

Hold-to-Kill: RIPTAC Expanding Induced Proximity from Target Engagement to Therapeutic Window

Qing Xue, Zhu Meng, Xinru Wang, Xue Yang, Zhaoxia Yin, Tanfeng Zhao, Yanan Zhao, Qian Wang, Wei Liu, Tiejun Bing,Fujun Zhang, Ben Wei,Lili Chai
ICE Bioscience, INC. Building 16, Yard 18, Kechuang 13th Street, Beijing, 100176
Email: bingtj@ice-biosci.com



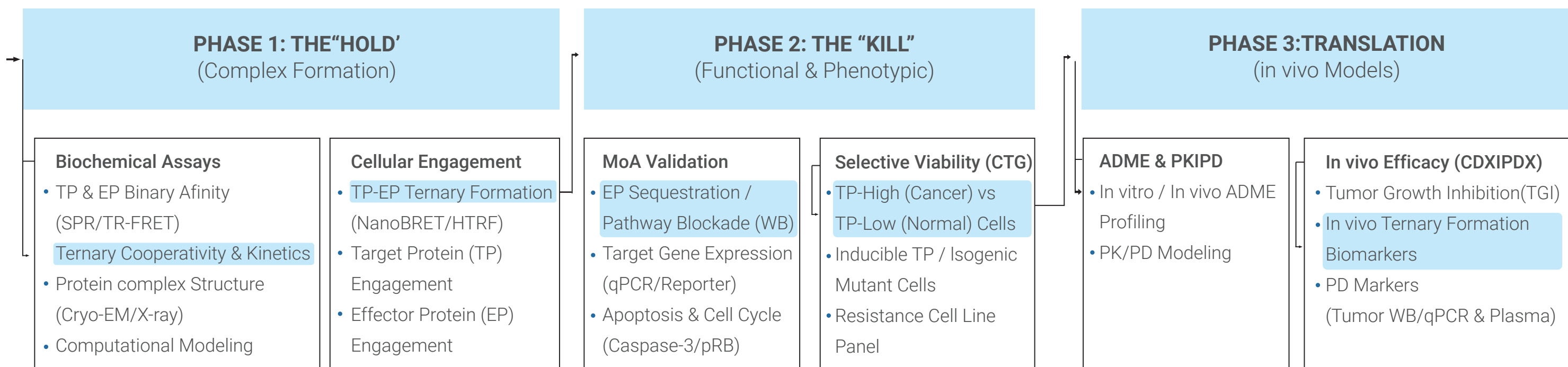
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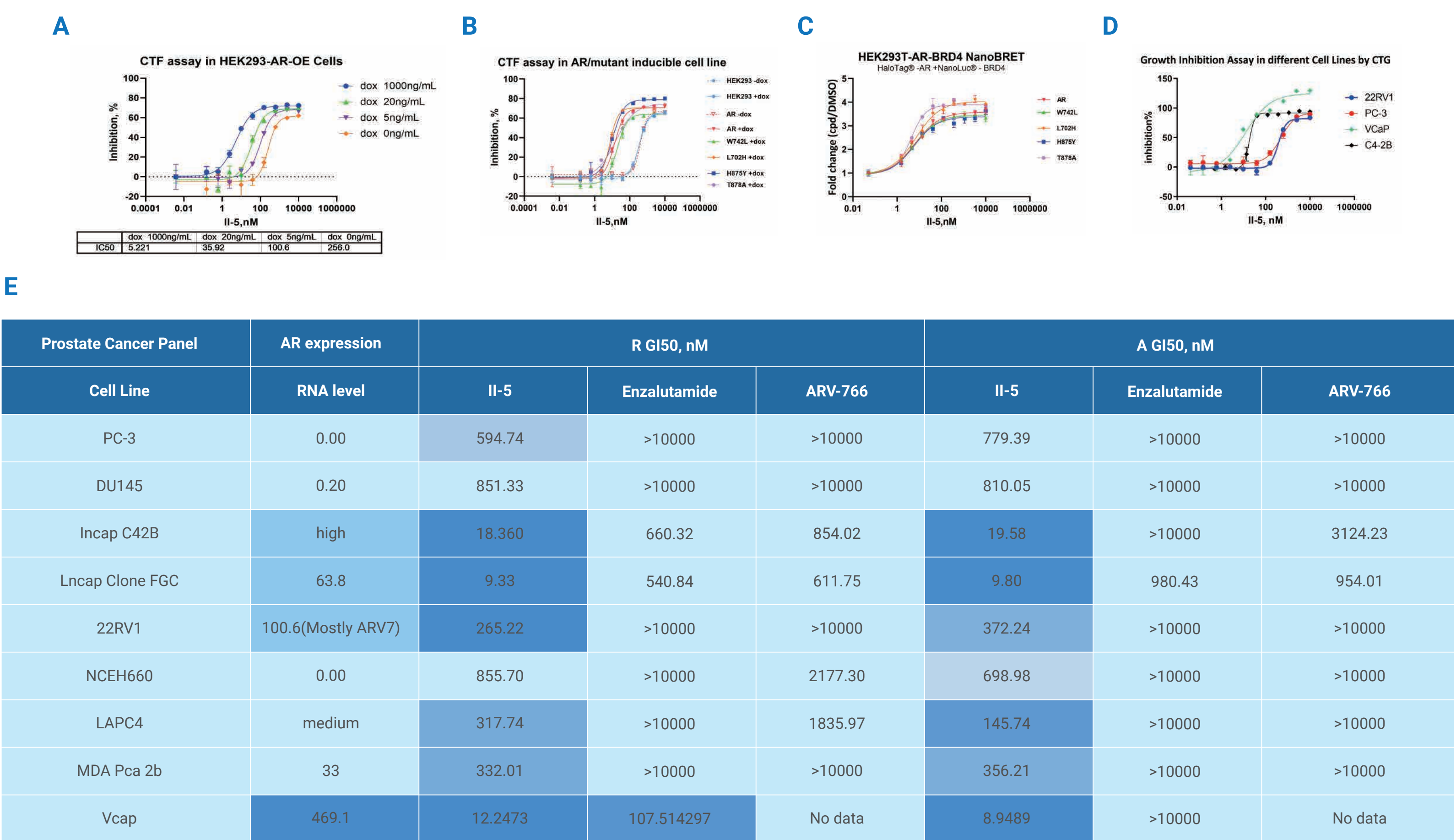
Abstract

