The Potential of PI3Kα Degradation to Generate Tumor-Restricted pHLA Targets and Impact Immune Response in PIK3CA-mutant Cancers

Denise Barnatan[1], Amit Geva[1], Talal Ben Lulu[2], Yardena Samuels[2], Moshe Elkabets[1]

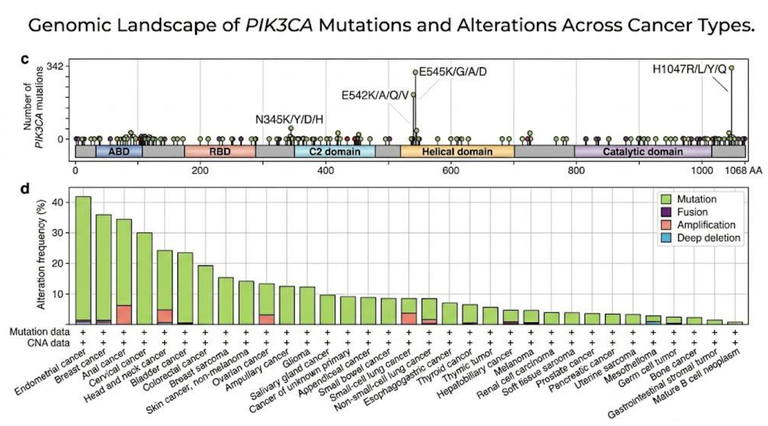
[1]The Shraga Segal Department of Microbiology, Immunology, and Genetics, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[2]Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel

Scientific background

Cancer therapy remains limited by insufficient selectivity, as both conventional chemotherapies and targeted agents often damage healthy tissues, leading to significant toxicity. This underscores the need for approaches that can precisely distinguish malignant cells from normal ones. Targeting tumor-specific molecular features presented on the cell surface offers a promising path to improve therapeutic specificity.

Mutations in *PIK3CA*, encoding the p110α subunit of PI3K, are among the most frequent oncogenic drivers across multiple cancers, including breast and endometrial malignancies. These mutations are present in large patient populations and are clinically actionable, as demonstrated by the mutant-selective degrader Inavolisib.

Degradation of mutant proteins leads to the presentation of mutation-derived peptides on HLA class I molecules (pHLA) at the cell surface. These pHLA complexes provide a unique and selective marker of cancer cells, creating an opportunity for highly specific targeting strategies that minimize off-target effects.



adapted from Castel, P., Toska, E., Engelman, J.A. et al, Nat Cancer (2021).

