# IS IT POSSIBLE TO DEGRADE c-MYC WITH LOW AFFINITY COMPOUND - BASED PROTACs?

A. Sánchez-Arfelis[1], A. Bertran-Mostazo[2], S. Scaffidi[2], R. Castaño[2], E. Molins[3], X. Barril[2,4], C. Escolano[1], C. Galdeano[2]

[1]*Laboratory of Medicinal Chemistry (CSIC Associated Unit), Faculty of Pharmacy and Food Sciences, and Institute of Biomedicine (IBUB), University of Barcelona (UB), Spain.*
[2]*Department of Pharmacy, and Pharmaceutical Technology, and Physical Chemistry, Faculty of Pharmacy and Food Sciences, and Institute of Biomedicine (IBUB), University of Barcelona (UB), Spain.*
[3]*Institute of Materials Science of Barcelona (ICMAB-CSIC), Campus UAB, E-08193 Cerdanyola, Spain.*
[4]*Catalan Institution for Research and Advanced Studies (ICREA), Spain.*

asanchezarf@ub.edu

c-Myc is a key therapeutic oncogene that orchestrates a potent pro-cancer programme across multiple cellular pathways. Previous attempts to developing any clinically useful drug directly targeting it have been unsuccessful, partly because it is an Intrinsically Disordered Protein (IDP) [1]. Indeed, the disordered nature of unbound c-Myc has become an inherent challenge for standard structure-based drug development and novel drug modalities are needed to develop therapeutics directly affecting c-Myc activity [2].

The overarching goal of our project is to develop PROTAC molecules that can bind allosterically to the Fbxw7 E3 ligase and to c-Myc, to retarget c-Myc for degradation [3]. The Fbxw7 gene is one of the most deregulated proteins in human cancer and the E3 ligase that naturally degrade c-Myc [4]. Given that and the intrinsic difficulty to develop potent compounds for c-Myc, we have hypothesised that PROTAC molecules targeting the natural pair E3 ligase-natural substrate (c-Myc-Fbxw7) could increase the efficacy and the specificity of the degradation for several reasons: employment of the same ubiquitination machinery, cellular and tissue co-localization, absolute abundance.

Thus, in this communication, as a proof of concept that c-Myc is degradable with small-molecule PROTAC, we will present the designed and synthesised first series of VHL- and CRBN-based PROTACs using a low affinity fragment-size derivative of 10058-F4, a c-Myc small-molecule inhibitor as the warhead ligand [5]. In fact, dose-response and proteasome-dependent degradation assays of c-Myc are ongoing and preliminary results are going to be presented. In parallel, following a fragment-based screening from a custom in-lab designed library of 700 fragments screened by SPR, we have identified fragments that bind to the Fbxw7 in the low micromolar range. These fragments have been confirmed by STD-NMR and have been further biophysically characterized. We are currently working on the binding mode and functional implications of these fragments.

**References:**

[1] Yu, C.; Niu, X.,Jin, F., Liu, Z., Jin, C. *et al. Sci. Rep*. **2016**, *6*, 22298.
[2] Madden, S.K., de Araujo, A.D., Gerhardt, M. *et al. Mol Cancer* **2021,** *20*, 3.
[3] Békés, M., Langley, D.R., Crews, C.M. *Nat Rev Drug Discov* **2022,** *21*, 181–200.
[4] Welcker, M.; Clurman, B. E. *Nat. Rev. Cancer*, **2008**, 8 (2), 83–93.
[5] Yin, X.; Giap, C., Lazo, J.S., Prochownik, E.V. *Oncogene*, **2003**, *22,* 6151-6159.