Molecular Cancer

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The Technical University of Munich Cancer Center - elevating cancer treatment through science

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The Technical University of Munich and the Ludwig Maximilian University Munich are both top-ranked universities on the national and international level and distinguished as "elite universities" within the national German Research Foundation (DFG)-funded excellence program. Both sites are established and leading cancer research institutions in Europe that have joined forces within the Comprehensive Cancer Center Munich (CCCM). This positions CCCM as a prominent global leader dedicated to advancing excellence in research and education in the field of cancer. The clear vision and goal of the CCCM is the guidance of clinical trials from inception to completion, focusing on the best research and science to strengthen the development of biologically and technologically innovative therapies and diagnostics. Supplemented by multidisciplinary programs for bi-directional translation, proof-of-concept studies and clinical research programs, these focus areas are further strengthened by a dedicated infrastructure for data management and artificial intelligence (AI). Patient participation is another key focus of the CCCM's joint activities, enhanced through novel establishments such as a Patient Advisory Board (PAB) which advocates for patients and families, identifies new areas for action, and addresses challenges relevant to them. Collaborative committees and task forces provide recommendations to the CCCM to support these efforts. Further, the CCCM strongly emphasizes its clinical and scientific interactions with oncologists outside the university hospitals. Continuous exchange of information on prevention, cancer-related physical/psychological challenges, and recent developments in cancer medicine and treatment modalities as well as outreach activities are pursued at multiple levels.

At the Technical University of Munich (TUM), the Comprehensive Cancer Center (CCCM-TUM) is deeply committed to fostering collaboration across all disciplines and departments focused on cancer medicine. As a vital partner of the TUM Cancer Center, CCCM-TUM plays a key role in the overarching governance within the faculty, offering stakeholders opportunities to collaborate and translate discoveries into innovations. In

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this capacity, it coordinates all activities related to cancer medicine and advocates for the interests of numerous basic and clinical researchers.

In this article, we would like to highlight some TUM specific activities, particularly focusing on the preclinical and clinical structures of the Department of Hematology/Oncology (https://med3.mri.tum.de). The content thus does not claim to provide a complete representation of research activities at the TUM Cancer Center.

Structurally, the TranslaTUM (Central Institute for Translational Cancer Research: https://www.translatum.tum.de) stands out as a uniquely established central research institute situated in close proximity to the TUM University Hospital. This initiative is dedicated to fostering translational research in medicine (Fig. 1). By emphasizing various interdisciplinary approaches to tackle complex medical challenges, TranslaTUM seeks to accelerate the development of novel treatments and focuses on bridging the gap between laboratory discoveries and clinical applications, facilitating the rapid implementation of innovative therapies and technologies into patient care.

Preclinical research

Preclinical research marks a cornerstone within the research concept of the TUM Hematology/Oncology Department that directly feeds into early compound/cellular therapy development and early phase clinical trials. We here exemplify two focus areas of the department, targeted protein degradation (TPD) approaches and cellular immunotherapeutic strategies.

Targeted protein degradation (TPD)

Targeted protein degradation (TPD) is a novel therapeutic approach that specifically exploits the degradative nature of the ubiquitin-proteasome system (UPS) and involves the selective elimination of disease-causing proteins within cells. This is achieved using molecules like proteolysis targeting chimeras (PROTACs) and molecular glues, which facilitate the binding of target proteins to the cell's natural degradation machinery. Unlike traditional inhibitors that merely block protein function, TPD leads to the complete degradation of the target proteins, providing a more definitive therapeutic outcome. This innovative strategy is particularly valuable for addressing cancers that involve proteins previously

Fig. 1 TranslaTUM - Central Research Institute to Promote Translational Cancer Research
Uniquely established center for translational oncology research, located in the immediate vicinity of the University Hospital TUM supporting rapid implementation of new findings and technologies in patient care. Photo: Andreas Heddergott/TUM

deemed "undruggable" by conventional methods. Next to TPD approaches, aberrant ubiquitin networks that play critical roles in cancer development and progression by disrupting the normal regulation of protein degradation and signaling pathways are a focus of this research program. Indeed, dysregulation within the UPS can lead to the accumulation of oncogenic proteins or the degradation of tumor suppressor proteins, thereby promoting uncontrolled cell growth. Mutations or alterations in ubiquitin ligases (E3s) and deubiquitinases (DUBs) are often observed in various cancers, contributing to malignancy and resistance to therapy. These aberrations can affect key processes such as DNA repair, apoptosis, cell cycle control, metabolism and immune escape further driving cancer pathogenesis. Targeting the components of aberrant ubiquitin networks offers a promising avenue for developing novel cancer therapies aimed at restoring normal cellular functions.