RIPTAC (Regulated Induced Proximity Targeting Chimeras) introduces a novel strategy that leverages induced proximity to achieve selective cancer cell killing. Using AR–BRD4 RIPTAC II-5 as a tool compound, we integrated biochemical screening, computational docking, and multi-level cellular and in vivo assays to establish a direct link between target engagement and therapeutic efficacy. Biochemical evaluation confirmed binary and ternary affinity, supported by computational simulations that predicted novel AR–BRD4 ternary protein–protein interactions (neoPPIs) consistent with cooperativity observed experimentally. II-5's distinct slow on/off binding kinetics stabilize ternary complexes, translating into superior activity in ternary formation and downstream signaling modulation. Cellular assays demonstrated that II-5 induces ternary complexes in HEK293T AR OE, VCaP, and LNCaP cells, correlating with strong inhibition of BRD4-driven signaling (c-Myc) while only moderately inhibit AR signaling (reporter and PSA). In vivo CDX models further validated ternary complex formation, PSA reduction, and pharmacodynamic biomarker responses, showing that ternary assembly is preserved across biochemical, cellular, and tumor tissue contexts. II-5 was highly potent in AR-high prostate cancer models, with efficacy scaling across AR mutants and expression levels, highlighting a mechanistic correlation between AR expression and therapeutic effect. This enables RIPTAC to address resistance mechanisms such as AR amplification, point mutations, etc. Safety panel profiling indicates an overall favorable profile with limited off-target activity. Beyond AR–BRD4, RIPTAC expands the induced proximity landscape, aligning with TCIP paradigms and demonstrating broader applicability across oncogenic drivers. Together, computational and experimental evidence converge to highlight ternary complex stability and AR expression dependence as the mechanistic drivers of RIPTAC's therapeutic window. Importantly, our induced proximity platform, built on extensive expertise in targeted protein degradation (TPD), can be rapidly migrated to other target pairs, enabling first-in-class drug discovery programs and supporting both domestic and international partners.

