Heinrich Heine Universität Düsseldorf

Heinrich-Heine-Universität Düsseldorf 40204 Düsseldorf
Dekanat der Mathematisch-Naturwissenschaftlichen Fakultät

An alle
hauptamtlichen Professoren/innen
und Privatdozenten/innen
des Faches Biologie der
Mathematisch-Naturwissenschaftlichen Fakultät

Mathematisch-Naturwissenschaftliche Fakultät

Dekanat

Promotionsangelegenheiten
Universitätsstraße 1
40225 Düsseldorf
Telefon: +49 (0)211 81 15092
E-Mail: promotionmnf@hhu.de

19.11.2024

Promotionsverfahren von **Herrn M.Sc. Pawel Stachura**
Auslage der Dissertation und Gutachten sowie Termin der mündlichen Prüfung
Anlage: Einseitige Zusammenfassung der Dissertation

Sehr geehrte Damen und Herren,

in dem oben genannten Promotionsverfahren wird die Annahme der Dissertation

Firing up the tumor: drug repurposing uncovers novel role of 5-Nonyloxytryptamine in boosting immunotherapies and uncovering ferroptosis inducing functions of volasertib in B-ALL

von den Berichterstattenden Prof. Dr. P. Lang, Prof. Dr. A. Borkhardt und Prof. Dr. med. C. Reinhardt beantragt. Sie kann zusammen mit den Gutachten in der Zeit

vom 29.11.2024 bis 10.12.2024

eingesehen werden. Bitte wenden Sie sich zur Einsicht an das Promotionsbüro (promotionmnf@hhu.de).

Einsprüche gegen diese Dissertation können nur zwei Tage nach der vorgenannten Frist geltend gemacht werden. Erfolgt kein Einspruch, so gilt die Dissertation als angenommen (§ 7 Ziffer (5) PO).

Sofern die Dissertation angenommen wird, findet die mündliche Prüfung am

13.12.2024 um 11:00 Uhr

im **Hörsaal 3 E** statt. Als Prüferinnen bzw. Prüfer sind vorgesehen:
Prof. Dr. P. Bauer, Prof. Dr. C. Esser und Prof. Dr. Dr. h.c. H. Stark.

Die Öffentlichkeit ist bei der Befragung zugelassen.

Mit freundlichen Grüßen
im Auftrag

Silke Krispin

Summary of doctoral thesis "Firing up the tumor: drug repurposing uncovers novel role of 5-Nonyloxytryptamine in boosting immunotherapies and uncovering ferroptosis inducing functions of volasertib in B-ALL" by Paweł Stachura

Recent research indicates that cancer development is influenced not only by the malignant cells themselves but also by interactions with surrounding stromal cells and immune infiltrates. The progression of cancer is facilitated by an immunosuppressive tumor microenvironment (TME), which enables immune escape. The concept of tumor "hotness," which describes the presence of an intra-tumoral T cell signature, is useful in predicting responsiveness to immunotherapies. "Hot" tumors, characterized by high immune cell infiltration, demonstrate a better prognosis when treated with immunotherapies compared to "cold" tumors that have minimal immune cell infiltration and/or exhausted/dysfunctional T cells. Enhancing tumor hotness involves modulating the TME to boost antigen presentation and T cell activation, which can be achieved by manipulating immune checkpoints, cytokine production, and immunogenic cell death pathways.

This doctoral thesis encompasses the biology and recent progress in understanding and boosting functions of dysfunctional T cells in cancer treatment. Many compounds including chemotherapeutics are now recognized for their immunomodulatory effects, warranting a reevaluation of their potential in combination therapies to improve anti-cancer immunity and tumor hotness. The immunomodulatory effects of 5-Nonyloxytryptamine (5-NL), a serotonin receptor agonist, were identified through drug screening. Initially developed for targeting serotonin receptors, 5-NL was found to enhance MHC class I expression on tumor cells, crucial for T cell recognition and elimination of tumor cells. This effect was linked to the modulation of several signaling pathways independent of classical serotonin signaling. 5-NL treatment led to activation of the AMPK pathway and subsequent phosphorylation of CREB, influencing the antigen-presenting machinery. *In vivo* settings indicate that combining 5-NL with anti-PD1 antibodies enhanced efficacy, suggesting its potential to convert "cold" tumors to "hot" tumors.

Another approach for increasing tumor hotness is the induction of immunogenic cell death (ICD) that transforms the TME from immunosuppressive to immune-activating. Ferroptosis, a form of regulated cell death characterized by lipid peroxide accumulation, has emerged as a promising strategy to enhance cancer therapy by inducing ICD. Using a deep-learning screening-based approach, volasertib, a chemotherapeutic agent, was revealed to have novel ferroptosis-inducing functions in several B-ALL cell lines, patient-derived xenograft samples and in an *in vivo* leukemia model. Volasertib treatment led to iron ion accumulation, glutathione depletion and membrane lipids peroxidation. Recent studies indicate that induction of ferroptosis has the potential to not only increase tumor immunogenicity but to also overcome chemoresistance. Combining ferroptosis inducers such as volasertib with immune checkpoint inhibitors or other immunotherapies could improve overall treatment efficacy, particularly in immunologically cold and apoptosis-resistant cancers.