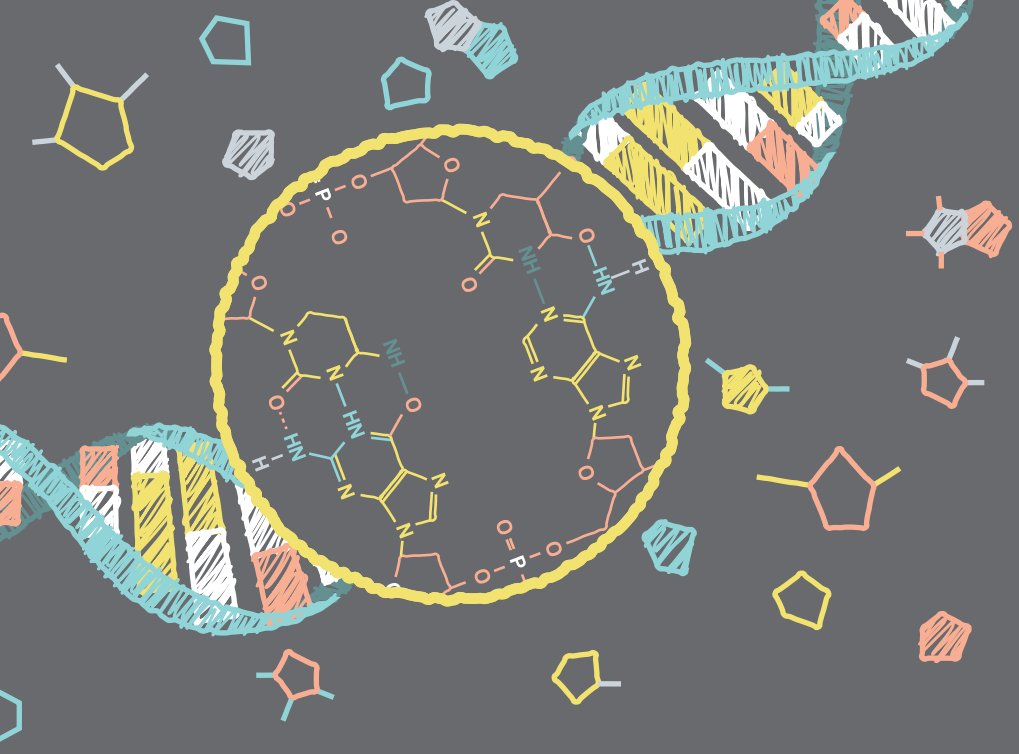
> Büttner's laboratory was one of the first in Europe to implement next-generation sequencing into routine clinical diagnostics

Moreover, the researchers found key differences between and within histological subtypes of the tumours, calling into question the validity of the original histomorphological diagnosis. Interestingly, the reassigned tumour subtypes – which were further confirmed by immunohistochemical analyses – disqualified most types of large-cell carcinoma. Tested on 5,145 lung cancer patients, the researchers' novel, genomics-based diagnostic algorithm proved successful in diagnosing some 75 per cent of the patients, adding validity to their reassignments of large-cell lung carcinomas. Most significantly, genome-based diagnosis improved the overall survival rates of patients with epidermal growth factor receptor (EGFR)-mutant and anaplastic lymphoma kinase gene (ALK)-rearranged cancers, hailing a seismic shift in tumour diagnostics. "Personally, I would compare this shift with the introduction of immunohistochemical staining in histopathology," Büttner states. "Comprehensive genomic analysis will lead to better tumour classification and diagnostics, more precise therapies and, crucially, to the ability to monitor tumours as they undergo therapy."

EPIGENETIC EXPLORATIONS

Not all tumours are the result of genomic mutations; indeed, it is thought that some are driven by epigenetic changes that cause pathological oncogene expression. For instance, overexpression and high activity of the lysine-specific histone demethylase (LSD1) is a major feature of lung cancer progression. At the NGM, the researchers are therefore using preclinical mouse models and clinical samples from patients to investigate the functions of LSD1 in driving lung cancer growth.