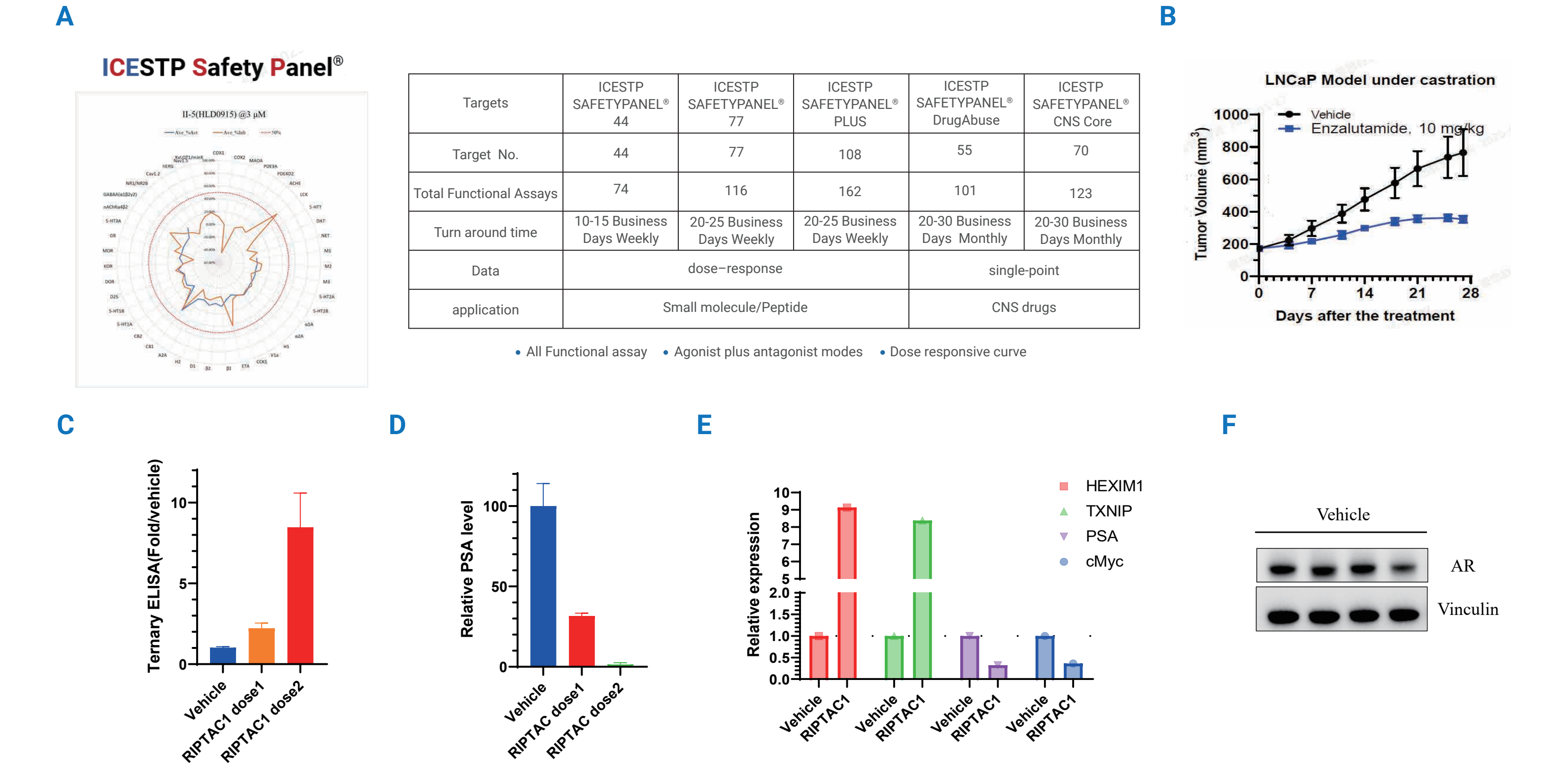
ICEbio RIPTAC platform



II-5 Activity Linked to AR Expression with Favorable Treatment Window



II-5: Safe Profile with In Vivo PD Modulation Through Ternary Complex



Binary and Ternary Binding of RIPTAC II-5: Cooperative and High Affinity

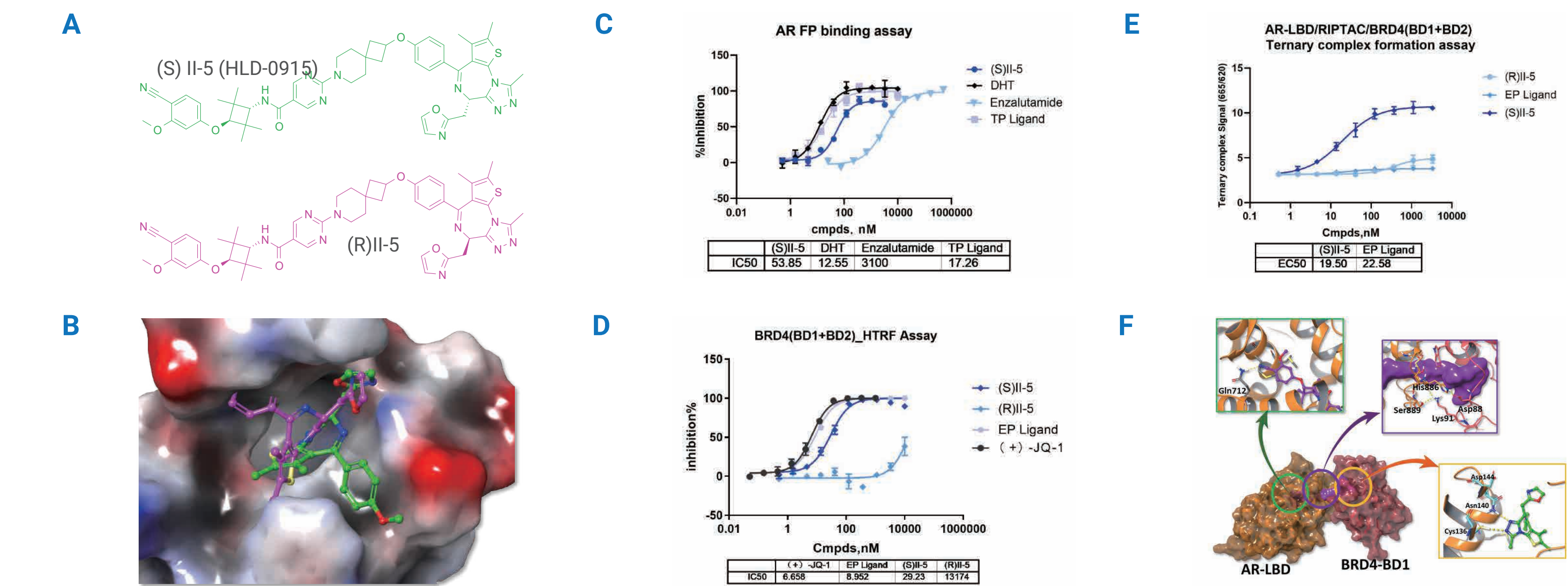


Figure 1. Biochemical evaluation of RIPTAC binary and ternary affinity(A) Structure of AR RIPTAC II-5 (S isomer, HLD-0915; R isomer, negative control).(B) Docking in BRD4 BD: (S)II-5 fits, (R)II-5 clashes (C) II-5 TP ligand shows similar potency as DHT, while II-5 also show strong potency in AR FP assays.(D) II-5 is highly active in BRD4 HTRF binding assays.(E) II-5 promotes AR-LBD/BRD4 ternary complex formation.(F) Ternary complex docking model shows neoPPI induced by II-5.