Preliminary Data

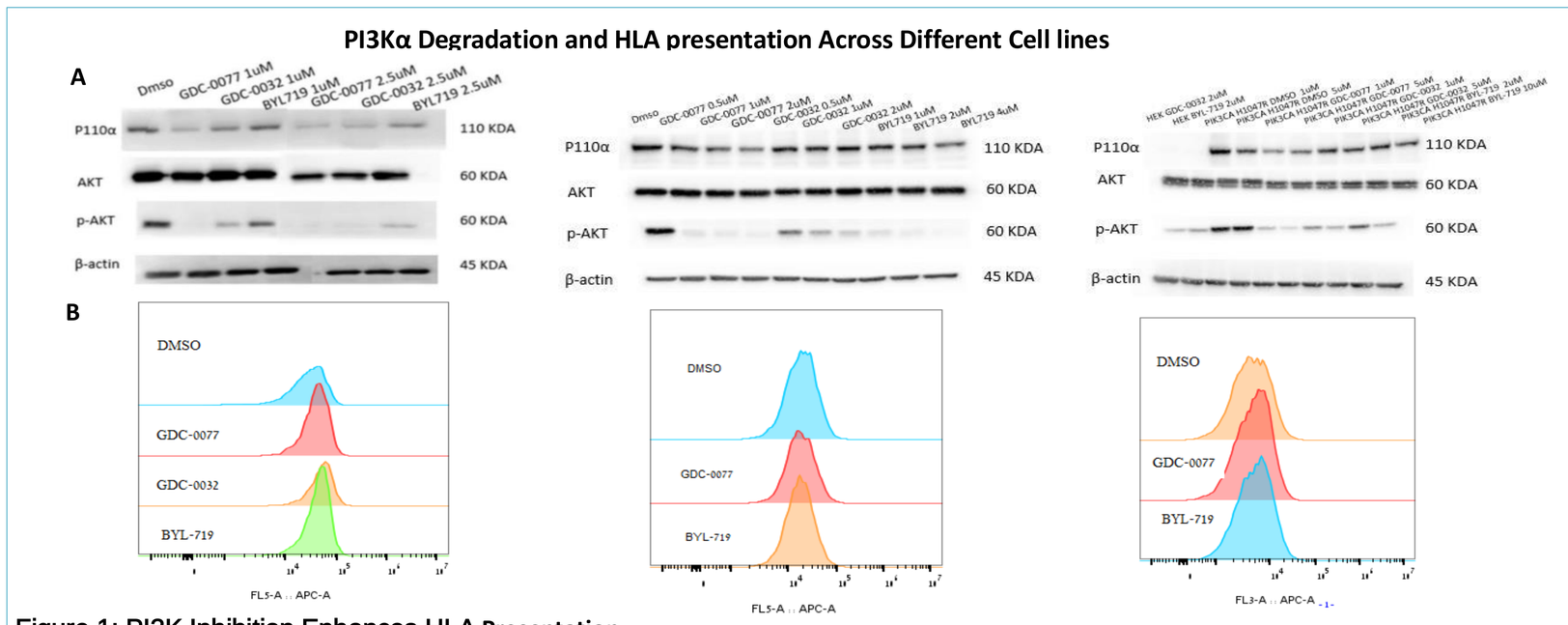


Figure 1: PI3K Inhibition Enhances HLA Presentation

(A) Western blot showing p110α degradation and reduced p-AKT levels in MDA-MB-453, S24 mouse, and HEK cells overexpressing the H1047R mutation following treatment with PI3K inhibitors (GDC-0077, GDC-0032, BYL-719). (B) Flow cytometry analysis of HLA surface presentation in MDA-MB-453 (left), S24 mouse (middle), and HEK H1047R-overexpressing (right) cells shows that GDC-0077 and GDC-0032 increase HLA levels compared to BYL-719 and DMSO. GDC-0077 induces the highest HLA expression in HEK H1047R cells, while BYL-719 reduces HLA presentation in all cell lines.