The concept of discovery-based science on the ubiquitin system combined with an application approach for academic compound development focusing on early ligase/DUB inhibitors and degraders of the PROTAC and molecular glue family marks the cornerstone of the German Research Foundation (DFG) funded Collaborative Research Center CRC/TRR 387 "Functionalizing the Ubiquitin System against Cancer - UbiQancer". This Munich based network in collaboration with the University of Würzburg and the University of Frankfurt was granted funding in 2024 and assembles the key national expertise in ubiquitin based clinical medicine, cancer biology, structural biology, medicinal chemistry and computational biology. This structure constitutes the central German network to bridge the imminent implementation gap of ubiquitin-based vulnerability and degrader technology research in cancer and the application of these insights into early academic compound development.

Cellular immunotherapy

The broad Cellular Immunotherapy Program within the Hematology/Oncology Department at TUM encompasses an extensive approach to pioneering advancements in oncological therapeutics through cutting-edge immunotherapeutic modalities. This initiative is designed to refine cancer treatment paradigms by employing innovative therapeutic strategies, such as tumor infiltrating lymphocytes (TILs), T-cell receptor (TCR) and chimeric antigen receptor (CAR) T cells (CAR-T), that leverage the immune system's potential against malignancies. The large-scale program is embedded within central structures that enhance research capabilities and collaborative efforts including the Bavarian Center for Cancer Research (BZKF) lighthouse "Cellular Immunotherapies" and other German networks with focus on lymphocyte engineering for therapeutic synthetic immunity (LETSimmun CRC/TRR 338). Specifically, we are engaged in the development of novel techniques for cell engineering, utilizing pioneering gene editing technologies to enhance the effectiveness of immunotherapies - also harnessing the innate cell properties of natural killer (NK) cells. Additionally, our program focuses on multifactorial determinants of response to immunotherapy, including interactions with the bone marrow (BM) microenvironment, the presence of clonal hematopoiesis and correlations with the gut microbiome. Further, our preclinical research program aims to elucidate resistance mechanisms to immunotherapy. Here, we particularly focus on strategies to enhance and restore the expression of key immunotherapy targets by modulating post-translational modifications, specifically ubiquitylation and phosphorylation, to prevent protein degradation. Additionally, we use this approach to investigate strategies to decrease the expression of immune cell inhibitory ligands on tumor cells, aiming to improve the efficacy of immune checkpoint inhibitory therapies. We anticipate that such insights, along with others derived from preclinical research, will pave the way for investigator-initiated trials (IITs) and will direct future cellular immunotherapeutic strategies.

Clinical frameworks

The TUM Hematology/Oncology Department is dedicated to enhancing the standard of care for oncology patients within the Munich Metropolitan Region, with an emphasis on precision medicine and advanced prevention strategies. This will be exemplified through two key clinical focus areas: the Center of Personalized Medicine and the CHIP Clinic TUM.

Center of Personalized Medicine

The Center of Personalized Medicine (ZPM) at TUM was founded to foster precision medicine across all areas of healthcare. The aim of the ZPM is to treat each patient optimally by integrating individual factors extensively, exceeding the functional diagnosis of the disease. Consequently, this also includes the constant tailoring of therapy to the progress of illness and recovery. The ZPM itself has been designed with a modular structure and the ZPM-Oncology serves as a template and use case for the foundation of other ZPMs with medical need in the area of precision medicine. Each ZPM displays an interdisciplinary structure and is organized around the seven core functions: molecular diagnostics, imaging, biobanking, individual therapy, data integration, training and education, and patient participation. At the ZPM-Oncology, patients with advanced malignant tumors for whom approved, or guideline-based therapies are not effective are offered advanced molecular diagnostic tests to find new and translational treatment options.