II-5 Engages BD1 and BD2 with Slow Binding Dynamics

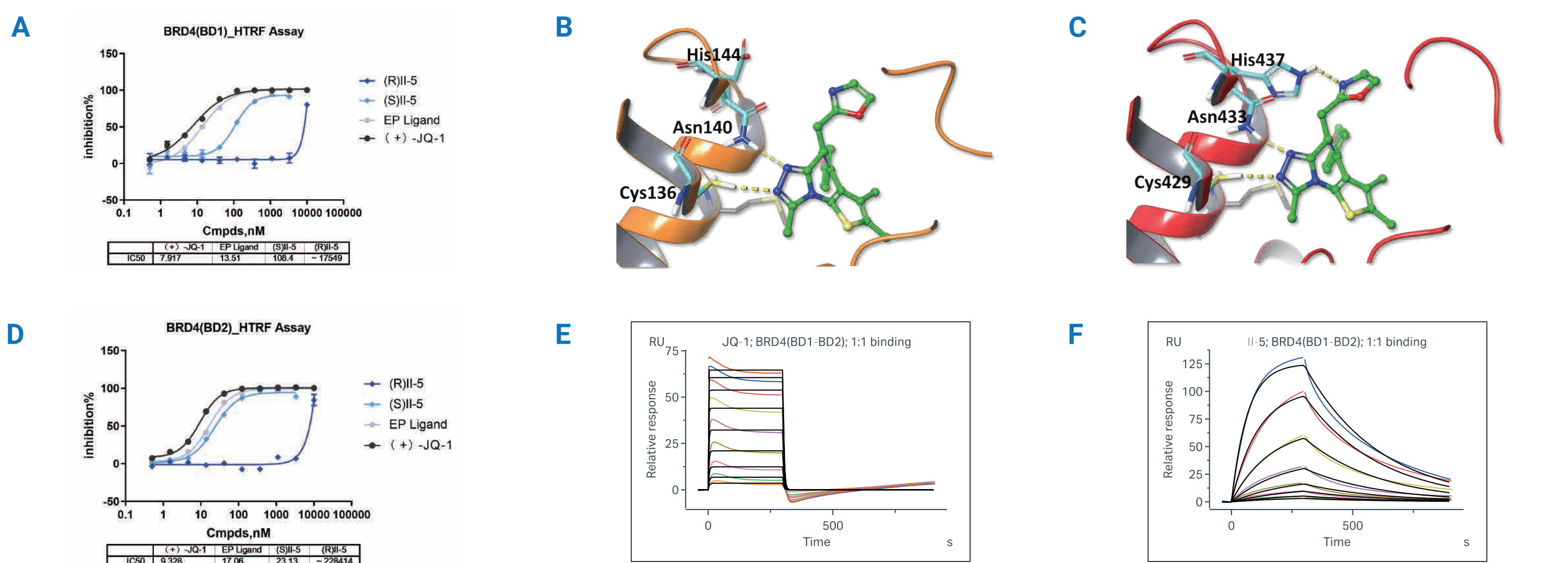


Figure 2. RIPTAC BRD4 binding model. (A) II-5 binds to the BRD4 BD1 domain with ~100 nM affinity; its EP ligand shows affinity comparable to JQ-1.(B–C) Docking results show II-5 binds BD1 and BD2 with similar poses.(D) II-5 also binds BD2.(E) SPR sensorgrams indicate JQ-1 is a fast on/off binder.(F) II-5 displays a distinct slow on/off binding mode, which may facilitate ternary complex formation.

