AsiDNA^{TM}, a new therapeutic strategy to target drug-tolerant persister cells and prevent cancer recurrence

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Short title: AsiDNA tackles Drug-tolerant persister cells

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Therapeutic resistance to chemotherapies and targeted therapies is still a major source of therapy failure. Several studies have shown that a small population of tumor cells may evade cell death by entering a reversible dormancy state known as the Drug-tolerant persister (DTP) state. These DTP cells (DTCs) survive drug therapy long enough to develop *de novo* mechanisms of resistance. Thus, developing therapeutic strategies to target these deadly survivors could be a game changer in the management of cancer.

AsiDNA^{TM} is a double-strand DNA molecule that mimics endogenous DNA breaks to interfere with the DNA damage (DD) response. This decoy agonist molecule induces a false DD signaling through DNA-PK over-activation, and thus hijacks several DNA repair proteins from sites of real DD. This AsiDNA^{TM}-induced protein hyperactivation also triggers massive metabolic deficiencies responsible of other cellular dysfunctions. To check if AsiDNA^{TM} could prevent the emergence of acquired resistance by targeting DTCs, we continuously treated several relevant tumor models with PARP inhibitors (PARPi), KRAS^{G12C}i and EGFRi and assessed the impact of AsiDNA^{TM} addition on resistance prevention.

Continuous treatment of cancer cells led to the emergence of a DTC population displaying distinct features such as senescence-associated phenotypic hallmarks including proliferation restriction and inflammatory secretome, a down-regulation of their DNA repair, and a switch in their energy production. Addition of AsiDNA^{TM} prevented resistance emergence through the abrogation of DTC re-proliferation, and the downregulation of major DNA repair pathways and fatty acid metabolism. This resistance prevention was also observed when adding AsiDNA^{TM} during the DTP state, indicating a DTC-dependent resistance abrogation. In line with this, we showed that DTCs are hyper-sensitive to AsiDNA^{TM}.

Our results provide the evidence that the concept of DTCs is applicable to different cancer treatments, and that AsiDNA^{TM} could be a therapeutic strategy to specifically address this aggressive source of therapy failure.