RNA Horizons 2024
Therapeutics Symposium
Unlocking the RNA's Potential in Medicine

September 25-27, 2024
Alfandega Congress Centre, Porto, Portugal

Unlocking the Potential of Alternative Splicing for Immunotherapy Drug Discovery

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Alternative splicing (AS), a process that generates multiple mRNA isoforms from a single gene, plays a crucial role in cancer biology. Through RNA-seq analysis, it is possible to identify AS-derived neoepitopes from aberrantly spliced transcripts that hold promise as targets for immuno-oncology therapies (IO). In this context, Envisagenics introduces SpliceCore, a drug discovery platform capable of analyzing thousands of RNA-seq samples with a unique reference transcriptome encompassing over 14 million splicing events, which provides an unparalleled search space for IO target discovery. Upon splicing quantification, SpliceCore uses AI algorithms to further prioritize novel neoepitopes based on antibody accessibility, tumor specificity and patient prevalence. I will present a case study for a novel isoform expressed in Non-Small Cell Lung Cancer (NSCLC). This novel drug target emerges as a promising antibody-drug conjugate (ADC) for NSCLC. We validated its expression using mass spectrometry, western blot, and novel binders developed in-house. Membrane localization and internalization assays confirm the target isoform suitability for ADC modality. In summary, SpliceCore exemplifies the application of AI to unlocking novel therapeutic targets. By focusing on neoepitopes, we pave the way for personalized and effective cancer therapies.