Currently, Büttner and his colleagues are engaged in a project that is examining the functions of histone methylases and demethylases in lung cancer; specifically they are studying LSD1-driven oncogenic signal pathways. The researchers are using advanced experimental techniques, including chromatin immunoprecipitation linked to the NGS of LSD1-targeted gene promoters, and applying them to both cell systems and transgenic mouse models with lung cancer-specific mutations: "As a bona fide oncogene, LSD1-driven cancers *in vitro* react to LSD1 inhibition," discloses Büttner. "It is our aim to



translate these findings *in vivo* and introduce epigenetic inhibitors into clinical practice for lung cancer therapy."

INTEGRATING BIG DATA

Büttner's laboratory was one of the first in Europe to implement NGS into routine clinical diagnostics and, at present, his team performs some 5,000 NGS-based tests every year. With each test ordinarily resulting in 1 GB of data, the analysis of these data represents a major challenge for the researchers and clinicians who are seeking to understand and diagnose disease: "This is a problem that must be addressed since data analysis has to be performed as part of a point-of-care analysis and provide informative results within a very short timeframe, in order to inform imminent therapeutic decisions," Büttner explains.

In response to this challenge, the NGM researchers have developed a proprietary data-analysis pipeline, enabling them to filter the data automatically, using different algorithms that identify the relevant mutations. Although the subsequent clinical interpretation involves extensive manual work and is hugely time-consuming, the NGM has invested significantly in its personnel, meaning that there is a sizeable and robust team of experts on hand to conduct the analyses.

A PARADIGM FOR THE FUTURE

As the first peripheral healthcare structure in Germany to be fully funded by healthcare providers, the NGM, steered by Professor Drs Jürgen Wolf and Roman Thomas alongside Büttner, is a forward-looking network and a paradigm for the delivery of innovative, comprehensive diagnostics and personalised treatment plans. The researchers are successfully identifying huge numbers of biomarkers for cancer, driving the development of targeted and precise therapeutic concepts.

With a firmly established lung cancer research programme, lung cancer remains the most frequently performed test at the NGM, followed by melanoma, gastrointestinal tumours and chronic lymphocytic leukaemia. Büttner and his team are planning to expand their diagnostic programmes and apply their research to other types of tumours: "We are constantly coming up with studies that aim to drive the rapid development of new and relevant diagnostics and therapies for cancer patients," Büttner enthuses. Ultimately, the researchers intend for their innovative diagnostic methods and personalised treatment strategies to bring tangible benefits to all cancer patients, improving prognoses and saving lives.

PREDICTIVE DIAGNOSTICS

One of the most exciting developments in cancer diagnosis is the field of predictive diagnostics. Through the analysis of tumour tissue specimens, Büttner and his team are able to classify tumours and use advanced technologies to identify the molecular mechanisms that drive the malignant growth of a specific cancer. These findings are significant because they enable oncologists to decide when to use therapy to target genomic lesions.

INTELLIGENCE

MOLECULAR PATHOLOGY OF LUNG CANCER

OBJECTIVE

To provide comprehensive histopathological and genomics-based biomarker diagnostics of lung cancer. Within the Network Genomic Medicine, every cancer biopsy is analysed on a central diagnostic platform, and each patient is counselled to provide established and cutting-edge personalised tumour therapies.

KEY COLLABORATORS

Professor Dr Jürgen Wolf, University Hospital of Cologne, Germany • **Professor Dr Roman Thomas**, University of Cologne, Germany • **Professor Dr Roland Schüle**, University of Freiburg, Germany

GERMAN PARTNERS

Center for Integrated Oncology (CIO) Cologne Bonn • German Cancer Aid • German Ministry for Science and Technology (BMBF) • German Research Foundation (DFG) • Ministry of Innovation, Science and Research North Rhine-Westphalia • Patients' Tumor Bank of Hope (PATH)

CORPORATE PARTNERS

Targos Molecular Pathology GmbH, Germany • Qiagen, Germany • Roche Molecular Diagnostics, USA • Pfizer, USA • Merck-Serono, Germany • Novartis, Switzerland • GlaxoSmithKline, UK • Bristol-Meyers Squibb, USA • AstraZeneca, UK

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REINHARD BÜTTNER currently serves as the leading German molecular pathologist at the University of Cologne Comprehensive Cancer CIO Cologne Bonn. With Professor Drs Jürgen Wolf and Roman Thomas, he founded the Network Genomic Medicine and is steering Germany´s leading initiative for personalised lung cancer medicine.

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