The ZPM-Oncology TUM includes one of the largest Molecular Tumor Boards in Germany bringing together experts from different oncologic and research disciplines. It was the third German ZPM to be certified by the German Cancer Society (DKG) in 2023. The ZPM-Oncology TUM currently advises almost every second patient on a clinical trial and in 2 out of 3 cases recommends a personalized, translational therapeutic option. To extend the crucial precision medicine pioneering work in oncology to other fields with a high medical need and suitable molecular(-genetic) diagnostics, a stepwise expansion beyond the oncologic pilot in the field of inflammation, neurology and cardiology is next intended and based on structural measures.

Further, the Early Clinical Trial Unit (ECTU) of the TUM Hematology/Oncology Department plays a pivotal role in advancing precision medicine by tailoring medical treatments to the unique characteristics of each patient. Comprising a multidisciplinary team of experts, the ECTU conducts early-phase clinical trials that explore innovative therapies incorporating scientifically identified personalized treatment approaches and biomarker development. A prime example of successful integration and application of precision medicine in early clinical investigator-initiated trials at TUM is the COLPRIT trial (EudraCT 2015-001817-28). This prospective study investigates CXCR4-directed radioligand therapy (RLT) and aims to evaluate the efficacy, tolerable dosage, and side effects of [^{90}Y]Pentixather RLT in patients with Multiple Myeloma and advanced Non-Hodgkin Lymphomas. Additionally, the SORATRAM trial (EudraCT 2016-003616-13), which investigates the use of Sorafenib and Trametinib in patients with advanced solid tumors harboring inactivating BRAF mutations, highlights the effective integration of molecular tumor boards (MTBs) and ECTUs within the framework of precision medicine.

CHIP Clinic TUM

In recent years, the Hematology/Oncology Department at TUM has specifically focused on advanced prevention strategies for blood cancer, with a particular focus on clonal hematopoiesis of indeterminate potential (CHIP) as pre-malignant state and pro-inflammatory condition. We are especially interested in CHIP's impact on human aging, novel immunotherapies like CAR-T, and the development of hematologic and non-malignant diseases. Based on large-scale prospective studies, we identified a high frequency of CHIP in individuals undergoing hip arthroplasty and a new association with autoimmune diseases (AID) and anemia. The unique access to CHIP BM allowed us to unravel intra-individual spatial heterogeneity and lineage-specific expansion patterns of specific ASXL1-CHIP clones including output towards lymphoid cell fractions during hematopoietic differentiation. Our findings, together with the rising evidence that CHIP leads to adverse outcomes in the aging population, led to the establishment of the nationwide first CHIP Clinic at TUM several years ago. To date, we have adopted a multidisciplinary approach in close collaboration with the German Heart Center in Munich. As one of the largest CHIP clinics in Germany, we have extensive access to and demonstrated the capability for large-scale identification of individuals with CHIP across diverse cohorts. Our established German CHIP Registry e.V. (https://www.chip-register.de), which is a web-based nationwide applicable GDPR-compliant health record application including CHIP carrier-portal and -participation, currently includes detailed data of thousands of prospectively monitored CHIP individuals. This registry will facilitate longitudinal studies, improve clinical management strategies for individuals with CHIP throughout Germany and has already led to joint publications. The unique data collection and analyses on demographics, sequential genetic profiles, clinical presentations, and long-term health outcomes related to CHIP will enable us to assess and incorporate novel factors associated with CHIP progression for the development of refined predictive risk models. Clinically validated relevant results will be translated into mechanistic preclinical studies to identify actionable targets for intercepting CHIP before it progresses to a malignant state, ultimately aiming to advance TUM science into medical practice.

Overall, the successful translation of discovery-based science into clinical practice and blood cancer prevention strategies at the Hematology/Oncology Department TUM underscores the dedication of our cancer center to merging scientific excellence with compassionate patient care.

Authors contributions
JSH data collection, drafting, editing, finalizing. HA drafting, editing. ALI drafting, editing. FB drafting, editing, finalizing.

Declaration

Competing interests
The authors declare that they have no competing interests.
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