Biophysical & Functional Characterization of Bifunctional Small Molecules enables TPD Drug Discovery
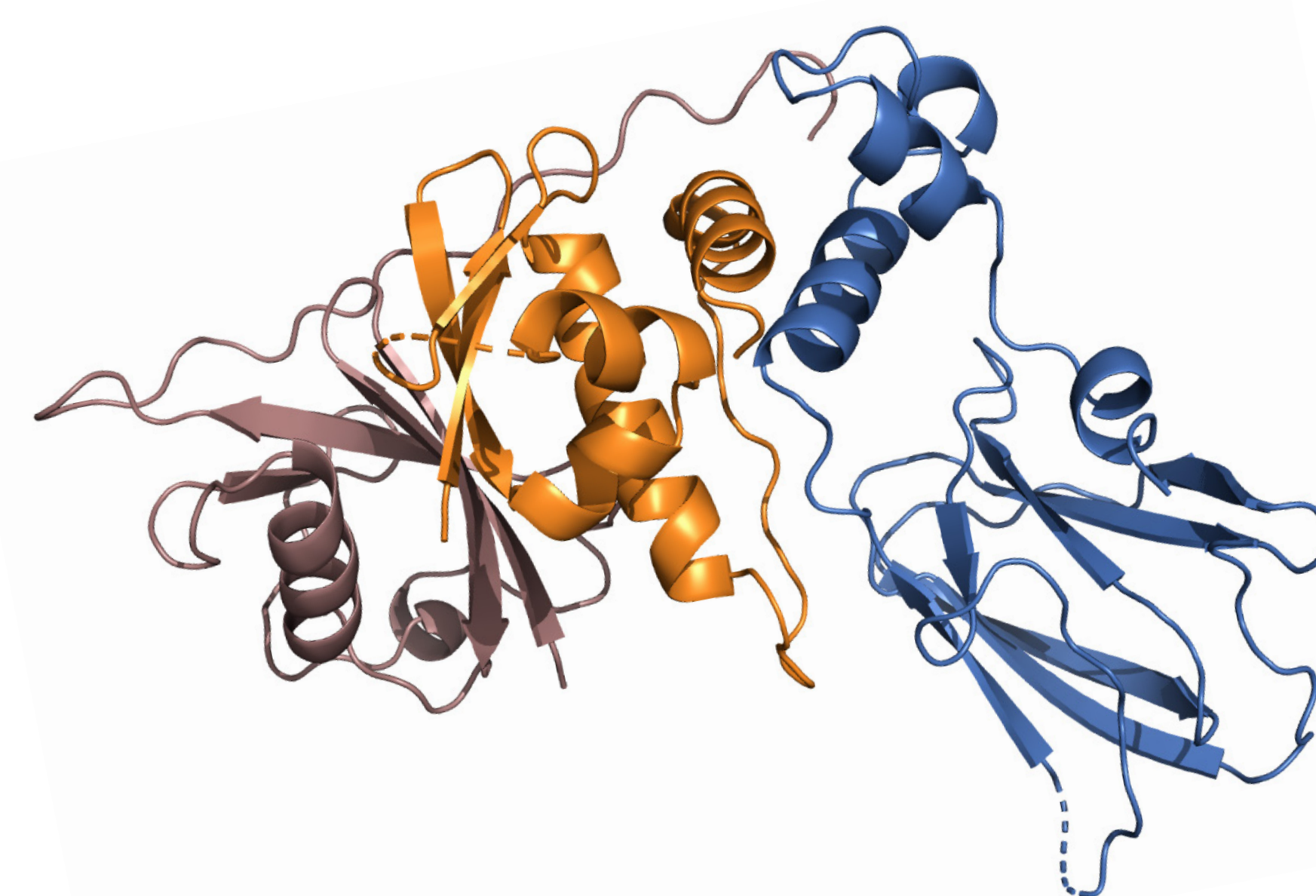
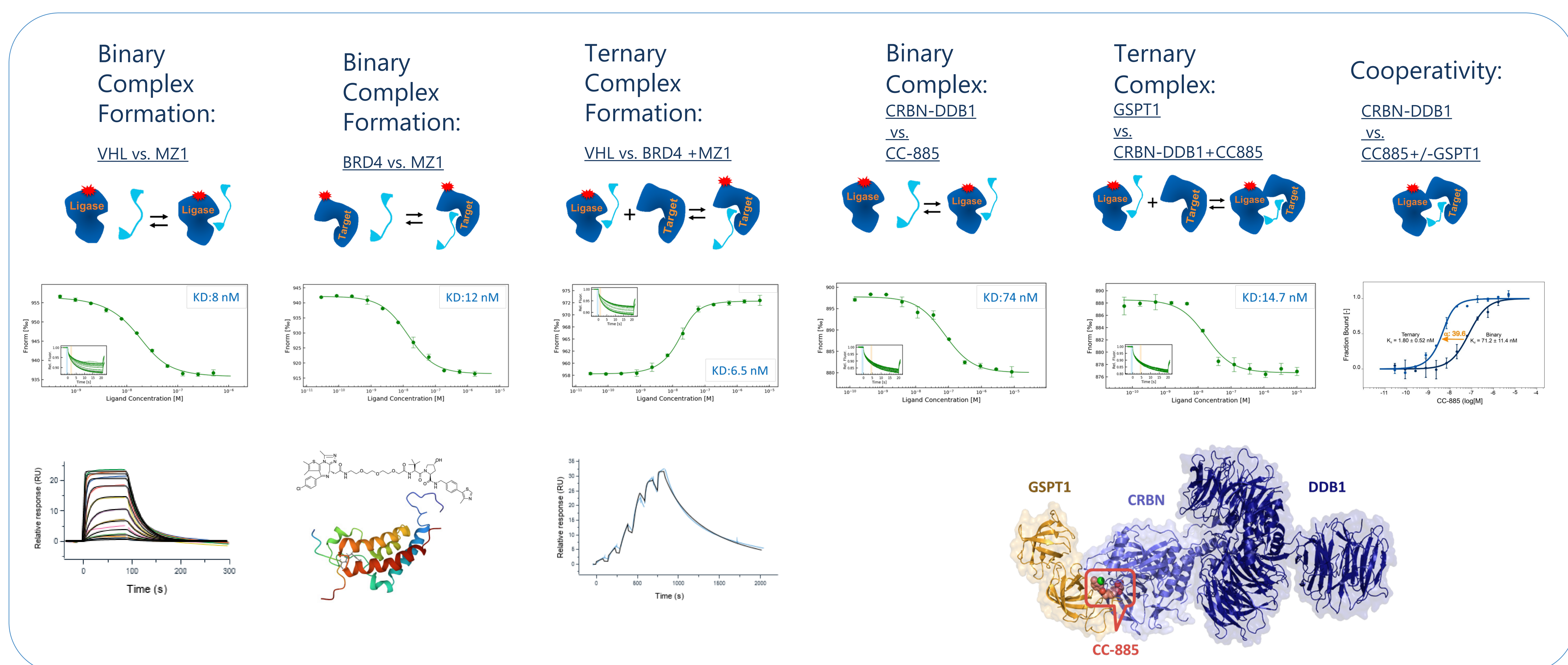Moran Jerabek-Willemsen, Lingbing Sun