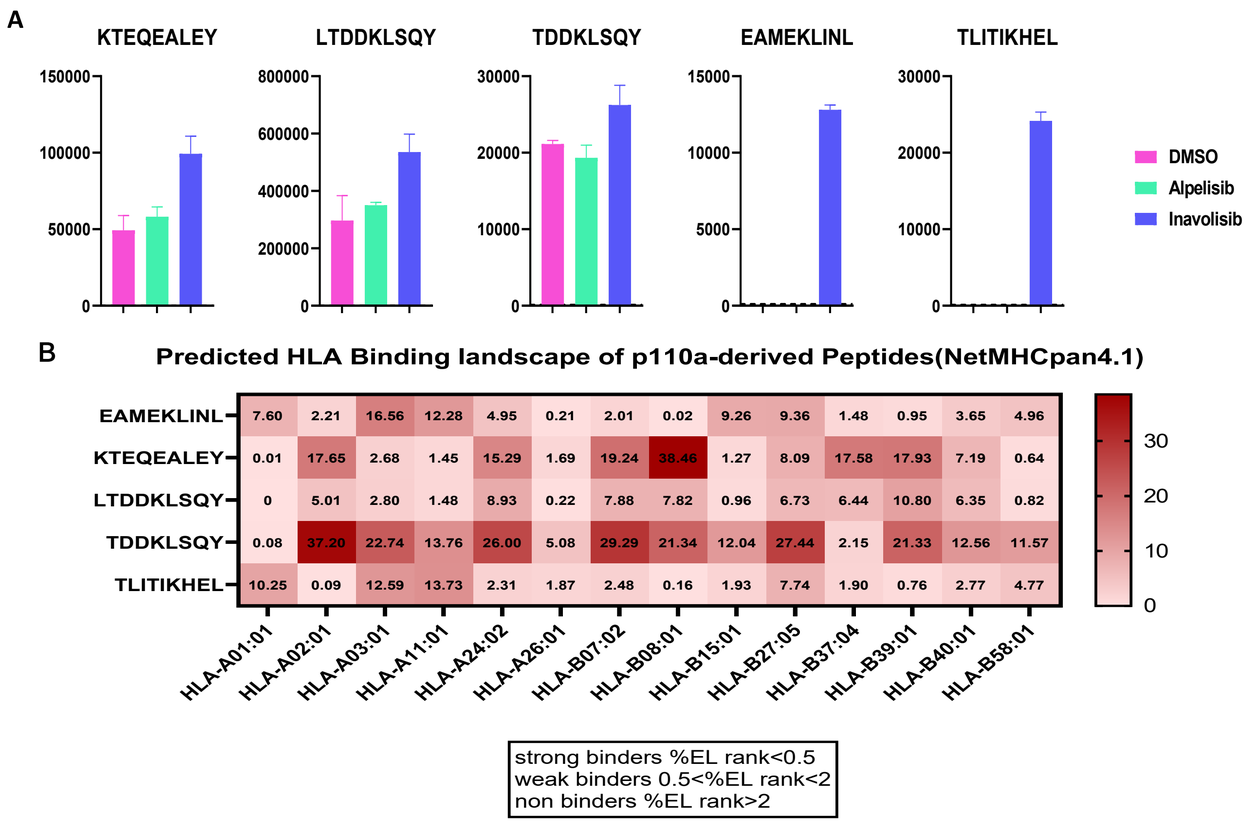


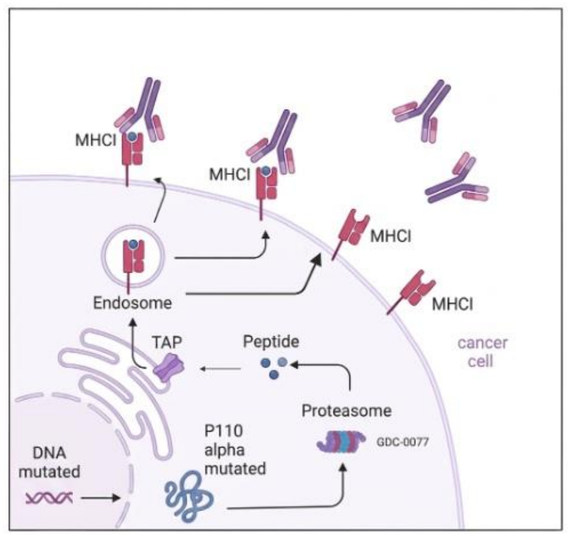
Figure 2: Differential HLA peptidome presentation following PI3K inhibition in MDA-MB-453 cells

(A) HLA peptidomics of MDA-MB-453 cells treated with DMSO, BYL719, or GDC-0077. Three peptides are upregulated under GDC-0077 versus DMSO and BYL719, and two peptides are uniquely detected only with GDC-0077.

(B) Heatmap of predicted binding affinities between these peptides and common HLA alleles.

Hypothesis

Targeted degradation of mutant p110α **reprograms** antigen processing and HLA class I presentation, creating a drug-dependent antigenic state in which specific peptide–HLA (pHLA) complexes appear on the tumor surface at targetable levels.



