CCR - IMPROMPTU

Monday, September 15th 2025, 13:00 PM

Oncology research at Boehringer Ingelheim Vienna: focus on targeted protein degradation

Paola Martinelli
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Venue: Lecture Hall B2, Borschkegasse 4a
Time: September 15th 2025, 13:00 PM
Hosts: Wolfgang Mikulits

CENTER FOR CANCER RESEARCH
MEDICAL UNIVERSITY OF VIENNA

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Targeted protein degradation (TPD) has emerged as a transformative therapeutic strategy in oncology, leveraging the ubiquitin-proteasome system (UPS) to selectively eliminate disease-driving proteins. However, only a handful of E3 ligases has been enabled for TPD until now, none of which is tumor selective. Melanoma-associated antigens A3 and A6 (MAGEA3/6) are tumor-testis antigens acting as E3 ligase substrate adapters and therefore represent a promising opportunity for tumor-restricted TPD. We used a combination of biochemistry, cell based proteogenomic analyses, and quantitative mass spectrometry, to explore the binding mechanisms of several MAGEA3/6 targets and identified a conserved helical degron motif critical for substrate recognition. Among the identified targets, the chromatin-associated protein NEWT1 was found to be a prominent substrate of MAGEA3-dependent degradation through the UPS. Detailed analysis revealed specific requirements for the productive interaction between MAGEA3 and NEWT1, with essential sequence determinants on both the MAGEA3 and NEWT1 sides. Analysis of publicly available omics datasets revealed that NEWT1 protein levels, but not mRNA levels, are inversely correlated with MAGEA3/6 expression in cancer cell lines of various lineages and in patient-derived samples of melanoma and lung squamous carcinoma—two indications with high prevalence of MAGEA3/6 expression—supporting that MAGEA3/6-driven post-translational regulation of NEWT1 happens in tumors. Ongoing investigation of the biological significance of the MAGEA3/6-NEWT1 axis and uncovered a link to the PTEN/PIK3/AKT signaling pathway, suggesting broader implications for tumor biology and therapeutic intervention. These findings highlight the potential of MAGEA3/6 as tools for selective protein degradation in cancer treatment and provide valuable information on the geometry of a productive protein-protein interaction.