A new ethisterone peptoid conjugate that blocks androgen receptor (AR) function can overcome enzalutamide resistance in prostate cancer models. The report, published in Cancer Research, describes the biological evaluation of a new set of multivalent peptoid conjugates (MPCs) and highlights the potential of new compounds based on innovative medicinal chemistry designs against diseases that are resistant to current treatments.

MPCs are sequence-specific oligomers that are synthetic variants of peptides. The peptoids are composed of N-substituted glycine monomers, so that the side chains are appended from the backbone nitrogen atoms. “Peptoids enable precise positioning of multiple ligands along the oligomer backbone,” explain Michael Garabedian and Kent Kirshenbaum from New York University, senior authors of the study. “This multivalent presentation of the ligand can improve ligand–receptor interaction, owing to increased local ligand concentration, and can impart new pharmacological ligand properties, owing to the oligomeric set-up.”

The team had previously designed a series of MPCs containing ethisterone ligands and investigated their mechanism of action as AR antagonists. In the current report, they performed structure–activity analyses on the most promising molecule MPC6 by comparing its properties with those of compounds with wider spacing between ethisterone ligands or modified peptoid backbone flexibility. Only MPC6 inhibited growth of enzalutamide-resistant LNCaP cells and comparison with ethisterone alone demonstrated that multivalency of the ligand was required for activity at applicable concentrations.

Further in vitro experiments showed that binding of MPC6 induced a distinct AR conformation and blocked interaction with AR coactivator peptides, possibly illustrating the reason for the lack in activity of related compounds that have a different chemical structure.

In contrast to enzalutamide, MPC6 also inhibited growth of cells expressing the AR splice variant AR-V7 and the expression of AR-V7 itself. MPC6 treatment of in vivo xenografts of the enzalutamide-resistant LNCaP cells showed significantly reduced tumour growth compared with vehicle administration.

“Next, we will perform additional medicinal chemistry to enhance MPC6 activity, working in collaboration to determine the X-ray crystal structure of MPC6 bound to AR to rationally inform modifications,” Garabedian concludes. “Our ultimate goal is to move this approach into clinical application for patients who are resistant to enzalutamide therapy.”

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