Strategic Research Pipeline

Phase I - Foundation

Establish inavolisib "licensing" across diverse models: cell lines, organoids, and primary patient samples.

Conduct MS-based **immunopeptidomics** profiling.

Define novel tumor-restricted pHLA targets.

Phase II - Antibody Discovery

Generate monoclonal antibodies (mAbs).

Validate target specificity in cancer models.

Characterize surface expression kinetics.

Phase III - ADC Development

Develop precision ADC directed at pHLA.

Assess ADC efficacy and therapeutic index.

Demonstrating translational potential for a first-in-class degrader-licensed therapy.

Antibody Discovery

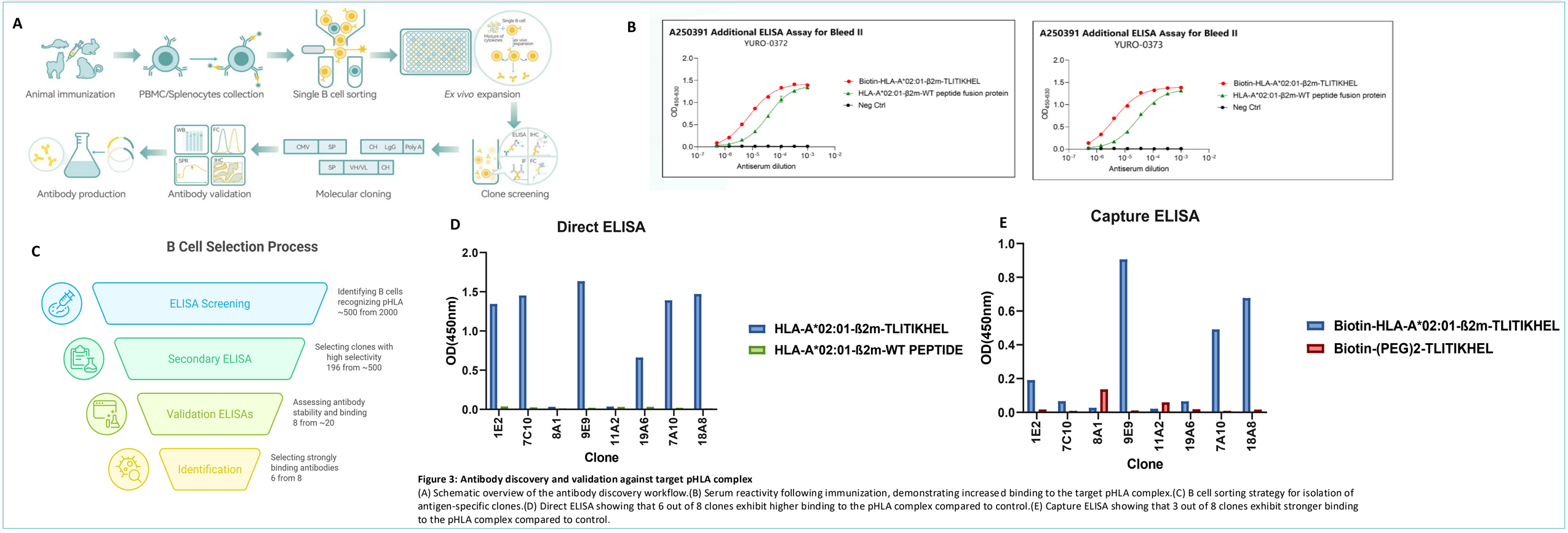


Figure 3: Antibody discovery and validation against target pHLA complex

(A) Schematic overview of the antibody discovery workflow.(B) Serum reactivity following immunization, demonstrating increased binding to the target pHLA complex.(C) B cell sorting strategy for isolation of antigen-specific clones.(D) Direct ELISA showing that 6 out of 8 clones exhibit higher binding to the pHLA complex compared to control.(E) Capture ELISA showing that 3 out of 8 clones exhibit stronger binding to the pHLA complex compared to control.