II-5 Ternary Complex Formation Drives Cellular Response (Hold to Kill)

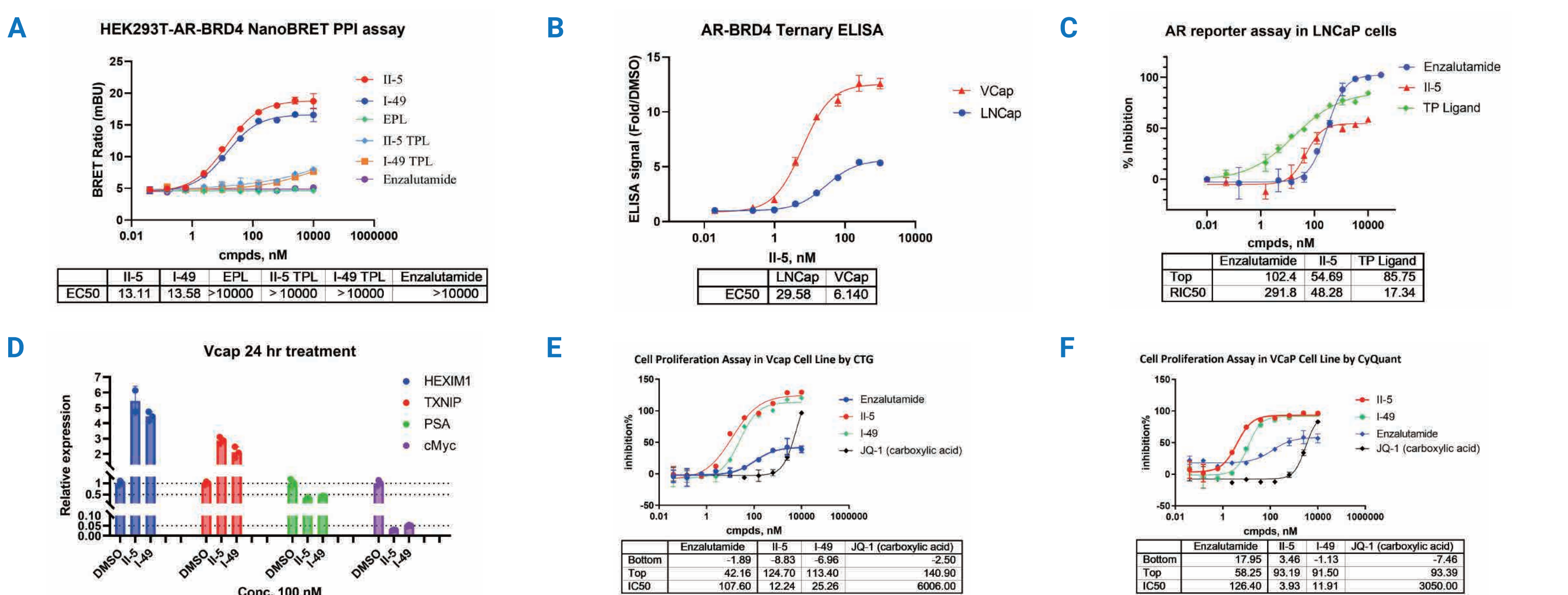


Figure 3. RIPTAC Hold-to-Kill model illustrated by compound II-5. (A) II-5 and I-49 induce ternary complex formation via nanoBRET in HEK293T cells.(B) II-5 induces endogenous ternary complexes in VCaP and LNCaP cells.(C) II-5 shows weaker AR reporter inhibition than its AR ligand.(D) II-5 strongly inhibits BRD4 signaling (c-Myc) but weakly inhibits AR signaling (PSA).(E, F) In AR-high VCaP cells, RIPTAC is more potent than Enzalutamide and JQ-1 (carboxylic acid), as shown by CTG (ATP) and CyQuant (DNA) assays.

Summary

ICE Biosciences' RIPTAC platform integrates biochemical screening, computational docking, and multi-level cellular and in vivo assays to connect target engagement with therapeutic efficacy. By combining ternary complex prediction, kinetic modeling, and validation across biochemical, cellular, and tumor tissue contexts, the platform establishes mechanistic links between AR expression and selective cancer cell inhibition. Supported by our extensive expertise in targeted protein degradation (TPD), the modular design enables rapid migration to new target pairs. This flexibility, together with translational profiling and safety evaluation, empowers domestic and international partners to accelerate first-in-class drug discovery programs and expand the induced proximity landscape with clinically meaningful insights.

Reference

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