WuXi AppTec 药明康德

Abstract

Traditional small molecule therapeutic mechanisms have recently been augmented by new strategies to specifically manipulate the levels of disease-related proteins. By employing bifunctional molecules, we can hijack endogenous cellular degradation pathways to bring about the targeted degradation of disease-related proteins. Bifunctional molecules consisting of a ligand that binds to an E3 ligase, connected by a linker to another ligand that binds to the disease-related protein, are often referred to as degraders. Robust and reliable biophysical and biochemical methods play an important role in the discovery of new protein degraders. In this work we introduce the WuXi AppTec Discovery Platform, which allows an in-depth biophysical and biochemical characterization of bifunctional small molecules.
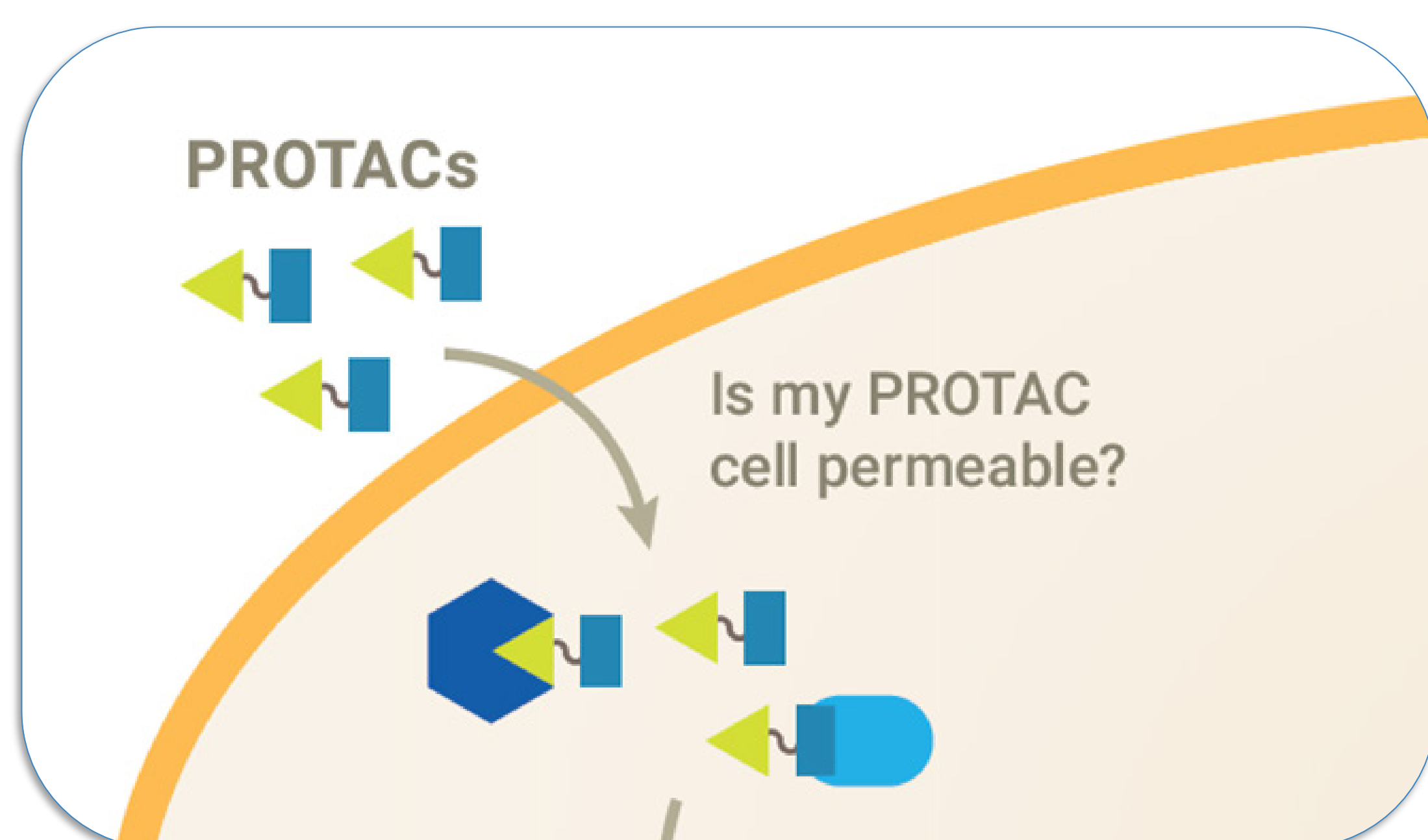
X-Ray Structure of VHL Complex generated in WuXi Biology
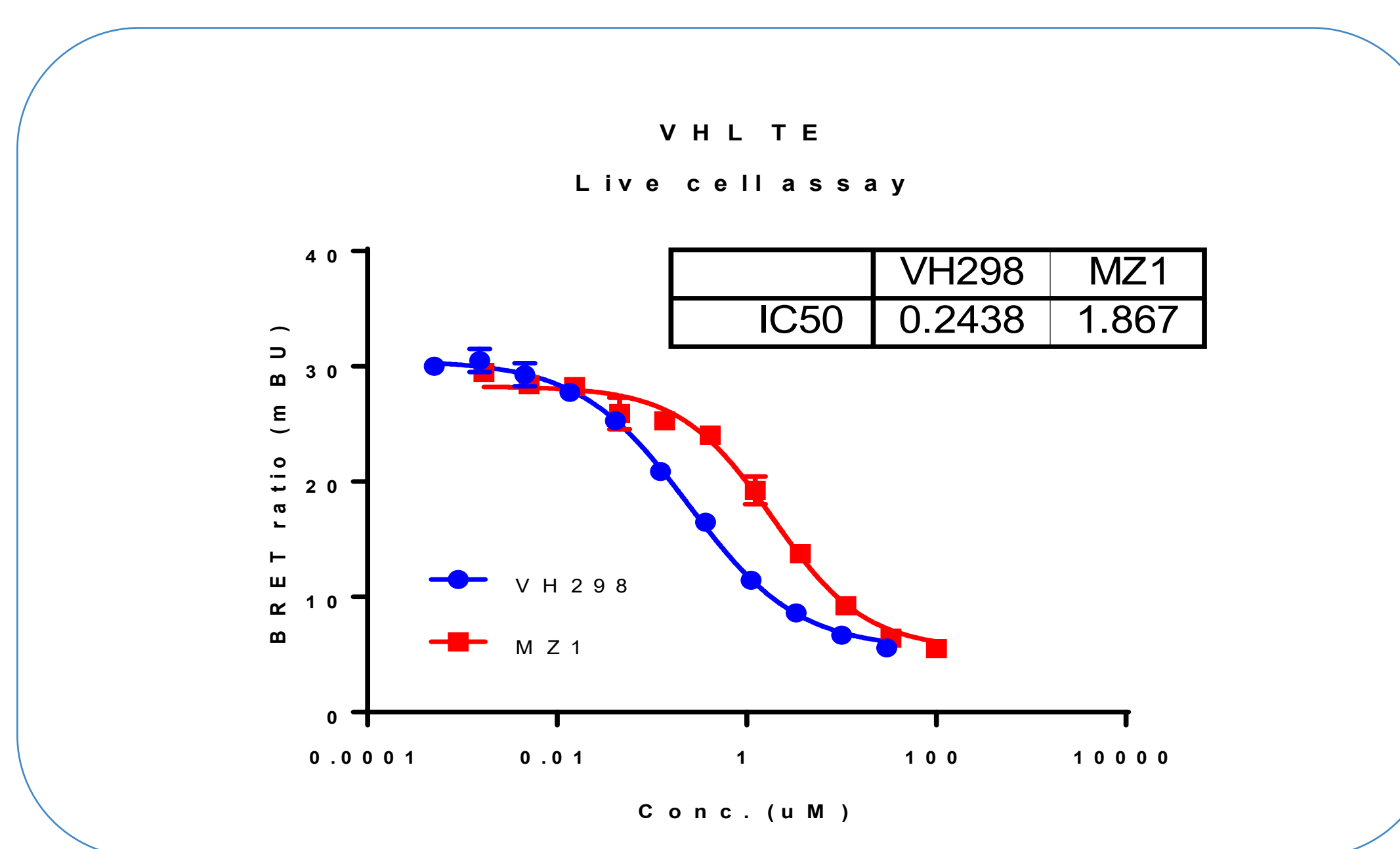
Biophysical Characterization

Binary Complex Formation: VHL vs. MZ1 — KD:8 nM

Binary Complex Formation: BRD4 vs. MZ1 — KD:12 nM

Ternary Complex Formation: VHL vs. BRD4 +MZ1 — KD:6.5 nM

Binary Complex: CRBN-DDB1 vs. CC-885 — KD:74 nM

Ternary Complex: GSPT1 vs. CRBN-DDB1+CC885 — KD:14.7 nM

Cooperativity: CRBN-DDB1 vs. CC885+/-GSPT1

GSPT1   CRBN   DDB1   CC-885

Target – Engagement in Cells

Cellular NanoBRET Assay

PROTACs

Is my PROTAC cell permeable?

VHL TE Live Cell Assay

VHL TE Live cell assay

	VH298	MZ1
IC50	0.2438	1.867

VH298
MZ1

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