# 第15屆臨床醫學研究所聯合教學研究研討會

# 2025.6.28(六)

# 第一階段(初審)：

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5. **入選結果公布日期：**2025年6月10日(二)後由刊登於臺北醫學大學臨床醫學研究所網頁(https://gicm.tmu.edu.tw/)並將結果將由大會承辦單位發信通知各所辦及投稿者。
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7. 學術研討會承辦人：臺北醫學大學臨床醫學研究所蔡坤志所長、鄭朝文老師、張育嘉老師、何佳芸秘書、林美智秘書。
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**Unveiling the role of NEDD8 upregulation in promoting metastasis and malignancy in BRAF-mutated melanoma**

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Background: Melanoma, the most lethal form of skin cancer, exhibits a dismal five-year survival rate of only 22.5% in advanced stages, highlighting the urgent need for innovative therapeutic approaches. Despite recent progress in targeted therapies and immune checkpoint inhibitors (ICIs), challenges such as severe side effects, poor long-term survival rates, and drug resistance persist. This study focuses on NEDD8-mediated neddylation, a crucial post-translational modification in cancer progression, as a potential target for the development of novel anti-melanoma drugs or adjunctive therapies.

Methods: Utilizing The Cancer Genome Atlas (TCGA) cohorts and the GSE30531 dataset, we investigated the transcriptional levels and prognostic significance of neuronal precursor cell-expressed developmentally downregulated protein 8 (NEDD8) in melanoma. Computational simulations via Gene Set Enrichment Analysis (GSEA) assessed the impact of enhanced NEDD8-mediated protein neddylation on melanoma evolution, particularly in cells harboring the BRAF V600E mutation, following treatment of MLN4924, a small molecule of NEDD8-activating enzyme inhibitor. In vitro migration assays and cycloheximide chase assays were employed to examine the consequences of MLN4924 treatment and NEDD8 gene knockdown on cell migration and the protein degradation of TGFBR2, respectively. Additionally, the association of NEDD8 gene expression with the efficacy of ICIs, including anti-PD-1 antibodies, anti-PD-L1 antibodies, and anti-CTL4 antibody, was explored using the Kaplan-Meier Plotter database.

Results: Analysis of TCGA data and cellular experiments revealed that upregulation of NEDD8 is associated with poor prognosis in melanoma, accompanied by the infiltration of myeloid-derived suppressive cells in the tumor microenvironment. Elevated endogenous NEDD8 levels were also correlated with increased migratory capabilities of cancer cells. GSEA suggested that MLN4924 disrupts epithelial-mesenchymal transition, TGF-β signaling, and NF-κB transcription factor activity, influencing transcription factor YBX1 and processes related to cancer proliferation, migration, and invasion. The study explored the impact of NEDD8 expression on existing targeted therapies and immunotherapies, indicating that high NEDD8 expression diminishes the effectiveness of ICIs. Upregulated NEDD8 activated the TGF-β signaling pathway, contributing to a tumor state conducive to metastasis and ICI resistance. Targeting protein neddylation by MLN4924 or repressing NEDD8 transcription showed potential in suppressing the metastatic potentials of melanoma cells with BRAF V600E mutation, possibly through blocking epithelial-mesenchymal transition progression, TGF-β signaling pathway, and NF-κB transcription factor activity.

Conclusions: NEDD8 overexpression impacts specific canonical or non-canonical neddylation substrates, presenting itself as a valuable predictive biomarker and drug target in melanoma. Inhibiting the neddylation pathway, especially non-canonical neddylation (targeting c-CBL [E3]), is anticipated to reduce metastatic capabilities in BRAF mutant melanoma and enhance responsiveness to ICIs, addressing the current bottleneck of poor long-term survival rates. This study provides insights into potential therapeutic strategies for improving melanoma outcomes.