DNA damage response inhibitors targeting synthetic lethal interactions for cancer treatment

Cristina Camps-Fajol[1*] & Jordi Surrallés[1,2,3,4]

[1] Joint Research Unit on Genomic Medicine, Universitat Autònoma de Barcelona (UAB)-IR SANT PAU, Barcelona, Spain
[2] Centro de Investigación Biomédica en Red de Enfermedades Raras, Instituto de Salud Carlos III (CIBERER, ISCIII), Madrid, Spain
[3] Department of Genetics and Microbiology, Faculty of Biosciences, Universitat Autònoma de Barcelona (UAB), Spain
[4] Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
* ccampsf@santpau.cat

Targeting synthetic lethal interactions has emerged as a promising strategy for cancer therapeutics, particularly by exploiting DNA damage response (DDR) pathways. A well-known example of this are PARP inhibitors (PARPi), that selectively kill homologous recombination-deficient (HRD) tumors, especially those harboring BRCA1/2 mutations. PARPi have been approved for breast, ovarian, prostate, pancreatic and endometrial cancer. Clinical studies have demonstrated that these inhibitors can extend progression-free survival in patients with these tumors alone or in combination with other treatments like chemotherapy or immunotherapy. Additionally, ongoing research is exploring their efficacy in other cancer types and in patients harboring mutations other than BRCA1/2, potentially broadening their therapeutic applications. Several other drugs inhibiting key DDR components, such as ATR, ATM and DNA-PK, have already progressed to clinical trials. Continued research is essential to fully understand the intricate network of synthetic lethality within DDR and maximize the therapeutic potential of these therapies. Another promising DDR pathway that can be targeted for cancer is the Fanconi anemia/BRCA (FA/BRCA) pathway, responsible for the repair of DNA interstrand cross-links. A key event in this pathway is the monoubiquitylation of the FANCD2-FANCI complex. With the goal to identify a FA/BRCA pathway inhibitor we have performed two high-content virtual screenings that have led to the identification of several compounds that have been further optimized obtaining several hits.